SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Rifampicin 150 mg Capsules*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifampicin 150 mg

Excipients with known effect
Each capsule contains

- 0.168 mg of FD&C Yellow #6 / Sunset Yellow
- 0.3173 mg of carmoisine
- 0.0933 mg of Ponceau 4R
- 0.1728 mg of sodium methylparaben
- 0.0192 mg of sodium propylparaben

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule,

Scarlet / scarlet hard gelatin size “2” capsule filled with brick red powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rifampicin 150 mg Capsules, used in combination with other active anti-tuberculosis drugs, is indicated for the treatment of tuberculosis caused by Mycobacterium tuberculosis.

Consideration should be given to official guidelines for treatment of tuberculosis (e.g. those of the WHO).

4.2 Posology and method of administration

Oral use

*For children for the treatment of tuberculosis (only for children who can swallow capsules):*
In children weighing 21-30 kg the daily dose is 2 capsules administered as a single dose.

*For heavier patients:*
In patients weighing 30-39 kg the daily dose is 2 capsules administered as a single dose.

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

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

In patients weighing > 70 kg the daily dose is 5 capsules administered as a single dose.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Rifampicin 150 mg Capsules should not be used in children weighing less than 21 kg since appropriate dose adjustments cannot be achieved with this product.

Rifampicin 150 mg Capsules should not be used for intermittent treatment regimens.

Rifampicin 150 mg Capsules should be taken on an empty stomach (at least one hour prior to or two hours after a meal) to ensure rapid and complete absorption.

**Hepatic impairment:**
Limited data indicate that the pharmacokinetics of rifampicin is altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin 150 mg Capsules must not be used in patients with severe liver disease (see section 4.3).

### 4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

Co-administration of Rifampicin 150 mg Capsules is contraindicated with
- Voriconazole
- any HIV protease inhibitor
the following agents for therapy of hepatitis C: boceprevir, daclatasvir, ledipasvir and sofosbuvir (see section 4.5).

### 4.4 Special warnings and precautions for use

**Liver toxicity:** Rifampicin may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin 150 mg Capsules 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 150 mg Capsules. Patient groups especially at risk for developing hepatitis include:

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

Furthermore, the following patients should be carefully monitored:

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

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesiae 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 150 mg Capsules 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 150 mg Capsules and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin 150 mg Capsules. A cholestatic pattern is usually caused by rifampicin. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Rifampicin 150 mg Capsules should be strongly considered. Reinstitution of rifampicin therapy should only be performed when symptoms and laboratory abnormalities have subsided.

**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 do appear (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure), Rifampicin 150 mg Capsules 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 150 mg Capsules should not be used.

**Haematological toxicity:** Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Rifampicin 150 mg Capsules. In case of severe haematological disturbances Rifampicin 150 mg Capsules must be discontinued.

**Drug interactions**

Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin 150 mg Capsules may reduce exposure and efficacy of many therapeutic drugs, including antiviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see sections 4.3 and 4.5).

**Contraception:**

Oral contraceptives do not provide adequate protection against conception when co-administered with Rifampicin 150 mg Capsules. This probably also pertains to other forms of hormonal contraceptives (e.g. patches, transdermal implants). Barrier or other non-hormonal methods of contraception should be used.

**Corticosteroids:**

Rifampicin 150 mg Capsules may reduce the efficacy of corticosteroids in Addison’s disease and induce an Addisonian crisis (see section 4.5).

**Other anti-tuberculosis drugs:**

If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored closely for hepatotoxicity.

**Porphyria:** Rifampicin 150 mg Capsules should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

**Discoloration of body fluids:** Rifampicin 150 mg Capsules may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears.
Laboratory monitoring: Full blood count and liver function should be monitored prior to and at regular intervals during treatment with Rifampicin 150 mg Capsules.

