

SUMMARY OF PRODCUT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg rifampicin , 275 mg ethambutol hydrochloride, 75 mg isoniazid and 400 mg pyrazinamide.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Light buff coloured biconvex capsule shaped film-coated tablets, plain on both sides.

The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) is indicated for the intensive phase of treating tuberculosis caused by *Mycobacterium tuberculosis* in adults and children weighing more than 20kg.

The most recent official guidelines (e.g. WHO) on the appropriate use of anti-tuberculosis medicines and local information on the prevalence of resistance to anti-tuberculosis medicines must be taken into consideration for deciding on the appropriateness of therapy with Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)

4.2 Posology and method of administration

Oral use

For children weighing 21-30 kg the daily dose is 2 tablets administered as a single dose. (Only in children who can swallow solid tablets.)

In patients weighing 30-39 kg the daily dose is 2 tablets administered as a single dose. In

patients weighing 40-54 kg the daily dose is 3 tablets administered as a single dose. In

patients weighing 55-70 kg the daily dose is 4 tablets administered as a single dose. In

patients weighing > 70 kg the daily dose is 5 tablets administered as a single dose

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should not be used for intermittent treatment regimens.

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should be taken on an empty stomach (at least one hour prior to or two hours after a meal). If taken with food to improve gastrointestinal tolerance, bioavailability may be impaired.

For situations where discontinuation of therapy with one of the active agents of this medicine, or dose reduction is necessary, separate preparations of the respective agents (rifampicin, isoniazid, pyrazinamide, ethambutol) should be used.

Renal impairment:

Since dose adjustments may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/min), it is recommended that separate preparations of rifampicin, isoniazid, pyrazinamide and ethambutol be administered (see section 4.4).

Hepatic impairment:

Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets must not be used in patients with severe liver disease (see section 4.3).

Children and adolescents / patients with a body weight < 20 kg

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets is not recommended 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 /Isoniazid /Pyrazinamide /Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets is interrupted for any reason including non-adherence, the product should not be used 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 the active substances or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

Optic neuritis

Acute gout

Co-administration of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride

150 mg/75 mg/400 mg/275 mg film-coated Tablets with voriconazole or any HIV-protease inhibitor is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Liver toxicity: Rifampicin, isoniazid, pyrazinamide and ethambutol may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150mg/75mg/400mg/275mg film-coated Tablets should be avoided in patients with preexisting hepatic impairment (ALT > 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets. Patient groups especially at risk for developing hepatitis include:

- age > 35 years,
- daily users of alcohol (see section 4.5),
- patients with active chronic liver disease
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients
- HIV positive patients.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness of greater than 3 days duration or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected,

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin, isoniazid or pyrazinamide. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until symptoms and laboratory abnormalities have subsided. In case of rechallenge, Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents should be used.

Visual acuity: Patients should be advised to report promptly any changes in visual acuity since ethambutol may cause ocular toxicity. Visual acuity tests should be performed prior to therapy and every four weeks during treatment; in patients with pre-existing visual defects every second week and, when considered necessary, more frequently.

Patients who cannot report their visual acuity, e.g. children, should be closely monitored for signs of ocular toxicity when treated with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets. Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy.

Therapy with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets must be discontinued immediately if visual disturbances emerge (see section 4.8).

Hypersensitivity: Rifampicin may cause a hypersensitivity syndrome including 'flu-like' symptoms or organ manifestations. The risk is higher on intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity should appear (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or renal failure), Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should immediately be discontinued. Such patients should not be rechallenged with rifampicin. If rifampicin therapy is temporarily discontinued, rifampicin should be restarted carefully at a reduced dose, and with close monitoring. In this situation, Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should not be used.

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

Peripheral neuropathy: This is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets, at doses of 10 mg per day.

Epilepsy and psychotic disorders: Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

Haematological toxicity: Since rifampicin treatment has been associated with haemolytic anaemia, leukopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets. In case of severe haematological disturbances Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets must be discontinued.

Hyperuricaemia and gout: Pyrazinamide and ethambutol may increase serum levels of uric acid and cause gout. Patients with a history of gout should be carefully monitored. Serum uric acid levels should be determined prior to starting therapy with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets.

