SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets*

This product is intended for use in children. Nonetheless safety information is provided with respect to adult health issues such as pregnancy and lactation, to allow full access to all relevant information.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:
Rifampicin 60 mg
Isoniazid 30 mg
Pyrazinamide 150 mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Brick red mottled circular, flat bevel edged uncoated tablet having plain surface on both sides. The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets is indicated in children weighing 5 to 20 kg, for the initial treatment phase of tuberculosis caused by Mycobacterium tuberculosis, according to the guidelines of WHO (Rapid Advice, Treatment of Tuberculosis in Children, 2010, available at: http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf)

4.2 Posology and method of administration

Oral use

In infants weighing 5-7 kg the daily dose is 1 tablet administered as a single dose.

In children weighing 8-14 kg the daily dose is 2 tablets administered as a single dose.

In children weighing 15-20 kg the daily dose is 3 tablets administered as a single dose.

Children weighing from 21 to 29 kg should be treated with other products containing higher amounts of the drugs. (See General references, WHO documents)

Children weighing more than 30 kg should be treated according to the current adult treatment guidelines.

The required number of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should be dispersed in approximately 50 ml water and the entire dispersion should be drunk. The reconstituted preparation (tablets dispersed in water) should be used within 10 minutes.

Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should not be used for intermittent treatment regimens.

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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, oral absorption and 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) should be used.

Renal impairment:
Since dose adjustments may be necessary in patients with renal impairment (creatinine clearance ≤ 30 ml/min), it is recommended that separate preparations of rifampicin, isoniazid, pyrazinamide 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 60mg/30mg/150mg Dispersible Tablets must not be used in patients with severe liver disease (see section 4.3).

Adult patients
For adult patients, other formulations of rifampicin, isoniazid and pyrazinamide should be used.

4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients.
Acute liver disease, icterus or severe liver impairment.
Acute gout.

Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with voriconazole or any protease inhibitor is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use
Liver toxicity: Rifampicin, isoniazid or pyrazinamide may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets. Patient groups especially at risk for developing hepatitis from the combination of rifampicin, isoniazid and pyrazinamide include:
- age > 35 years,
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5),
- patients with active chronic liver disease and injection 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 and 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 paraesthesiae of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and/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 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 in the presence of continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents used.

**Hypersensitivity:** Rifampicin may cause a hypersensitivity syndrome including ‘flu-like’ symptoms and/or organ manifestation. The risk is higher in 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 acute renal failure), Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets, at doses of 10 mg per day.

**Epilepsy and psychotic disorders:** Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets. In case of severe haematological disturbances Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets must be discontinued.
Hyperuricaemia and gout: Pyrazinamide 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 60mg/30mg/150mg Dispersible Tablets.

Renal insufficiency: In renal insufficiency, the clearance of pyrazinamide and isoniazid is delayed, causing an increased systemic exposure. In case of renal insufficiency, Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should not be used, as dose modifications of the active components may be necessary (see section 4.2).

Nephrotoxicity: Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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.

Drug interactions: Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible Tablets. This probably also pertains to other formulations 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 60mg/30mg/150mg Dispersible Tablets may reduce the efficacy of corticosteroids in Addison’s disease and induce an Addisonian crisis (see section 4.5).

Porphyria: Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible 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 60mg/30mg/150mg Dispersible 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.

Alcohol: The intake of alcoholic beverages should be avoided during treatment with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets (see section 4.5).

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 60mg/30mg/150mg Dispersible Tablets.

Excipients: This medicinal product contains aspartame, which is a source of phenylalanine and may be harmful for people with phenylketonuria.
4.5 Interactions with other medicinal products and other forms of interaction

Rifampicin is a very potent inducer of the hepatic and intestinal cytochrome P-450 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 coadministered 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 60mg/30mg/150mg Dispersible Tablets.

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. However, when co-treating with rifampicin, as when using Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. Insofar, as it has been investigated, the net effect of 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) 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 60mg/30mg/150mg Dispersible 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 therapeutic agents, 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 60mg/30mg/150mg Dispersible Tablets, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets is not exhaustive, but is a selection of interactions of putative importance. Data on interactions is mainly derived from studies in adults. The scope of the table is largely based on the WHO Essential Medicines List.

