1. NAME OF THE MEDICINAL PRODUCT

Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Rifampicin 150 mg
Ethambutol hydrochloride 275 mg
Isoniazid 75 mg

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Maroon coloured, circular, biconvex, film-coated tablets having plain surface on both the sides. The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is indicated for the initial treatment phase of tuberculosis, caused by Mycobacterium tuberculosis, according to the guidelines of WHO. (Treatment of Tuberculosis: guidelines 4th edition, WHO, available at: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

4.2 Posology and method of administration

Oral use
In children weighing 21-30 kg the daily dose is 2 tablets administered as a single dose. (Only for 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets should not be used for intermittent treatment regimens.

Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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.

* Trade names are not prequalified. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only
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, ethambutol) should be used.

**Renal impairment:**
Since dose adjustments may be necessary in patients with renal impairment (creatinine clearance \( \leq 50 \text{ ml/min} \)), it is recommended that separate preparations of rifampicin, isoniazid 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is not recommended for patients with a body weight below 20 kg, since appropriate dose adjustments cannot be made.

### 4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Acute liver disease, icterus or severe liver impairment.
Optic neuritis (ethambutol).

Co-administration of Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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 and/or isoniazid may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets. Patient groups especially at risk for developing hepatitis 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
- 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.
All 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 paraesthesias of the hands and feet, persistent fatigue and/or 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin or isoniazid. 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents used.

**Visual acuity:** Patients should be advised to report promptly any changes in visual acuity since ethambutol may cause ocular toxicity. Visual acuity 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets must be discontinued immediately if visual disturbances emerge (see section 4.8).

**Hypersensitivity:** Rifampicin may cause a hypersensitivity syndrome including ‘flu-like’ symptoms and/or organ manifestations. 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 anemia, dyspnoea, shock or acute renal failure), Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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.

**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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets, at doses of 10 mg per day.

**Epilepsy and psychotic disorders:** Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets. In case of severe haematological disturbances Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets must be discontinued.

**Hyperuricaemia and gout:** Ethambutol is excreted via the same pathway as uric acid, thereby leading to increased serum concentration of uric acid. Concomitant therapy with isoniazid or pyridoxin may enhance this effect. Patients with pre-existing hyperuricaemia or symptoms of gout should be monitored for signs of deterioration when treated with ethambutol (see sections 4.5 and 4.8).

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

**Nephrotoxicity:** Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets may reduce the efficacy of corticosteroids in Addison’s disease and induce an Addisonian crisis (see section 4.5).

**Porphyria:** Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets.

Excipients: This medicinal product contains a colorant (Color Ponceau 4R Lake) which may cause allergic reactions.

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/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg 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) ethambutol is considerably less likely to interact pharmacokinetically with other drugs.

Mainly due to rifampicin, Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is not exhaustive, but is a selection of interactions of putative importance. 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>
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<tbody>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></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><strong>Stavudine</strong></td>
<td></td>
<td></td>
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<tr>
<td>Didanosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
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<td></td>
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<tr>
<td>Emtricitabine</td>
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</tbody>
</table>