Excipients: Rifampicin 150 mg Capsules contains sodium methylparaben, sodium propylparaben, FD&C Yellow #6 / Sunset Yellow, carmoisine and Ponceau 4R 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 150 mg Capsules.

Rifampicin 150 mg Capsules may interact with a very large number of other drugs, primarily by reducing the exposure to coadministered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many 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 150 mg Capsules, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin 150 mg Capsules 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>
</tr>
</thead>
<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><strong>Nucleoside analogues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</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>No interaction expected</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etricitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil</td>
<td>Tenofovir AUC ↓ 13%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.</td>
<td>Efficacy of abacavir should be closely monitored in co-treatment.</td>
</tr>
<tr>
<td><strong>Non-nucleoside analogues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Efavirenz AUC ↓ 26%</td>
<td>When co-treating with Rifampicin 150 mg Capsules, it may be considered to increase the efavirenz dose to 800 mg q.d.</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>nevirapine: AUC ↓ 58%</td>
<td>Since neither appropriate</td>
</tr>
</tbody>
</table>
## Drugs by Therapeutic Area

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Etravirine</strong></td>
<td>Rifampicin is likely to significantly reduce exposure to etravirine.</td>
<td>Co-treatment of Rifampicin 150 mg Capsules and etravirine should be avoided.</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to compensate for this by increasing doses of the PIs, or an increase in ritonavir-boosting, have been ill-tolerated with a high rate of hepatotoxicity.</td>
<td>Rifampicin 150 mg Capsules must not be co-administered with HIV protease inhibitors (see section 4.3).</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Raltegravir AUC ↓ 40%</td>
<td>Co-treatment should be avoided. If deemed necessary, consider an increase of the raltegravir dose to 800 mg b.i.d.</td>
</tr>
</tbody>
</table>
| **Dolutegravir**          | Dolutegravir ↓ AUC ↓ 54%  
Cmax ↓ 43%  
Cτ ↓ 72% | A dose adjustment of dolutegravir is recommended. |
| **Maraviroc**             | Maraviroc AUC ↓ 63% | Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d. |
| **Antivirals for Chronic Hepatitis C** | ↓ Daclatasvir  
AUC: 0.21 (0.19, 0.23)  
Cmax: 0.44 (0.40, 0.48) | Co-administration with daclatasvir is contraindicated (see section 4.3) |
| **Simeprevir**            | Simeprevir AUC 0.52 (0.41-0.67)  
↓ Simeprevir Cmax 1.31 (1.03-1.66)  
↓ Simeprevir Cmin 0.08 (0.06-0.11) | It is not recommended to co-administer simeprevir with rifampicin as co-administration may result in loss of therapeutic effect of simeprevir. |
<p>| <strong>Boceprevir</strong>            | No data are available. | The combination of rifampicin |</p>
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</thead>
<tbody>
<tr>
<td></td>
<td>The concomitant use may significantly reduce the plasma exposure of boceprevir through induction of CYP.</td>
<td>with boceprevir is contraindicated (see section 4.3)</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Ledipasvir ↓ Cmax 0.65 (0.56, 0.76) ↓ AUC 0.41 (0.36, 0.48)</td>
<td>Coadministration with ledipasvir is contraindicated (see section 4.3)</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sofosbuvir ↓ Cmax 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) Cmin (NA) GS-331007 ↔ Cmax 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) Cmin (NA)</td>
<td>Coadministration with sofosbuvir is contraindicated (see section 4.3).</td>
</tr>
</tbody>
</table>

**Antifungals**

<table>
<thead>
<tr>
<th>Ketoconazole</th>
<th>Ketoconazole AUC ↓ 80%</th>
<th>Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Fluconazole AUC ↓ 23%</td>
<td>Efficacy should be monitored. An increased dose of fluconazole may be required.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Itraconazole AUC ↓ &gt;64-88%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Voriconazole AUC ↓ 96%</td>
<td>Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.</td>
</tr>
</tbody>
</table>

