WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB259 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 150mg rifampicin.

Excipients with potential clinical effect

Each hard gelatin 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

[TB259 trade name] is a scarlet hard gelatin size "2" capsules with an opaque brown cap and body. They are plain with no markings. They contain brick red powder. The capsules are to be swallowed whole.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB259 trade name] is 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.

[TB259 trade name] is 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, [TB259 trade name] 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 [TB259 trade name] exactly as prescribed and to complete the full course.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

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, [TB259 trade name] 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	2 capsules daily
30 to less than 35 kg	3 capsules daily
35 to less than 65 kg	4 capsules daily
65 kg and over	5 capsules daily

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

Body weight	**Number of capsules**
Under 8 kg	*Use alternative product*
8 to less than 15 kg	1 capsule daily
15 to less than 25 kg	2 capsules daily
25 kg and over	*As for adults, above*

[TB259 trade name] 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

[TB259 trade name] 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, [TB259 trade name] may be given once a month, in combination with clofazimine and dapsone.

The recommended dose in *adults and adolescents 15 years and older* is 4 capsules of [TB259 trade name] (rifampicin 600 mg) taken once a month.

In *patients aged 10 to 14 years and weighing at least 40 kg*, 3 capsules (rifampicin 450 mg) may be given each month.

For *patients under 10 years of age or weighing less than 40 kg* 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 [TB259 trade name]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 4 capsules of [TB259 trade name] (rifampicin 600 mg).

For *patients aged 10 to14 years*, the recommended dose is 3 capsules of [TB259 trade name] (rifampicin 450 mg).

In *children between 2-10 years* the recommended dose of rifampicin depends on body weight as follows:

Body weight	**Number of capsules**
10 to less than 20 kg	1 capsule
20 kg and over	2 capsules

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. [TB259 trade name] must not be used in patients with severe liver disease (see section 4.3).

Method of administration

[TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name] and periodically throughout treatment. A rise in bilirubin and/or transaminase level is common when starting therapy with [TB259 trade name]. 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 [TB259 trade name] 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, [TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name]. 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), [TB259 trade name] 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, [TB259 trade name] 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). [TB259 trade name] 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 [TB259 trade name]. In case of severe haematological disturbances, [TB259 trade name] 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 [TB259 trade name], treatment should be discontinued and thorough evaluation for TMA performed. Treatment with [TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name]. 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:

[TB259 trade name] may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria

[TB259 trade name] should be used with caution in patients with porphyria, since enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids

[TB259 trade name] 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

[TB259 trade name] contains sodium methylparaben, sodium propylparaben, FD&C Yellow #6 / Sunset Yellow, carmoisine and Ponceau 4R which may cause allergic reactions.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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 [TB259 trade name].

Whenever co-prescribing any drug together with [TB259 trade name], the possibility of a drug-drug interaction should be considered. [TB259 trade name] 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, [TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name], 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, [TB259 trade name] must not be used with nevirapine
Etravirine	Rifampicin is likely to significantly reduce etravirine concentration	Co-treatment of [TB259 trade name] with etravirine should be avoided
Rilpivirine	Rilpivirine AUC ↓ 80%	[TB259 trade name] must not be co-administered with rilpivirine
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.	[TB259 trade name] must not be co-administered with protease inhibitors (see section 4.3).
Other antiretrovirals		
Bictegravir	Bictegravir AUC ↓ 75%	[TB259 trade name] must not be co-administered with bictegravir (see section 4.3).

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Dolutegravir	Dolutegravir AUC ↓ 54% C_{max}↓ 43%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with [TB259 trade name] 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	[TB259 trade name] 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)
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

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
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
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

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
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 [TB259 trade name] and paracetamol (acetaminophen)should be avoided.
Anticonvulsants		
Carbamazepine	Rifampicin is expected to decrease the serum concentration of carbamazepine.	Co-administration of [TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name] 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).

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
Tacrolimus Sirolimus Everolimus	Tacrolimus AUC (intravenous) ↓ 35%; AUC (oral) ↓ 70% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of [TB259 trade name] 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	[TB259 trade name] 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 [TB259 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required
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 [TB259 trade name] 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.