No interaction expected
<table>
<thead>
<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenofovir DF / rifampicin</strong></td>
<td>Tenofovir AUC ↓ 13%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td><strong>Abacavir / rifampicin</strong></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><strong>Non-nucleoside analogues</strong>&lt;br&gt;<strong>Efavirenz / rifampicin</strong></td>
<td>Efavirenz AUC ↓ 26%</td>
<td>When co-treating with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets, consider increase of the efavirenz dose to 800 mg q.d.</td>
</tr>
<tr>
<td><strong>Nevirapine / rifampicin</strong></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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets and rifampicin is not recommended.</td>
</tr>
<tr>
<td><strong>Etravirine / rifampicin</strong></td>
<td>Rifampicin is likely to significantly reduce exposure to etravirine.</td>
<td>Co-treatment of Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets and etravirine should be avoided.</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong>&lt;br&gt;<strong>Fosamprenavir / rifampicin</strong>&lt;br&gt;<strong>Saquinavir</strong>&lt;br&gt;<strong>Indinavir</strong>&lt;br&gt;<strong>Ritonavir</strong>&lt;br&gt;<strong>Nelfinavir</strong>&lt;br&gt;<strong>Lopinavir</strong>&lt;br&gt;<strong>Atazanavir</strong>&lt;br&gt;<strong>Tipranavir</strong>&lt;br&gt;<strong>Darunavir</strong></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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets should not be co-administered with HIV protease inhibitors (PI).</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raltegravir / rifampicin</strong></td>
<td>Raltegravir AUC ↓ 40%</td>
<td>Avoid co-treatment. If deemed necessary, consider an increase of the raltegravir dose to 800 mg twice daily.</td>
</tr>
<tr>
<td><strong>Maraviroc / rifampicin</strong></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><strong>Ketoconazole / rifampicin</strong></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><strong>Fluconazole / rifampicin</strong></td>
<td>Fluconazole AUC ↓ 23%</td>
<td>Monitor therapeutic effect. An increased dose of fluconazole may be required.</td>
</tr>
<tr>
<td><strong>Itraconazole / rifampicin</strong></td>
<td>Itraconazole AUC ↓ &gt;64-88%</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>Voriconazole / rifampicin</strong></td>
<td>Voriconazole AUC ↓ 96%</td>
<td>Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.</td>
</tr>
<tr>
<td><strong>Antibacterials/Antituberculotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin / rifampicin</strong></td>
<td>Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Chloramphenicol / rifampicin</strong></td>
<td>Case reports indicate &gt;60-80% reduction of chloramphenicol exposure.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Ciprofloxacin / rifampicin</strong></td>
<td>No significant interaction</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td><strong>Doxycycline / rifampicin</strong></td>
<td>Doxycycline AUC ↓ 50-60%</td>
<td>If co-treatment is considered necessary, the dose of doxycycline should be doubled.</td>
</tr>
<tr>
<td><strong>Metronidazole / rifampicin</strong></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><strong>Sulfamethoxazole / rifampicin</strong></td>
<td>Sulfamethoxazole AUC ↓ 23%</td>
<td>Interaction probably not clinically significant. Monitor efficacy.</td>
</tr>
<tr>
<td><strong>Trimethoprim / rifampicin</strong></td>
<td>Trimethoprim AUC ↓ 47%</td>
<td>Monitor efficacy. A dose increase of trimethoprim may be required.</td>
</tr>
<tr>
<td><strong>Ethionamide / rifampicin</strong></td>
<td></td>
<td>Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.</td>
</tr>
<tr>
<td><strong>Antimalarials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chloroquine / rifampicin</strong></td>
<td></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>
</tr>
<tr>
<td><strong>Atovaquone / rifampicin</strong></td>
<td>Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Mefloquine / rifampicin</strong></td>
<td>Mefloquine AUC ↓ 68%</td>
<td>Co-administration should be avoided</td>
</tr>
<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>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
<thead>
<tr>
<th><strong>Interaction</strong></th>
<th><strong>Recommendations concerning co-administration</strong></th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td><strong>ANALGESICS, ANTIPYRETICS, NON-Steroidal ANTI-INFLAMMATORY DRUGS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Morphine / rifampicin</strong></td>
<td>Morphine AUC p.o. ↓ 30%</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>
</tr>
<tr>
<td><strong>Methadone / rifampicin</strong></td>
<td>Methadone AUC ↓ 33-66%</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>
</tr>
<tr>
<td><strong>ANTICONVULSANTS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Carbamazepine / rifampicin / isoniazid</strong></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>
</tr>
<tr>
<td><strong>Phenobarbital / rifampicin / isoniazid</strong></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>
</tr>
<tr>
<td><strong>Phenytoin / rifampicin / isoniazid</strong></td>
<td>Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.</td>
</tr>
<tr>
<td><strong>Valproic acid / rifampicin</strong></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>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Lamotrigine / rifampicin</td>
<td>Lamotrigine AUC ↓ 45%</td>
</tr>
<tr>
<td>IMMUNOSUPPRESSIVES</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>
</tr>
<tr>
<td>Tacrolimus / rifampicin</td>
<td>Tacrolimus AUC i.v. ↓ 35%; AUC p.o. ↓ 70%</td>
</tr>
<tr>
<td>CARDIOVASCULAR MEDICINES</td>
<td></td>
</tr>
<tr>
<td>Warfarin / rifampicin</td>
<td>Warfarin AUC ↓ 85%</td>
</tr>
<tr>
<td>Atenolol / rifampicin</td>
<td>Atenolol AUC ↓ 19%</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>
</tr>
<tr>
<td>Digoxin / rifampicin</td>
<td>AUC p.o. ↓ 30%</td>
</tr>
<tr>
<td>Lidocaine / rifampicin</td>
<td>Lidocaine CL i.v. ↑ 15%</td>
</tr>
<tr>
<td>Amlodipine / rifampicin</td>
<td>Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin</td>
</tr>
<tr>
<td>Enalapril / rifampicin</td>
<td>No interaction expected</td>
</tr>
<tr>
<td>Simvastatin / rifampicin</td>
<td>Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
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</tr>
<tr>
<td><strong>GASTROINTESTINAL MEDICINES</strong></td>
<td></td>
</tr>
<tr>
<td>Ranitidine / rifampicin</td>
<td>Ranitidine AUC ↓ 52%</td>
</tr>
<tr>
<td>Antacids / ethambutol / isoniazid / rifampicin</td>
<td>Antacids may reduce the bioavailability of rifampicin by up to one third. Aluminium hydroxide impairs the absorption of ethambutol and isoniazid.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PSYCHOTHERAPEUTIC MEDICINES</strong></td>
<td></td>
</tr>
<tr>
<td>Diazepam / rifampicin</td>
<td>Diazepam AUC ↓ &gt;70%</td>
</tr>
<tr>
<td>Chlorpromazine / rifampicin / isoniazid</td>
<td>Rifampicin may reduce chlorpromazine exposure. Also, concomitant use of chlorpromazine with isoniazid may impair the metabolism of isoniazid.</td>
</tr>
<tr>
<td>Haloperidol / rifampicin</td>
<td>Haloperidol clearance is substantially increased by rifampicin.</td>
</tr>
<tr>
<td>Amitriptyline / rifampicin</td>
<td>Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance.</td>
</tr>
<tr>
<td><strong>HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisolone / rifampicin other systemically administered corticosteroids</td>
<td>Prednisolone AUC ↓ 66%</td>
</tr>
<tr>
<td>Glibenclamide / rifampicin</td>
<td>Glibenclamide AUC ↓ 34%</td>
</tr>
<tr>
<td>Insulin</td>
<td></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>Levothyroxine / rifampicin</strong></td>
<td>Case reports indicate that rifampicin may decrease the effect of levothyroxine.</td>
<td>TSH levels should be monitored.</td>
</tr>
<tr>
<td><strong>Ethinylestradiol / rifampicin</strong></td>
<td>Ethinylestradiol AUC ↓ 66%</td>
<td>Co-administration with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
<tr>
<td><strong>Norethindrone / rifampicin</strong></td>
<td>Norethindrone AUC ↓ 51%</td>
<td>Co-administration with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Praziquantel / rifampicin</strong></td>
<td>Praziquantel AUC ↓ 80-99%</td>
<td>Co-treatment with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets should be avoided.</td>
</tr>
<tr>
<td><strong>Disulfiram / isoniazid / ethambutol</strong></td>
<td>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.</td>
<td>Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets.</td>
</tr>
<tr>
<td><strong>Enflurane / isoniazid</strong></td>
<td>Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane</td>
<td>Avoid coadministration of Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets with enflurane.</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.
4.6 Pregnancy and lactation