**Antibacterials/Antituberculotics**

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.</th>
<th>Co-administration should be avoided.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Case reports indicate &gt;60-80% reduction of chloramphenicol exposure.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>No significant interaction</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Doxycyclin</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</td>
<td>Metronidazole AUC i.v.↓ 33%</td>
<td>The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Efficacy should be monitored.</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Sulfamethoxazole AUC ↓ 23%</td>
<td>Interaction probably not clinically significant. Efficacy should be monitored.</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

<table>
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<tr>
<th>Drugs</th>
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<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trimethoprim</strong></td>
<td>Trimethoprim AUC ↓ 47%</td>
<td>A dose increase of trimethoprim may be required. Efficacy should be monitored.</td>
</tr>
<tr>
<td><strong>Ethionamide</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>P-aminosalicylic acid</strong></td>
<td>In vitro data show reduced uptake of P-aminosalicylic acid by the OATP1B1 transporter due to inhibition by rifampicin.</td>
<td>If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels</td>
</tr>
</tbody>
</table>

### Antimalarials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chloroquine</strong></td>
<td></td>
<td>Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Atovaquone</strong></td>
<td>Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Mefloquine</strong></td>
<td>Mefloquine AUC ↓ 68%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Amodiaquine</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</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>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Artemisinin and its derivatives</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>Co-administration should be avoided.</td>
</tr>
</tbody>
</table>

### ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
<table>
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<tr>
<th>Drugs by Therapeutic Area</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Morphine AUC p.o ↓ 30%</td>
<td>Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.</td>
<td>Efficacy should be monitored and codeine dose increased if necessary.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone AUC ↓ 33-66%</td>
<td>Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate.</td>
</tr>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>Rifampicin may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive.</td>
<td>Co-administration of Rifampicin 150 mg Capsules and acetaminophen (paracetamol) should be avoided.</td>
</tr>
<tr>
<td>ANTICONVULSANTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Rifampicin is expected to decrease the serum concentration of carbamazepine.</td>
<td>Co-administration of Rifampicin 150 mg Capsules and carbamazepine should be avoided.</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other.</td>
<td>Co-administration of Rifampicin 150 mg Capsules and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin AUC i.v. ↓ 42%</td>
<td>Co-treatment with phenytoin and Rifampicin 150 mg Capsules should be avoided.</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Interaction studies are lacking. Since 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 deemed necessary, efficacy and, if possible, also plasma concentrations of valproic acid, should be carefully monitored.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamotrigine AUC ↓ 45%</td>
<td>Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.</td>
</tr>
<tr>
<td>IMMUNOSUPPRESSIVES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</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 concentrations of cyclosporine should be monitored and doses adapted.</td>
</tr>
<tr>
<td>Drugs by Therapeutic Area</td>
<td>Interaction</td>
<td>Recommendations concerning co-administration</td>
</tr>
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</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td>Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 70%</td>
<td>Co-administration of Rifampicin 150 mg Capsules 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><strong>CARDIOVASCULAR MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin AUC ↓ 85%</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Atenolol AUC ↓ 19%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Verapamil</td>
<td>S-VERAPAMIL p.o CL/F ↑ 32-fold; With i.v. S-VERAPAMIL, CL ↑ 1.3-fold</td>
<td>Rifampicin 150 mg Capsules and verapamil per-oraly 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>Digoxin</td>
<td>AUC p.o ↓ 30%</td>
<td>When co-administering Rifampicin 150 mg Capsules with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Lidocaine CL i.v. ↑ 15%</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin.</td>
<td>Efficacy should be monitored.</td>
</tr>
<tr>
<td>Enalapril</td>
<td>No interaction expected</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%</td>
<td>Co-administration is not recommended.</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Ranitidine AUC ↓ 52%</td>
<td>Efficacy should be monitored, and ranitidine dose increased if necessary.</td>
</tr>
<tr>
<td>Antacids</td>
<td>Antacids may reduce the bioavailability of rifampicin by up to one third.</td>
<td>The clinical importance is unknown.</td>
</tr>
<tr>
<td><strong>PSYCHOTHERAPEUTIC MEDICINES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Diazepam AUC ↓ &gt;70%</td>
<td>Co-treatment is not recommended. If deemed</td>
</tr>
</tbody>
</table>
### Drugs by Therapeutic Area