Drugs (grouped by therapeutic area)	**Interaction**	**Recommendation on co-administration**
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 [TB259 trade name] 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 [TB259 trade name] with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed
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 [TB259 trade name] may decrease contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Norethisterone	Norethisterone AUC ↓ 51%	Co-administration with [TB259 trade name] 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 [TB259 trade name] and halothane should be avoided,
Praziquantel	Praziquantel AUC ↓ 80–99%	Co-treatment with [TB259 trade name] should be avoided
Theophylline	Rifampicin may increase the serum concentration of theophylline.	Theophylline dose adjustment may be needed.
↓ Decreased	AUC area under the curve (bioavailability)	
↑ Increased	C_{max} maximum (peak) concentration (in plasma or blood)	
↔ No change	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

[TB259 trade name] 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 [TB259 trade name] 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 [TB259 trade name] on human male or female fertility.

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. Patients should be warned about the adverse reaction profile of this medicine, and should be advised that if they experience dizziness they should avoid potentially hazardous tasks such as driving and operating machinery.

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

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

Absorption of [TB259 trade name]
The absorption characteristics of [TB259 trade name] have been determined after administration of a single dose capsule in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable'	**Mean value* (± standard deviation)**
	Rifampicin
Maximum concentration (C_{max})	2656 ± 819 ng/mL (2546)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	12539 ± 3901 ng.h/mL --
Time to attain maximum concentration (t_{max})	1.50 ± 0.57 h

***** arithmetic mean

Pharmacokinetics of Rifampicin

	Rifampicin
Absorption	
Absolute bioavailability	90 – 95%
Oral bioavailability	> 90%
Food effect	No effect on extent of absorption. Rate of absorption is reduced.
Distribution	
Volume of distribution (mean)	55 L
Plasma proteinbinding *in vitro*	60 – 90%
Tissue distribution	CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Concentrations in liver, spleen, kidneys and lung tissue are higher than serum concentrations. Penetrates vaginal and cervical tissue and cervicovaginal fluid. Passes the placenta; serum concentrations in fetus are about ⅓ of those in mother.
Metabolism	
General	Primarily hepatic, rapidly deacetylated.
Active metabolite(s)	25-o-deacetyl rifampicin
Elimination	
Elimination half life	3 – 5 hours Decreases to 2 – 3hours after repeated administration
Mean systemic clearance (Cl/F)	5.7 – 9.0 L/hour
% of dose excreted in urine	30%
% of dose excreted in faeces	60 – 65%
Pharmacokinetic linearity	Non linear
Drug interactions *(in vitro*)	Rifampicin induces hepatic enzymes
Transporters	Solute carrier transporters (SLC) ATP Binding Cassette transporters (ABC) P-glycoprotein
Metabolizing enzymes	CYP450

Special populations

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

The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. The half-life of rifampicin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900-mg oral dose of rifampicin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively.

In one study, paediatric patients 6 to 58 months old were given rifampicin suspended in simple syrup or as dry powder mixed with apple sauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 µg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the apple sauce mixture, respectively. After the administration of either preparation, the $t_{1/2}$ of rifampicin averaged 2.9 hours. It should be noted that in other studies in paediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 µg/mL to 15 µg/mL have been reported.

5.3 Preclinical safety data

After oral administration of 100 mg/kg bodyweight rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg, swelling and hydropic degeneration of the liver were observed. In monkeys, vomiting, anorexia and weight loss were observed at chronic doses of 105 mg/kg/day.

Because only limited evidence is available for the carcinogenicity of rifampicin in mice, and in 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. 100–150 mg/kg 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

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per *capsule*.

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.

Blister pack: Store capsules in blisters in the provided carton.

6.5 Nature and contents of container

Alu/Alu strip pack

[TB259 trade name] is provided in an aluminium on aluminium strip pack, each containing 10 capsules. Available in cartons of 10 x 10 capsules.

HDPE bulk pack

[TB259 trade name] is provided 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, each containing 100 capsules. Available in packs of 1×100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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TB259

9. DATE OF PREQUALIFICATION

7 September 2016

10. DATE OF REVISION OF THE TEXT

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