WHO-PQ recommended clinical and preclinical information for the health care provider

This information reflects the recommendations of current WHO guidelines and the scope of WHO's prequalification programme.

1. TYPE OF THE MEDICINAL PRODUCT

Rifampicin 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 300 mg rifampicin
For product-specific information, see WHOPAR part 4.

3. PHARMACEUTICAL FORM

Hard, capsules
For product-specific information, see WHOPAR part 4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rifampicin 300 mg hard capsules are indicated in combination with other tuberculosis medicines for the treatment of tuberculosis due to *Mycobacterium tuberculosis.* It is also indicated on its own or together with other medicines for the prevention of tuberculosis in persons at risk.

Rifampicin 300 mg hard capsules are indicated in combination with other medicines for the treatment of leprosy. It is also indicated for post-exposure prophylaxis (PEP) in persons who have been in contact with a leprosy patient.

Treatment regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Oral use.

Posology

When used to treat tuberculosis or leprosy, Rifampicin 300 mg hard capsules is always given in combination with other medicines, according to the selected regimen. A suitable fixed dose combination product should be preferred if available.

Patients should be advised to take Rifampicin 300 mg hard capsules exactly as prescribed and to complete the full course.

Treatment of tuberculosis

Drug-susceptible tuberculosis

For the treatment of drug-susceptible pulmonary tuberculosis a combination regimen containing daily rifampicin is normally given for 6 months. The recommended regimen consists of a 2-month intensive phase, comprising isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a 4-month continuation phase in which rifampicin is given only with isoniazid. In children and adolescents under the age of 16 and with non-severe infection, continuation therapy may optionally be given just for 2 months.

The dose of rifampicin depends on age as follows:

10 years and older:	10 mg/kg (range 8-12 kg)
Less than 10 years:	15 mg/kg (range 10-20 mg/kg)

If a suitable fixed-dose combination product is not available, Rifampicin 300 mg hard capsules may be used in such a regimen in the following doses:

Patients 10 years of age and older:

Body weight	**Number of capsules**
25 to less than 30 kg	1 capsule daily
30 to less than 35 kg	*Use alternative product*
35 kg and over	2 capsules daily*

*An alternative formulation may be considered in patients weighing more than 65 kg in order to supply an adequate dose of rifampicin.

Patients under 10 years of age (only for patients who can swallow capsules):

Body weight	**Number of capsules**
Under 15 kg	*Use alternative product*
15 to less than 25 kg	1 capsule daily
25 kg and over	*As for adults, above*

Rifampicin 300 mg hard capsules should not be used for intermittent treatment regimens.

Isoniazid-resistant tuberculosis

In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months. Doses of rifampicin are similar to those used for drug-susceptible tuberculosis, above.

Prevention of tuberculosis

Rifampicin 300 mg hard capsules may be used alone or in combination with isoniazid for the prevention of tuberculosis in persons at risk. Preventive treatment should be given in line with applicable guidelines, such as those of WHO.

The recommended daily doses of rifampicin for prevention of tuberculosis are similar to those given for treatment of drug-susceptible tuberculosis, above.

When given as *monotherapy*, treatment is given for 4 months.

When given *with daily isoniazid*, the combined regimen is given for 3 months.

Treatment of leprosy

For the treatment of leprosy, Rifampicin 300 mg hard capsules may be given once a month, in combination with clofazimine and dapsone.

The recommended dose in *adults and adolescents 15 years and older* is 2 capsules of Rifampicin 300 mg hard capsules (rifampicin 600 mg) taken once a month.

In *patients 14 years and younger* a suitable product should be used to supply a rifampicin dose of 10 mg/kg body weight.

Treatment is given for 12 months in patients with multibacillary leprosy, and for 6 months in paucibacillary leprosy.

Prevention of leprosy

A single dose of Rifampicin 300 mg hard capsules is given for prevention of leprosy in persons who have been in contact with a leprosy patient and in whom existing leprosy or tuberculosis have been excluded.

The recommended dose in *adults and adolescents 15 years and older* is 2 capsules of Rifampicin 300 mg hard capsules (rifampicin 600 mg),

For *patients aged 10 to14 years*, alternative products to supply a rifampicin dose of 450 mg should be used.