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<td><strong>Chlorpromazine</strong></td>
<td>Rifampicin may reduce chlorpromazine exposure.</td>
<td>Co-administration should be avoided.</td>
</tr>
<tr>
<td><strong>Haloperidol</strong></td>
<td>Haloperidol clearance is substantially increased by rifampicin.</td>
<td>If co-treatment of Rifampicin 150 mg Capsules with haloperidol is deemed necessary, efficacy of haloperidol should be monitored. A dose increase may be required.</td>
</tr>
<tr>
<td><strong>Amitriptyline</strong></td>
<td>Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance.</td>
<td>Co-treatment should be avoided. If necessary, efficacy and, if possible, also plasma concentrations of amitriptyline should be monitored.</td>
</tr>
<tr>
<td><strong>Prednisolone</strong></td>
<td>Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.</td>
<td>Co-administration of Rifampicin 150 mg Capsules with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.</td>
</tr>
<tr>
<td><strong>Glibenclamide</strong></td>
<td>Glibenclamide AUC ↓ 34%</td>
<td>Blood glucose levels should be closely monitored. A dose increase of glibenclamide may be required.</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>No interaction expected.</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td><strong>Levothyroxine</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</strong></td>
<td>Ethinylestradiol AUC ↓ 66%</td>
<td>Co-administration with Rifampicin 150 mg Capsules may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
<tr>
<td><strong>Norethindrone</strong></td>
<td>Norethindrone AUC ↓ 51%</td>
<td>Co-administration with Rifampicin 150 mg Capsules may be associated with decreased contraceptive effect. Barrier- or other non-hormonal methods of contraception should be used.</td>
</tr>
<tr>
<td><strong>Praziquantel</strong></td>
<td>Praziquantel AUC ↓ 80-99%</td>
<td>Co-treatment with Rifampicin</td>
</tr>
</tbody>
</table>
Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration
---|---|---

**Interference with laboratory and diagnostic tests**
Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

**4.6 Pregnancy and lactation**

*Pregnancy:*
Although rifampicin has been reported to cross the placental barrier and appear in the cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Rifampicin 150 mg Capsules should be used in pregnancy only if the benefits are considered to outweigh the risks. When rifampicin is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant for which treatment with vitamin K1 may be indicated.

*Lactation:*
Rifampicin is excreted in 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.

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

Cutaneous reactions which are mild and self-limiting may occur and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. Urticaria and more serious hypersensitivity cutaneous reactions have occurred but are uncommon. Exfoliate dermatitis, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyells syndrome and vasculitis have been reported rarely.

Gastrointestinal reactions consist of anorexia, nausea, vomiting, abdominal discomfort, and diarrhoea. Pseudomembranous colitis has been reported with rifampicin therapy.

Hepatitis can be caused by rifampicin and liver function tests should be monitored (see section 4.4).

Central Nervous system: Psychoses have been rarely reported.

Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
Disseminated intravascular coagulation has also been rarely reported.

Eosinophilia, leucopenia, oedema, muscle weakness, and myopathy have been reported to occur in a small percentage of patients treated with rifampicin.

Agranulocytosis has been very rarely reported.

Rare reports of adrenal insufficiency in patient with compromised adrenal function have been observed.