Pregnancy:
No adverse effects of isoniazid or ethambutol 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/Ethambutol hydrochloride 150mg/75mg/275mg Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Lactation
Rifampicin, isoniazid 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

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 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 therapy 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 (≥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, 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, 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, Stephens Johnson Syndrome.

Eye disorders:
Rare: Exudative conjunctivitis.
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 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 BW in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring/support of ventilation and correction of metabolic acidosis. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial, drugs for treatment of tuberculosis
ATC Code for rifampicin: J04AB02
ATC Code for isoniazid: J04AC01
ATC Code for ethambutol: J04AK02

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.

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 antituberculous 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/Ethambutol hydrochloride 150mg/75mg/275mg 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 11.33 µg/ml (± 2.54), and the corresponding value for AUC was 71.15 µg.h/ml (± 20.51). The median (± SD) rifampicin tmax value was 2.27 (± 0.47) 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 gut wall and liver.

Following single dose administration of 4 x Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg 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 5.57 µg/ml (± 1.56), and the corresponding value for AUC was 29.20 µg.h/ml (± 16.44). The median (± SD) isoniazid tmax value was 1.18 (± 0.67) 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.

Ethambutol

Absorption:
Approximately 80% of ethambutol is absorbed after oral administration.

Following single dose administration of 4 x Rifampicin/Isoniazid/Ethambutol hydrochloride 150mg/75mg/275mg Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) ethambutol Cmax value was 2.09 µg/ml (± 0.81), and the corresponding value for AUC was 13.18 µg.h/ml (± 3.82). The median (± SD) ethambutol tmax value was 3.06 (± 0.66) 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 aldehydic intermediate, followed by conversion to a dicarboxylic acid

Elimination:
The plasma concentration falls biphasically, the half-life being about 4 hrs initially and 10 hrs 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. From 20 to 22% of the initial dose is excreted in the faeces as unchanged drug.

Special populations:
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 (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 / ETHAMBUTOL: 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

Tablet core: Colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinised starch and shellac (bleached).

Film-coat: Color Ponceau 4R Lake, hypromellose, polyethylene glycol 400, purified talc and titanium dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

Bulk pack (HDPE bottle): 24 months
Blister pack (Alu-PVDC/PVC): 24 months
Blister pack (Alu-PVC/PE/PVDC): 36 months
Strip pack (Alu-Alu): 36 months

6.4 Special precautions for storage

Store at temperature not exceeding 25°C in a dry place. Tablets should be stored in the original container. Close the container tightly immediately after taking out tablets.

6.5 Nature and contents of container

1000 tablets packed in a triple laminated Al/PET/LDPE bag. The bag is packed in a round, white opaque HDPE bottle, sealed with an aluminium tagger and closed with a polypropylene screw cap.

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. Pack sizes: 84 (28x3), 280 (28x10), 672 (28x24).

Al/PVC/PE/PVDC blister of 10 tablets. Such 10 blisters per box. Pack sizes: (10x10) tablets.

Al/PVC/PE/PVDC blister of 28 tablets. Such 3 or 24 blisters per box. Pack sizes: 84 (28x3) and 672 (28x24) tablets.

Alu-Alu blister strips. Pack size: 5x6 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. SUPPLIER

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Section 6 updated in February 2018.
Section 6 updated in February 2019.

Reference list:

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4.4
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4.5
On drug interactions:
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Isoniazid

4.6

4.8