Renal insufficiency: In renal insufficiency, the clearance of pyrazinamide, ethambutol and isoniazid is delayed, causing an increased systemic exposure. In case of renal insufficiency, Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should not be used, as dose modifications of the active components may be necessary (see section 4.2)

Nephrotoxicity: Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets should be discontinued in case of clinical signs of nephrotoxicity.

Diabetes Mellitus: Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

Concomitant medicines: Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

Contraception: Oral contraceptives do not provide adequate protection against conception when co-administered with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets. This probably also pertains to other forms of hormonal contraceptives (e.g. patches, transdermal implants). Barrier- or other non-hormonal methods of contraception should be used.

Treatment with corticosteroids: Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

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

Discoloration of body fluids: Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets 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 monitored prior to and at regular intervals during treatment with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets.

Excipients:

This medicinal product contains a colorant (sunset yellow) which may cause allergic reactions. This medicinal product also contains castor oil, which may cause stomach upset and diarrhoea.

4.5 Interactions 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. Administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the concomitant administration of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets.

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. 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/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. In so far, as it 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 of isoniazid 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/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets 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. Whenever co-prescribing any drug together with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets is not exhaustive, but is a selection of interactions of putative importance. The scope of the table is largely based on the WHO Model List of Essential Medicines.

Other interactions

Interactions between Rifampicin /Isoniazid /Pyrazinamide /Ethambutol Hydrochloride Tablets and other medicines are listed below (increased exposure is shown as “↑”, decreased exposure as “↓”, no change as “↔”).

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
INFECTION		
<i>Antiretrovirals</i>		
<i>Nucleoside analogues</i>		
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 DF / 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.
<i>Non-nucleoside analogues</i>		
Efavirenz / rifampicin	Efavirenz AUC ↓ 26%	When co-treating with Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets, consider increase of the efavirenz dose to 800 mg daily.

Nevirapine / rifampicin	nevirapine: AUC ↓ 58%	Since neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established, concomitant use of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and nevirapine is not recommended.
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and etravirine should be avoided
<i>Protease inhibitors</i>		
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Fosamprenavir / rifampicin Saquinavir Indinavir Ritonavir Nelfinavir Lopinavir Atazanavir Tipranavir Darunavir	PI exposure will be reduced to subtherapeutic level, due to interaction with rifampicin. Attempts to dose adjust by increased doses, or an increase in ritonavir-boosting, are ill-tolerated with a high rate of hepatotoxicity.	Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)film-coated Tablets should not be co- administered with HIV protease inhibitors.
<i>Others</i>		
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.
<i>Antifungals</i>		
Ketoconazole / rifampicin	Ketoconazole AU C ↓ 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 AU C ↓ >64- 88%	Co-administration should be avoided.

Voriconazole / rifampicin	Voriconazole AU C ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
<i>Antibacterials/Antituberculotics</i>		
Clarithromycin / rifampicin	Chlarithromycin mean serum concentration ↓ 85%. 14-OH chlarithromycin levels unchanged.	Co-administration should be avoided.
Chloramphenicol / rifampicin	Case reports indicate >60-80% reduction of chloramphenicol exposure.	Co-administration should be avoided.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
Ciprofloxacin / rifampicin	No significant interaction	No dose adjustmentrequired.
Ofloxacin /Pyrazinamide Levofloxacin	Co-treatment with pyrazinamide and either of these fluoroquinolones has been	Co-treatment of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film- coated Tablets and either of these agents is not recommended. However, whendeemed
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 berequired.

Ethionamide / rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
<i>Antimalarials</i>		
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%	Co-administration should be avoided.
Mefloquine / rifampicin	Mefloquine AUC ↓ 68%	Co-administration should be avoided
Amodiaquine / rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Co-administration should be avoided.
Drugs by Therapeutic Area	Interaction	Recommendations concerning 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 its derivatives / rifampicin	Empirical data are not available. During co-treatment with rifampicin, lower levels of artemisinin 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.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Paracetamol / rifampicin / isoniazid	Rifampicin may increase the	Co-administration of Rifampicin/Isoniazid/Pyrazinamide/Ethambutol
ANTICONVULSANTS		
Carbamazepine / rifampicin / isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine. Isoniazid appears to have an increased risk of hepatotoxicity when co-treating with carbamazepine.	Co-administration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and carbamazepine should be avoided.