For *children below 10 years weighing at least 20 kg*, the recommended dose is 1 capsule of Rifampicin 300 mg hard capsules (rifampicin 300 mg).

Special populations

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 300 mg hard capsules must not be used in patients with severe liver disease (see section 4.3).

Method of administration

Rifampicin 300 mg hard 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.

4.3 Contraindications

Hypersensitivity to the active substance or to other rifamycins, or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

Co-administration of Rifampicin 300 mg hard capsules with certain other medicines whose therapeutic effect or adverse effects may be significantly affected by rifampicin or which may significantly reduce rifampicin's efficacy (see 'Some combinations may be contra-indicated' in section 4.5).

4.4 Special warnings and precautions for use

Liver toxicity

Cases of drug-induced liver injury, including fatal cases (especially when used in combination with other anti-tuberculosis drugs), have been reported in patients treated with rifampicin with an onset of a few days to a few months following treatment initiation (see section 4.8). In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with Rifampicin 300 mg hard capsules and periodically throughout treatment. A rise in bilirubin and/or transaminase level is common when starting therapy with Rifampicin 300 mg hard capsules. 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 300 mg hard capsules should be strongly considered. Reinstitution of rifampicin therapy should only be performed when symptoms and laboratory abnormalities have subsided.

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 fatigue or weakness of greater than 3 days duration or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, Rifampicin 300 mg hard capsules should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage. Rifampicin should not be re-introduced in patients with an episode of hepatic injury during treatment with rifampicin for which no other cause of liver injury has been determined.

Whenever possible, the use of Rifampicin 300 mg hard capsules should be **avoided in patients with pre-existing 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 300 mg hard 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),
- pregnant patients,
- HIV positive patients.

Hypersensitivity

Rifampicin may cause a hypersensitivity syndrome including 'flu-like' symptoms 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 300 mg hard capsules should immediately be discontinued. Such patients should not be rechallenged with rifampicin.

There have also been reports of severe cutaneous adverse reactions (SCARs) including Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) in association with rifampicin; these can be life-threatening or fatal. Most of these reactions occurred within 2 days to 2 months after treatment initiation but the time to onset can vary.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Rifampicin 300 mg hard capsules should be withdrawn immediately, and an alternative treatment considered (as appropriate).

Respiratory effects

After initial improvement of tuberculosis under therapy including rifampicin, the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions or the development of new lesions have been detected. Such reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. In case a paradoxical reaction is suspected, symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary. Furthermore, continuation of the planned tuberculosis combination therapy is recommended.

Patients should be advised to seek medical advice immediately if their symptoms worsen. The symptoms that occur are usually specific to the affected tissues. Possible general symptoms include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8).

There have also been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving rifampicin for treatment of tuberculosis (see section 4.8). Rifampicin 300 mg hard capsules should be permanently discontinued if this occurs.

Haematological toxicity

Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be performed before starting treatment and monitored regularly throughout therapy

with Rifampicin 300 mg hard capsules. In case of severe haematological disturbances, Rifampicin 300 mg hard capsules must be discontinued. Vitamin K supplementation may be considered in patients at risk of vitamin-K dependent coagulopathy.

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with rifampicin use. If laboratory or clinical findings associated with TMA occur in a patient receiving Rifampicin 300 mg hard capsules, treatment should be discontinued and thorough evaluation for TMA performed. Treatment with Rifampicin 300 mg hard capsules should not be resumed in patients who develop TMA and patients should be treated accordingly (consider plasma exchange).

Drug interactions

Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin 300 mg hard capsules may reduce exposure and efficacy of many therapeutic drugs, including antiviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives. In addition, an increased risk of hepatotoxicity or other adverse effects may occur with some combinations. See section 4.5 for a discussion of rifampicin interactions.

Contraception:

Oral contraceptives do not provide adequate protection against conception when co-administered with Rifampicin 300 mg hard 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 300 mg hard capsules may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria

Rifampicin 300 mg hard capsules should be used with caution in patients with porphyria, since enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids

Rifampicin 300 mg hard capsules may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears. The patient should be advised of this possibility. Patients who wear soft contact lenses should be warned that they may be permanently stained.

Excipients

Information on excipients with a recognised clinical effect can be found in the product information as approved by the reference authority, stated in WHOPAR part 1.

4.5 Interaction 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 co-administered drugs. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping the concomitant administration of Rifampicin 300 mg hard capsules.