Reactions usually occurring with intermittent dosage regimens and most probably of immunological origin include:

- ‘Flu Syndrome’ consisting of episodes of fever, chills, headache, dizziness, and bone pain appearing most commonly during the 3rd to the 6th month of therapy. The frequency of the syndrome varies but may occur in up to 50% of patients given once-weekly regimens with a dose of rifampicin of 25mg/kg or more.
- Shortness of breath and wheezing
- Decrease in blood pressure and shock
- Anaphylaxis
- Acute haemolytic anaemia
- Acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis.

If serious complications arise, e.g. renal failure, thrombocytopenia or haemolytic anaemia, rifampicin should be stopped and never restarted.

Occasional disturbances of the menstrual cycle have been reported in women receiving long term anti-tuberculosis therapy with regimens containing rifampicin.

Rifampicin may produce a reddish discolouration of the urine, sweat, sputum and tears. The patient should be forewarned of this. Soft contact lenses may be permanently stained.

4.9 Overdose

Symptoms:
When overdosed, rifampicin may cause a reddish-orange discolouration of the skin (‘red man syndrome’). Further symptoms include hypotension, sinus tachycardia, ventricular arrhythmias, seizures, facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14 g has caused cardiopulmonary arrest.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimycobacterials, antibiotics ATC Code: J04AB02.
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).

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 1 x Rifampicin 150 mg Capsules 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 2.656 µg/ml (± 0.819), and the corresponding value for AUC was 12.203 µg.h/ml (± 3.899). The mean (± SD) rifampicin tmax value was 1.50 (± 0.57) 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule fill: Maize starch, magnesium stearate, microcrystalline cellulose, povidone, purified talc and sodium lauryl sulphate

Capsule shell: Gelatin, sodium methylparaben, sodium propylparaben, sodium lauryl sulphate, titanium dioxide, FD&C Yellow #6 / Sunset yellow, carmoisine and ponceau 4R

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature not exceeding 25°C, in a dry place. Protect from light. Dispense in tight container.

6.5 Nature and contents of container

Strip of 10 x 10 Capsules

10 Capsules packed in an Al-Al strip, such 10 strips packed in a box along with the package information leaflet.

Bulk pack of 100 Capsules

100 Capsules packed in self-sealing LDPE bag (4 inch x 6 inch), plain triple laminated (LDPE/AL/PET) sachet (5 inch x 7 inch) and then to 350 ml round wide mouth opaque milky white HDPE container with HDPE screw thread cap along with the leaflet.

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 Limited
304, Atlanta Arcade
Marol Church Road
Andheri (East)
Mumbai – 400 059, India
Tel: +91-22-66762800
Fax: +91 -22-28216599
E-mail: exports@macleodsphara.com

8. WHO Reference Number (Prequalification Programme)
TB259

9. Date of First Prequalification
7 September 2016

10. Date of Revision of the Text:
March 2017

Reference list:

General references

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014, available at:
http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf


Rapid Advice, Treatment of Tuberculosis in Children, 2010, available at:

WHO, Dosing Instructions for the use of currently available fixed-dose combination TB medicines for children, September 2009, available at:

MHRA, Rifampicin Capsules 150 mg SmPC, available at:

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


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

Thompson: Micromedex, Drugdex 2007, Rifampicin (systemic)

Fachinformation Eremfat Tabletten (Fatol Arzneimittel GmbH), Januar 2006

References for specific sections of the SPC

4.4
On the hepatotoxicity of TB drugs:
4.5


Stockley’s Drug Interactions. Available at: [www.medicinescomplete.com](http://www.medicinescomplete.com).
The SPHINX Drug Interaction Database. Available at: [http://drugdb.janusinfo.se/sfinx/interactions/index_menus.jsp](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

4.6

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5.3
Rifampicin
International Programme on Chemical Safety:
[http://www.inchem.org/documents/pims/pharm/rifam.htm#SubSectionTitle:7.1.1%20Toxicodynamics](http://www.inchem.org/documents/pims/pharm/rifam.htm#SubSectionTitle:7.1.1%20Toxicodynamics)