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine / rifampicin</td>
<td>Zidovudine AUC ↓ 47%</td>
<td>The clinical significance of the lowered zidovudine exposure is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.</td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir DF / rifampicin</td>
<td>Tenofovir AUC ↓ 13%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Abacavir / rifampicin</td>
<td>Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.</td>
<td>Clinical efficacy should be closely monitored in co-treatment.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td><strong>Non-nucleoside analogues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz / rifampicin</td>
<td>Efavirenz AUC ↓ 26%</td>
<td>When co-treating with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets, the efavirenz dose should be increased to 800 mg q.d.</td>
</tr>
<tr>
<td>Nevirapine / rifampicin</td>
<td>Nevirapine: AUC ↓ 58%</td>
<td>Since neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established, concomitant use of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and rifampicin is not recommended.</td>
</tr>
<tr>
<td>Etravirine / rifampicin</td>
<td>Rifampicin is likely to significantly reduce exposure to etravirine.</td>
<td>Co-treatment of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and etravirine should be avoided.</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir / rifampicin</td>
<td>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.</td>
<td>Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets must not be co-administered with HIV protease inhibitors (PI).</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir / rifampicin</td>
<td>Raltegravir AUC ↓ 40%</td>
<td>Avoid co-treatment. If deemed necessary, consider an increase of the raltegravir dose to 600 mg b.i.d.</td>
</tr>
<tr>
<td>Maraviroc / rifampicin</td>
<td>Maraviroc AUC ↓ 63%</td>
<td>Avoid co-treatment. If deemed necessary, the maraviroc dose should be increased to 600 mg twice daily.</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole / rifampicin</td>
<td>Ketoconazole AUC ↓ 80%</td>
<td>Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.</td>
</tr>
<tr>
<td>Fluconazole / rifampicin</td>
<td>Fluconazol AUC ↓ 23%</td>
<td>Monitor therapeutic effect. An increased dose of fluconazole may be required.</td>
</tr>
<tr>
<td>Itraconazole / rifampicin</td>
<td>Itraconazole AUC ↓ &gt;64-88%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Voriconazole / rifampicin</td>
<td>Voriconazole AUC ↓ 96%</td>
<td>Co-administration is contraindicated. If necessary, rifampicin should be substituted for rifampicin.</td>
</tr>
<tr>
<td><strong>Antibacterials/Antituberculotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin / rifampicin</td>
<td>Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Chloramphenicol / rifampicin</td>
<td>Case reports indicate &gt;60-80% reduction of chloramphenicol exposure.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Ciprofloxacin / rifampicin</td>
<td>No significant interaction</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Ofloxacin / Pyrazinamide Levofoxacin</td>
<td>Co-treatment with pyrazinamide and either of these fluoroquinolones has been associated with a high levels of adverse events (e.g. hepatic, gastrointestinal, musculoskeletal). leading to discontinuation of therapy</td>
<td>Co-treatment of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and either of these agents is not recommended. However, when deemed necessary, careful safety monitoring should be applied.</td>
</tr>
<tr>
<td>Doxycyclin / rifampicin</td>
<td>Doxycyclin AUC ↓ 50-60%</td>
<td>If co-treatment is considered necessary, the dose of doxycyclin should be doubled.</td>
</tr>
<tr>
<td>Metronidazole / rifampicin</td>
<td>Metronidazole AUC i.v. ↓ 33%</td>
<td>The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Monitor efficacy.</td>
</tr>
<tr>
<td>Sulfamethoxazole / rifampicin</td>
<td>Sulfamethoxazole AUC ↓ 23%</td>
<td>Interaction probably not clinically significant. Monitor efficacy.</td>
</tr>
<tr>
<td>Trimethoprim / rifampicin</td>
<td>Trimethoprim AUC ↓ 47%</td>
<td>Monitor efficacy. A dose increase of trimethoprim may be required.</td>
</tr>
<tr>
<td>Ethionamide / rifampicin</td>
<td>Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.</td>
<td></td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloroquine / rifampicin</td>
<td>Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Avoid co-administration.</td>
<td></td>
</tr>
<tr>
<td>Atovaquone / rifampicin</td>
<td>Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Mefloquine / rifampicin</td>
<td>Mefloquine AUC ↓ 68%</td>
<td>Co-administration should be avoided</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amodiaquine / rifampicin</strong></td>
<td>Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Quinine / rifampicin</strong></td>
<td>Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates.</td>
<td>Co-administration should be avoided. If co-administration is deemed necessary, an increased dose of quinine should be considered.</td>
</tr>
<tr>
<td><strong>Lumefantrine / rifampicin</strong></td>
<td>Empirical data are not available. Since lumefantrine is metabolised by CYP3A, lower levels are expected with rifampicin co-treatment.</td>
<td>Avoid co-administration.</td>
</tr>
<tr>
<td><strong>Artemisinin and its derivatives / rifampicin</strong></td>
<td>Empirical data are not available. During co-treatment with rifampicin, lower levels of artemisinin and its derivatives may be expected.</td>
<td>Avoid co-administration.</td>
</tr>
<tr>
<td><strong>ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphine / rifampicin</strong></td>