Whenever co-prescribing any drug together with Rifampicin 300 mg hard capsules, the possibility of a drug-drug interaction should be considered. Rifampicin 300 mg hard capsules 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 many important therapeutic agents, no interaction data with rifampicin are available. However, clinically significant reductions in drug exposure may occur.

Some combinations may be contra-indicated: in particular, Rifampicin 300 mg hard capsules must not be given with HIV protease inhibitors and some other HIV medicines, direct-acting antivirals for hepatitis C therapy, or the antifungal voriconazole. For more information on these and other combinations that should be avoided, see the table below.

The following list of drug interactions with Rifampicin 300 mg hard capsule 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.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
HIV antiretrovirals		
Nucleoside analogues		
Zidovudine	Zidovudine AUC ↓ 47%	The clinical significance of the lowered zidovudine exposure is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.
Stavudine Didanosine Lamivudine Emtricitabine	No interaction expected	No dose adjustment required
Tenofovir disoproxil fumarate	Tenofovir AUC ↓13%	No dose adjustment required
Abacavir	Empirical data are lacking, but rifampicin may decrease abacavir concentration by inducing glucuronidation	Efficacy of abacavir should be closely monitored in co-treatment
Non-nucleoside analogues		
Efavirenz	Efavirenz AUC ↓ 26%	When co-treating with Rifampicin 300 mg hard capsules, consideration may be given to increasing the efavirenz dose (to 800 mg once daily in adults)
Nevirapine	Nevirapine: AUC ↓ 58%	Since neither the appropriate nevirapine dose when given with rifampicin, nor the safety of the combination has been established, Rifampicin 300 mg hard capsules must not be used with nevirapine
Etravirine	Rifampicin is likely to significantly reduce etravirine concentration	Co-treatment of Rifampicin 300 mg hard capsules with etravirine should be avoided
Rilpivirine	Rilpivirine AUC ↓ 80%	Rifampicin 300 mg hard capsules must not be co-administered with rilpivirine

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Protease inhibitors		
Atazanavir (also atazanavir with cobicistat) Darunavir (also darunavir with cobicistat) Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir	Protease inhibitor exposure will be reduced to sub-therapeutic level due to interaction with rifampicin. Rifampicin also reduces levels of cobicistat (used for boosting atazanavir and darunavir) and can lead to loss of therapeutic effect and possible development of resistance Concomitant use of rifampicin with saquinavir/ritonavir also increases potential hepatotoxicity.	Rifampicin 300 mg hard capsules must not be co-administered with protease inhibitors (see section 4.3).
Other antiretrovirals		
Bictegravir	Bictegravir AUC ↓ 75%	Rifampicin 300 mg hard capsules must not be co-administered with bictegravir (see section 4.3).
Dolutegravir	Dolutegravir AUC ↓ 54% C_{max}↓ 43%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with Rifampicin 300 mg hard capsules in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
Elvitegravir with cobicistat	Rifampicin significantly reduces levels of elvitegravir and cobicistat and can lead to loss of therapeutic effect and possible development of resistance	Rifampicin 300 mg hard capsules must not be co-administered with elvitegravir and cobicistat (see section 4.3).
Raltegravir	Raltegravir AUC ↓ 40%	If co-treatment is necessary, increasing the raltegravir dose (to 600 mg twice daily in adults) should be considered.
Maraviroc	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If maraviroc is necessary, the dose should be increased (to 600 mg twice daily in adults).
Antivirals for treating chronic hepatitis C		
Daclatasvir	Daclatasvir ↓AUC 0.21 (0.19, 0.23) ↓C_{max} 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) ↓ C_{max} 1.31 (1.03- 0.66) ↑ C_{min} 0.08 (0.06- 0.11) ↓	It is not recommended to co- administer simeprevir with rifampicin as coadministration may result in loss of therapeutic effect of simeprevir (see section 4.3).
Boceprevir	No data are available. The concomitant use may significantly reduce the plasma exposure of boceprevir through induction of CYP.	The combination of rifampicin with boceprevir is contraindicated (see section 4.3)