Phenobarbital / rifampicin / isoniazid	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isoniazid may increase the risk of hepatotoxicity.	Co-administration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin / rifampicin / isoniazid	Phenytoin intravenous AUC ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and phenytoin should be avoided.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
Valproic acid / rifampicin	Though interaction studies are lacking, valproic acid is eliminated through hepatic metabolism, including glucuronidation. Reduced plasma	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		

Cyclosporine / rifampicin	Several studies and case reports have shown substantially increased cyclosporine clearance when co-administered with rifampicin.	Co-administration should be avoided. If deemed necessary, plasma drug concentrations of cyclosporine should be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
Tacrolimus / rifampicin	Tacrolimus AUC intravenous ↓35%; AUC oral ↓70%	Co-administration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets and tacrolimus should be avoided. If deemed necessary, plasma drug concentrations of tacrolimus should be monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Warfarin / rifampicin	Warfarin AUC ↓ 85%	Co-administration should be avoided.
Atenolol / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Verapamil / rifampicin	S-verapamil oral CL/F ↑ 32-fold. With intravenous S-verapamil, CL ↑ 1.3-fold	Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)film-coated Tablets and verapamil per-orally should not be co-administered. If verapamil is given intravenously, the therapeutic effect should be carefully monitored; dose adjustment may be required.
Digoxin / rifampicin	Digoxin oral AUC ↓ 30%	When co-administering Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets with digoxin, the clinical efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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	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 Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)film-coated Tablets is necessary. Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)film-coated Tablets 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, concomitant use of chlorpromazine with isoniazid may impair the metabolism of isoniazid.	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity.
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Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Haloperidol / rifampicin	Haloperidol clearance is substantially increased by rifampicin.	If co-treatment of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets 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 / rifampicin other systemically administered corticosteroids	Prednisolone AUC ↓ 66% Corticosteroid exposure is likely to be substantially decreased when co-treating with rifampicin. This applies to other corticosteroids as well.	Co-administration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets 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 levels 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-administration with Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets may be associated with decreased contraceptive effect. Barrier- or other non- hormonal methods of contraception should be used.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co- administration
Norethindrone /rifampicin	Norethindrone AUC ↓ 51%	Co-administration with Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets 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 Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film- coated Tablets should be avoided.
Disulfiram / isoniazid / ethambutol	Concurrent use of disulfiram together with isoniazid may result in increased incidence of effects on the central nervous system and concurrent use with ethambutol may entail an increased risk for ocular toxicity.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP)mg film-coated Tablets.
Enflurane / Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane	Avoid coadministration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets 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 Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets should be avoided.
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Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Allopurinol / Pyrazinamide	Pyrazinamide major (active) metabolite pyrazoic acid ↑ 70% Since pyrazinoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia	Avoid co-administration of Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets with allopurinol.

Interactions with food and drink

Alcohol: concurrent daily use of alcohol may result in an increased 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 (see section 4.4).

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, thus interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or 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 utilise 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. Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Breast-feeding

Rifampicin, isoniazid, pyrazinamide and ethambutol are excreted into the breast milk of lactating mothers. 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

Forecox Trac (Rifampicin 150, Isoniazid 75, Pyrazinamide 400 & Ethambutol 275mg Tablets USP) film-coated Tablets 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 duration of 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 a reduction in 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/day. 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 upon discontinuation of therapy. To avoid development of irreversible optic atrophy, visual acuity should be regularly monitored and ethambutol must be immediately discontinued when visual disturbances occur (see section 4.4).

The 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 randomized controlled trials, but on published literature data, generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($\leq 1/10,000$), 'not known'.

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 (see section 4.4).

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 increases of serumtransaminases.

Uncommon: Increases of serum bilirubin and alkaline phosphatases, hepatitis.

Renal and urinary disorders

Rare: acute renal failure, interstitial nephritis.

Not known: urinary retention.

Metabolic and nutrition 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 systems disorders

Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis, blood clotting affected

Respiratory, thoracic and mediastinal 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 discolouration 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

4.9 Overdose

Symptoms

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or 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 edema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14g has caused cardiopulmonary arrest.