<td>Morphine AUC p.o ↓ 30%</td>
<td>Co-treatment should be avoided. If necessary, monitor clinical effects and increase dose if necessary.</td>
</tr>
<tr>
<td><strong>Codeine / rifampicin</strong></td>
<td>Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.</td>
<td>Monitor clinical effect and increase codeine dose if necessary.</td>
</tr>
<tr>
<td><strong>Methadone / rifampicin</strong></td>
<td>Methadone AUC ↓ 33-66%</td>
<td>Monitor for possible withdrawal effects, and increase methadone dose as appropriate.</td>
</tr>
<tr>
<td><strong>Paracetamol / rifampicin / isoniazid</strong></td>
<td>Rifampicin may increase the glucuronidation of paracetamol and decrease the effect. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive. Concurrent use with isoniazid may increase hepatotoxicity</td>
<td>Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and paracetamol should be avoided.</td>
</tr>
</tbody>
</table>
## Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine / rifampicin / isoniazid</td>
<td>Rifampicin is expected to decrease the serum concentration of carbamazepine. Isoniazid appears to have an increased risk of hepatotoxicity when co-treating with carbamazepine.</td>
<td>Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and carbamazepine should be avoided.</td>
</tr>
<tr>
<td>Phenobarbital / rifampicin / isoniazid</td>
<td>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.</td>
<td>Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.</td>
</tr>
<tr>
<td>Phenobarbital / rifampicin / isoniazid</td>
<td>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.</td>
<td>Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.</td>
</tr>
<tr>
<td>Valproic acid / rifampicin</td>
<td>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.</td>
<td>Co-treatment should be avoided. If necessary, therapeutic efficacy and, if possible, plasma concentrations of valproic acid, should be carefully monitored.</td>
</tr>
<tr>
<td>Lamotrigine / rifampicin</td>
<td>Lamotrigine AUC ↓ 45%</td>
<td>Co-treatment should be avoided. If deemed necessary, increase lamotrigine dose as appropriate.</td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSIVES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine / rifampicin</td>
<td>Several studies and case reports have shown substantially increased cyclosporine clearance when co-administered with rifampicin.</td>
<td>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).</td>
</tr>
<tr>
<td>Tacrolimus / rifampicin</td>
<td>Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 70%</td>
<td>Co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and tacrolimus should be avoided. If deemed necessary, plasma drug concentrations of tacrolimus should be monitored, and the dose increased as appropriate.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin / rifampicin</td>
<td>Warfarin AUC ↓ 85%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Atenolol / rifampicin</td>
<td>Atenolol AUC ↓ 19%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Verapamil / rifampicin</td>
<td>S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold</td>
<td>Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets and verapamil per-orally should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required.</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine / rifampicin</td>
<td>Ranitidine AUC ↓ 52%</td>
<td>Monitor for ranitidine efficacy, and increase dose if necessary.</td>
</tr>
<tr>
<td><strong>PSYCHOTHERAPEUTIC MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam / rifampicin</td>
<td>Diazepam AUC ↓ &gt;70%</td>
<td>Co-treatment is not recommended. If necessary, diazepam doses may need to be increased.</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chlorpromazine / rifampicin / isoniazid</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Chlorpromazine / rifampicin / isoniazid</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Haloperidol / rifampicin</strong></td>
<td>Haloperidol clearance is substantially increased by rifampicin. If co-treatment of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with haloperidol is deemed necessary, monitor the clinical efficacy of haloperidol. A dose increase may be required.</td>
</tr>
<tr>
<td><strong>Amitriptyline / rifampicin</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES</strong></td>
<td>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 Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with corticosteroids should be avoided. If necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.</td>
</tr>
<tr>
<td><strong>Prednisolone / rifampicin</strong></td>
<td>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 Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with corticosteroids should be avoided. If necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.</td>
</tr>
<tr>
<td><strong>Glibenclamide / rifampicin</strong></td>
<td>Glibenclamide AUC ↓ 34% Monitor blood glucose levels closely. A dose increase of glibenclamide may be required.</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>No interaction expected</td>
</tr>
<tr>
<td><strong>Levothyroxine / rifampicin</strong></td>
<td>Case reports indicate that rifampicin may decrease the effect of levothyroxine. TSH levels should be monitored.</td>
</tr>
<tr>
<td><strong>Ethynylestradiol / rifampicin</strong></td>
<td>Ethynylestradiol AUC ↓ 66% Co-administration with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethindrone / rifampicin</td>
<td>Norethindrone AUC ↓ 51% Co-administration with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
</tbody>
</table>