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Ledipasvir	Ledipasvir ↓C_{max} 0.65 (0.56, 0.76) ↓ AUC 0.41 (0.36, 0.48)	Co-administration with ledipasvir is contraindicated (see section 4.3)
Sofosbuvir	Sofosbuvir ↓C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) C_{min} (NA)	Co-administration with sofosbuvir is contraindicated (see section 4.3).
Antifungals		
Ketoconazole	Ketoconazole AUC ↓80%	Co-administration should be avoided. If deemed necessary, a higher dose of ketoconazole may be required
Fluconazole	Fluconazole AUC ↓ 23%	Efficacy should be monitored. A higher dose of fluconazole may be required
Itraconazole	Itraconazole AUC ↓ 64–88% (or more)	Co-administration should be avoided
Voriconazole	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials including antituberculosis antibacterials		
Clarithromycin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged	Co-administration should be avoided
Chloramphenicol	Case reports indicate > 60–80% reduction of chloramphenicol exposure.	Co-administration should be avoided
Ciprofloxacin	No significant interaction	No dose adjustment required
Doxycycline	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled
Metronidazole	Metronidazole AUC (intravenous) ↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored
Sulfamethoxazole	Sulfamethoxazole AUC ↓ 23%	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored
Trimethoprim	Trimethoprim AUC ↓ 47%	A dose increase of trimethoprim may be required. Efficacy should be monitored
Ethionamide		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
P-aminosalicylic acid	In vitro data show reduced uptake of P-aminosalicylic acid by the OATP1B1 transporter due to inhibition by rifampicin.	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
Antimalarials		
Chloroquine		Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Coadministration should be avoided
Atovaquone	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Co-administration should be avoided
Mefloquine	Mefloquine AUC ↓ 68%	Co-administration should be avoided
Amodiaquine	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Co-administration should be avoided
Quinine	Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates.	Co-administration should be avoided. If co-administration is necessary, a higher dose of quinine should be considered
Lumefantrine	Lumefantrine AUC ↓68%	Co-administration should be avoided
Artemisinin and derivatives	Artemether AUC ↓ 89% Dihydroarthemisinin AUC ↓ 85%	Co-administration should be avoided
Analgesics, Antipyretics, Non-steroidal anti-inflammatory drugs		
Morphine	Morphine AUC (by mouth) ↓ 30%	Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased
Codeine	Plasma level of morphine, an active metabolite of codeine, is likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary
Methadone	Methadone AUC ↓ 33–66%	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
Paracetamol (acetaminophen)	Rifampicin may increase the glucuronidation of paracetamol and decrease its efficacy	Co-administration of Rifampicin 300 mg hard capsules and paracetamol (acetaminophen) should be avoided.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Anticonvulsants		
Carbamazepine	Rifampicin is expected to decrease the serum concentration of carbamazepine.	Co-administration of Rifampicin 300 mg hard capsules and carbamazepine should be avoided
Phenobarbital	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each may lower the plasma concentrations of the other.	Co-administration of Rifampicin 300 mg hard capsules and phenobarbital should be undertaken with caution, with monitoring of clinical effects and, if possible, plasma drug concentrations
Phenytoin	Phenytoin AUC (intravenous) ↓ 42%	Co-treatment with phenytoin and Rifampicin 300 mg hard capsules should be avoided
Valproic acid	Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, rifampicin is likely to reduce plasma level of valproic acid	Co-treatment should be avoided. If deemed necessary, efficacy and, if possible, plasma concentrations of valproic acid, should be monitored
Lamotrigine	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased.
Immunosuppressives		
Cyclosporine	Rifampicin can substantially increase cyclosporine clearance	Co-administration should be avoided. If deemed necessary, plasma concentration of cyclosporine should be monitored and doses adapted accordingly (3–5 fold increases in cyclosporine dose have been required).
Tacrolimus Sirolimus Everolimus	Tacrolimus AUC (intravenous) ↓ 35%; AUC (oral) ↓ 70% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of Rifampicin 300 mg hard capsules and mTOR inhibitors should be avoided. If deemed necessary, plasma concentrations should be monitored, and the dose increased as appropriate.
Cardiovascular medicines		
Warfarin	Warfarin AUC ↓ 85%	Co-administration should be avoided
Atenolol	Atenolol AUC ↓ 19%	No dose adjustment required
Verapamil	S-verapamil (oral) CL/F ↑ 32fold With (intravenous) S-verapamil, CL ↑ 1.3-fold	Rifampicin 300 mg hard capsules and oral verapamil should not be co-administered. If verapamil is given intravenously, the therapeutic effect should be carefully monitored; dose adjustment may be required
Digoxin	AUC (oral)↓ 30%	When co-administering Rifampicin 300 mg hard capsules with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Lidocaine	Lidocaine CL (intravenous) ↑ 15%	No dose adjustment required
Amlodipine	Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin	Efficacy should be monitored
Enalapril	No interaction expected	No dose adjustment required
Simvastatin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended
Atorvastatin	Atorvastatin AUC ↓ 80%	Co-administration is not recommended
Gastrointestinal medicines		
Ranitidine	Ranitidine AUC ↓ 52%	Efficacy should be monitored, and ranitidine dose increased if necessary
Antacids	Antacids may reduce the bioavailability of rifampicin by up to one-third	The clinical importance is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used, if cotreatment with Rifampicin 300 mg hard capsules is necessary
Psychotherapeutic medicines		
Diazepam Midazolam Triazolam Alprazolam Nitrazepam	Diazepam AUC↓ > 70% Midazolam AUC ↓ 98% Triazolam AUC ↓ 95% Alprazolam AUC ↓ 88% Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals.
Zolpidem Zopiclone	Zolpidem AUC↓73% Zopiclone AUC↓82%	Co-administration should be avoided.
Chlorpromazine	Rifampicin may reduce chlorpromazine exposure.	Co-administration should be avoided.
Haloperidol Clozapine	Haloperidol clearance is substantially increased by rifampicin, theoretical considerations imply that same applies to clozapine.	If co-treatment of Rifampicin 300 mg hard capsules with haloperidol is necessary, efficacy of haloperidol should be monitored. A dose increase may be required
Amitriptyline Nortriptyline	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases clearance of tricyclic antidepressants.	Co-treatment should be avoided. If necessary, monitor for clinical response, side effects, and, if possible, plasma concentrations.
Hormones; other endocrine medicines and contraceptives		
Prednisolone and other systemically administered corticosteroids	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of Rifampicin 300 mg hard 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