Data on pyrazinamide overdosing are scarce. However, liver toxicity and hyperuricemia 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/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

In vitro, rifampicin is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. The mode of action is by inhibition of 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 due to 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 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

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 4 x Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (\pm SD) rifampicin C_{max} value was 9.83 μ g/ml (\pm 1.70), and the corresponding value for AUC was 65.07 μ g.hour/ml (\pm 13.35). The median (\pm SD) rifampicin t_{max} value was 1.92 (\pm 0.62) 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 metabolized by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetyl rifampicin. 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.

Special populations

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

Isoniazid

Absorption

After oral administration, isoniazid is rapidly absorbed with a bioavailability of \geq 80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first-pass) metabolism in the gut wall and liver.

Following single dose administration of 4 x Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (\pm SD) isoniazid C_{\max} value was 5.69 $\mu\text{g/ml}$ (\pm 1.56), and the corresponding value for AUC was 32.26 $\mu\text{g}\cdot\text{hour/ml}$ (\pm 15.19). The median (\pm SD) isoniazid t_{\max} value was 1.37 (\pm 0.62) hours.

Distribution

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 litre/kg; protein binding is very low (0-10%)

Metabolism

Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolising enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen 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. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

Pyrazinamide

Absorption

Pyrazinamide is almost completely absorbed from the gastrointestinal tract.

Following single dose administration of 4 x Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (\pm SD) pyrazinamide C_{\max} value was 31.40 $\mu\text{g/ml}$ (\pm 2.55), and the corresponding value for AUC was 515.4 $\mu\text{g}\cdot\text{hour/ml}$ (\pm 61.8). The median (\pm SD) pyrazinamide t_{\max} value was 1.98 (\pm 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-hydroxypyrazinoic acid.

Elimination

Pyrazinamide is eliminated renally, 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.

Ethambutol*Absorption*

Approximately 80% of ethambutol is absorbed after oral administration.

Following single dose administration of 4 x Rifampicin/Isoniazid/Pyrazinamide/Ethambutol Hydrochloride 150 mg/75 mg/400 mg/275 mg film-coated Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (\pm SD) ethambutol C_{max} value was 3.27 μ g/ml (\pm 1.09), and the corresponding value for AUC was 19.34 μ g.hour/ml (\pm 3.35). The median (\pm SD) ethambutol t_{max} value was 3.02 (\pm 0.58) 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 an 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 being excreted unchanged in the urine and another 7 to 15% as inactive aldehyde and carboxylic acid metabolites. Between 20 to 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.

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 of only limited evidence available on the carcinogenicity of rifampicin in mice and the absence of epidemiological studies, no evaluation of the carcinogenicity of rifampicin to humans can be made.

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 body weight daily in rodents have been reported to cause cleft palate and spina bifida. In rats neither fertility nor peri- or 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

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core: Calcium stearate, colloidal anhydrous silica, croscarmellose sodium, crospovidone, disodium edetate, maize starch, povidone, purified talc and shellac (golden).

Film coating: Hypromellose, Polyvinyl Alcohol part Hydrolysed, Titanium Dioxide, Talc, Lecithin, Xanthan Gum and Lake of Sunset Yellow.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bulk pack (HDPE bottle) and blister pack (Alu-PVC/PVDC): 36 months Blister (Alu-PVC/PE/PVDC) packs: 36 months

6.4 Special precautions for storage

For bulk HDPE bottle pack: Store at temperature not exceeding 25°C in a dry place Protect from light.

For amber colour Alu-PVC/PE/PVDC and Alu-PVC/PVDC blister packs: Store at a temperature not exceeding 25°C. Protect from light

6.5 Nature and contents of container

Transparent LDPE bag, containing 1000 tablets, packed in a triple laminated aluminiumsachet which is further packed in an HDPE bottle along with a leaflet. Each bottle is sealed with an aluminium tagger and closed with a screw cap.

Al/PVC/PE/PVDC blister of 28 tablets. Such 3 or 24 blisters per box. Pack sizes:28x24 tablets.

Al/PVC/PE/PVDC blister of 28 tablets. Such 6 blisters per box. Pack size: 28x6

Al/PVC/PE/PVDC blister of 28 tablets. Such 6 or 24 blisters per box. Pack sizes: 168(28x6) and 672(28x24) tablets.

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 AUTHORISATION HOLDER

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