### OTHERS

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praziquantel / rifampicin</td>
<td>Praziquantel AUC ↓ 80-99% Co-treatment with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should be avoided.</td>
</tr>
<tr>
<td>Disulfiram / isoniazid</td>
<td>Concurrent use of disulfiram together with isoniazid may result in increased incidence of effects on the central nervous system. Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets.</td>
</tr>
<tr>
<td>Enflurane / Isoniazid</td>
<td>Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane Avoid co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with enflurane.</td>
</tr>
<tr>
<td>Probenecid / Pyrazinamide</td>
<td>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/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should be avoided.</td>
</tr>
<tr>
<td>Allopurinol / Pyrazinamide</td>
<td>Pyrazinamide major (active) metabolite pyrazoic acid ↑ 70% Since pyrazoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia Avoid co-administration of Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets with allopurinol.</td>
</tr>
</tbody>
</table>

---

**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, 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.

4.6 Pregnancy and lactation

Pregnancy:
No adverse effects of isoniazid 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/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Lactation:
Rifampicin, isoniazid and pyrazinamide 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

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of this medicine, especially with regard to ocular and neurotoxicity, should be borne in mind when considering 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-TB medications.

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 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 (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), ‘not known’.
Nervous system disorders
Very common: Peripheral neuropathy, usually preceded by paraesthesias 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, lethargia, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy.
Not known: tremor, vertigo, hyperreflexia, insomnia.

Psychiatric disorders
Uncommon: memory impairment, toxic psychosis.
Not known: confusion, disorientation, hallucination.

Gastrointestinal disorders
Common: Diarrhoea, abdominal pain, nausea, anorexia, vomiting.
Rare: Erosive gastritis, pseudomembranous colitis.
Not known: metallic taste, dry mouth, flatulence, constipation.

Hepatobiliary disorders:
Very common: Transient increases of serum transaminases.
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.
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, anaphylaxia, 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.

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 reaction, exfoliative dermatitis, pemphigoid reactions, purpura.
Not known: Lyell’s Syndrome, Stevens-Johnson Syndrome.
Eye disorders:
Common: Ocular redness.
Rare: Exudative conjunctivitis.
Not known: Optic atrophy or neuritis.

Reproductive system and breast disorders
Common: Disturbances of the menstrual cycle.

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.

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 BW 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: J04AM05

Mechanism of action
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 antituberculous agent.

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 10 x Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) rifampicin Cmax value was 12.0 µg/ml (± 2.1), and the corresponding value for AUC was 85.1 µg.h/ml (± 17.9). The mean (± SD) rifampicin tmax value was 1.30 (± 0.75) hours.

Distribution
Rifampicin is 60-90% bound to plasma proteins and has a volume of distribution of approximately 0.9 l/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 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.

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 ≥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 wall of small intestine and liver.

Following single dose administration of 10 x Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) isoniazid Cmax value was 6.76 µg/ml (± 0.98), and the corresponding value for AUC was 31.9 µg.h/ml (± 13.8). The mean (± SD) isoniazid tmax value was 0.66 (± 0.37) hours.
Distribution:
Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/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.