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Glibenclamide Glimepiride Repaglinide	Glibenclamide AUC ↓ 39% Glimepiride AUC ↓ 34% Repaglinide AUC ↓ 57%	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
Insulin	No interaction expected	No dose adjustment required.
Levothyroxine	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored
Ethinylestradiol	Ethinylestradiol AUC ↓ 66%	Co-administration with Rifampicin 300 mg hard capsules may decrease contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Norethisterone	Norethisterone AUC ↓ 51%	Co-administration with Rifampicin 300 mg hard capsules may decrease contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Other medicines		
Halothane	Increased risk of hepatotoxicity.	Concomitant use of Rifampicin 300 mg hard capsules and halothane should be avoided,
Praziquantel	Praziquantel AUC ↓ 80–99%	Co-treatment with Rifampicin 300 mg hard capsules should be avoided
Theophylline	Rifampicin may increase the serum concentration of theophylline.	Theophylline dose adjustment may be needed.
↓ Decreased ↑ Increased ↔ No change	AUC area under the curve (bioavailability) C_{max} maximum (peak) concentration (in plasma or blood) C_{min} minimum (trough) concentration (in plasma or blood)	

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 Fertility, pregnancy and breastfeeding

Pregnancy

Rifampicin 300 mg hard capsules can be used during pregnancy as part of a combination regimen to treat tuberculosis.

At very high doses in animals rifampicin has been shown to have teratogenic effects (see section 5.3). There are no well controlled studies with rifampicin in pregnant women. However, it is considered that rifampicin does not pose any additional risks to the patient or fetus. Tuberculosis can be particularly dangerous in pregnancy and should be managed with effective treatment. Close monitoring during pregnancy will allow any concerns to be managed promptly.

When Rifampicin 300 mg hard capsules 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.

Breast-feeding

Rifampicin is excreted in the breast milk of lactating mothers, and may result in discoloration of the milk. No adverse effects in the baby have been reported and women should not be discouraged from breast-feeding. However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

Fertility

There are no data on the effects Rifampicin 300 mg hard capsules on human male or female fertility.

4.7 Effects on ability to drive and use machines

This medicine contains rifampicin, which may have an effect on you. More information can be found in the product information as approved by the reference authority, stated in WHOPAR part 1.

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.

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. Frequency of some adverse effects differs in patients receiving daily doses of rifampicin from those taking the medicine less frequently. 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'.

Infections and infestations

Frequency not known	Pseudomembranous colitis, influenza

Blood and lymphatic system disorders

Uncommon	Transient leucopenia, Haemolysis, haemolytic anaemia
Not known	Thrombocytopenia and thrombocytopenic purpura (common with intermittent therapy)*, thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, vitamin-K dependent coagulation disorders

Immune system disorders

Frequency not known	Anaphylactic reaction

Endocrine disorders

Frequency not known	Adrenal insufficiency, induction of crisis in patients with Addison's disease

Psychiatric disorders

Frequency not known	Psychotic disorder, mental confusion

Nervous system disorders

Common	Headache, dizziness, tiredness, drowsiness
Rare	Ataxia

Frequency not known	Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura

Eye disorders

Common	Reddening of the eyes, tear discoloration, permanent discoloration of soft contact lenses
Rare	Visual disturbances, exudative conjunctivitis

Vascular disorders

Frequency not known	Shock, vasculitis, bleeding

Respiratory, thoracic and mediastinal disorders

Frequency not known	Dyspnoea, wheezing, discoloured sputum, interstitial lung disease (including pneumonitis)

Gastrointestinal disorders

Common	Nausea, vomiting, decreased appetite
Uncommon	Diarrhoea
Frequency not known	Abdominal discomfort, erosive gastritis, pancreatitis, tooth discoloration (which may be permanent)

Hepatobiliary disorders

Common	Asymptomatic increase in liver enzymes
Frequency not known	Drug-induced liver injury, hepatitis, hyperbilirubinaemia

Skin and subcutaneous tissue disorders

Common	Flushing, itching with or without skin rash, urticaria
Frequency not known	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis, allergic dermatitis, pemphigoid

Musculoskeletal and connective tissue disorders

Frequency not known	Muscle weakness, myopathy, bone pain

Renal and urinary disorders

Frequency not known	Acute kidney injury (usually due to renal tubular necrosis or tubulointerstitial nephritis)

Pregnancy, puerperium and perinatal conditions

Frequency not known	Post-partum haemorrhage, fetal-maternal haemorrhage

Reproductive system and breast disorders

Rare	Menstrual disturbances (in extreme cases, amenorrhoea);

Congenital, familial and genetic disorders

Frequency not known	Porphyria

General disorders and administration site conditions

Very common	Pyrexia, chills

Common	Paradoxical drug reaction (appearance of new tuberculosis symptoms despite adherence and absence of resistance)**; reddish discoloration of body fluids and secretions such as e.g. urine, sputum, lacrimal fluid, faeces, saliva and sweat;
Frequency not known	Oedema
Investigations	
Common	Increased blood bilirubin, increased aspartate aminotransferase, increased alanine aminotransferase
Frequency not known	Decreased blood pressure, increased blood creatinine, increased hepatic enzymes

* Thrombocytopenia and thrombocytopenic purpura occur more frequently with intermittent therapy than with continuous daily treatment, during which they occur only very rarely. When rifampicin administration has been continued after the occurrence of purpura, cerebral haemorrhage and fatalities have been reported.

** Incidence of paradoxical drug reaction has been reported to vary between 9.2% and 25% in some data sets

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 - 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 – 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in paediatric patients aged 1 - 4 years old of 100 mg/kg for one to two doses have been reported.

Treatment

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) may help promote excretion of the drug. Haemodialysis may be of value in some patients.

5. PHARMACOLOGICAL PROPERTIES

Information on pharmacological properties is shown in the product information as approved by the reference authority, stated in WHOPAR part 1. Additional data for those uses approved by WHO may be found in the references given at the end of this document.

6. PHARMACEUTICAL PARTICULARS

Information on the pharmaceutical particulars is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

7. SUPPLIER

Information on the supplier is shown in the product information as approved by the reference authority, stated in WHOPAR part 1.

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

The WHO reference number is shown in WHOPAR part 1

9. DATE OF PREQUALIFICATION

The date of prequalification can be found in WHOPAR part 1.

10. DATE OF REVISION OF THE TEXT

May 2026

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General references

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Section 4.4

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