Pharmacokinetics in 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 10 x Rifampicin/Isoniazid/Pyrazinamide 60mg/30mg/150mg Dispersible Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) pyrazinamide Cmax value was 35.6 µg/ml (± 6.9), and the corresponding value for AUC was 486 µg.h/ml (± 105). The mean (± SD) pyrazinamide tmax value was 1.66 (± 1.50) hours.

Distribution:
Pyrazinamide is widely distributed to most fluid compartments and tissues. The volume of distribution has been reported as 0.57-0.84 l/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.
Special populations:
Impaired renal function: 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.

5.3 Preclinical safety data
RIFAMPICIN: After oral administration of 100 mg/kg bodyweight (bw) rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg bw 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 bw/day.

Because of only limited evidence available for 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. 100 to 150 mg/kg bw 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 / 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, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Aspartame, bleached shellac, croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, povidone and strawberry flavour.

6.2 Incompatibilities:
Not applicable.

6.3 Shelf life
2 years for the unopened container. Once the primary pack is opened, the tablets should be used within one month. Reconstituted (tablet dispersed in water) preparation should be used within 10 minutes of preparation.
6.4  Special precautions for storage
Storage condition for the bottle: Do not store above 30°C. Protect from light.

6.5  Nature and contents of container
Al/PET/LDPE triple laminated bag kept in HDPE bottle. Pack size: Bottle of 1000 tablets.

Al/Al strip pack of 10 tablets. Such 3 or 10 strips per box. Pack sizes: 30 (3x10) and 100 (10x10).

Al/Al strip pack of 3 tablets. Such 28 strips per box. Pack size: 84 (3x28) tablets.

Al/Al strip pack of 6 tablets. Such 14 or 15 strips per box. Pack size: 84 (6x14) tablets and 90 (6x15) tablets.

Al/Al strip pack of 14 tablets. Such 6 strips per box. Pack size: 84 (14x6) tablets.

Al/Al strip pack of 28 tablets. Such 3 strips per box. Pack size: 84 (28x3) tablets.

Al/PVC/PVDC blister of 10 tablets. Such 3, 10 or 24 blisters per box. Pack sizes: 30 (10x3), 100 (10x10), 240 (10x24).

Al/PVC/PVDC blister of 28 tablets. Such 3, 10 or 24 blisters per box. 84 (28x3), 280 (28x10), 672 (28x24).

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.  SUPPLIER
Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade,
Marol Church Road,
Andheri (East),
Mumbai- 400 059,
India
Tel: +91 22 6676 2800
Fax: +91 22 2821 6599
e-mail: exports@macleodspharma.com

8.  WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
TB180

9.  DATE OF FIRST PREQUALIFICATION
3 March 2009

10.  DATE OF REVISION OF THE TEXT
Reference list:


Dollery ed. Therapeutic Drugs, 2nd ed. Churchill Livingstone, Edinborough 1999


WHO, Geneva, 2006: Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children

ATS, CDC, and IDSA, Treatment of Tuberculosis, MMWR 2003; 52

Thompson: Micromedex, Drugdex 2007, Isoniazid (systemic), Pyrazinamide (systemic), Rifampicin (systemic)


Fachinformation Isonizid Tabletten (Fatol Arzneimittel GmbH), June 2001

Rimstar SPC. Available at: http://www.lakemedelsverket.se/upload/SPC_PIL/Pdf/enhumspc/Rimstar%20film-coated%20tablet%20ENG.pdf

References for specific sections of the SPC

4.4 On the hepatotoxicity of TB drugs:


4.5 On drug interactions:

Stockley’s Drug Interactions. Available at: www.medicinescomplete.com

The SPHINX Drug Interaction Database. Available at: http://drugdb.janusinfo.se/sfinx/interactions/index_menus.jsp


Rifampicin

LaPorte CJ et al. Antimicrobial Agents and Chemotherapy 2004;48:1553-60


Fromm MF et al. Hepatology 1996;24:796-801

Kyriazopoulou V et al. J Clin Endocrinol Metab. 1984;59:1204-6

Isoniazid

Pyrazinamide
Horsfall PA et al. Tubercle 1979; 60: 13-24
Papastavros T et al. CMAJ 2002; 67: 131-6

4.6

4.8

5.2