# 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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

# 1. NAME OF THE MEDICINAL PRODUCT

[TB068 trade name]†

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 150 mg Rifampicin and 75 mg Isoniazid

For a full list of excipients see section 6.1.

# 3. PHARMACEUTICAL FORM

Brick-red coloured, capsule shaped, biconvex, film coated tablets with break-line on one side and plain on the other side.
The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

[TB068 trade name] is indicated in adolescents and adults 10 years and older and weighing at least 25 kg

- for the continuation treatment phase of tuberculosis caused by *Mycobacterium tuberculosis.*
- for tuberculosis preventive treatment.

Consideration should be given to official treatment guidelines for tuberculosis such as those of. WHO and other national or international guidelines.

## 4.2 Posology and method of administration

***Posology***

[TB068 trade name] is taken once daily.

The recommended dose for both treatment and preventive treatment in adolescents and adults 10 years or older and weighing at least 25 kg is

- Isoniazid: 5 mg/kg (4–6 mg/kg) daily
- Rifampicin: 10 mg/kg (8–12 mg/kg) daily

| **Weight** | **Dose** |
|---|---|
| Under 25 kg | [TB068 trade name] is not suitable; use alternative product to give suitable doses of the active ingredients |
| 25–39 kg | 2 tablets administered as a single dose once daily |
| 40–54 kg | 3 tablets administered as a single dose once daily |
| 55–69 kg | 4 tablets administered as a single dose once daily |
| 70 kg and over | 5 tablets or more, depending on patients' bodyweight, administered as a single dose once daily |

Official guidelines such as those of WHO, or other national or international guidelines, should be consulted.

The duration of therapy is dependent on the therapeutic indication as well as the combination of drugs used together with isoniazid.

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

[TB068 trade name] should not be used for intermittent treatment regimens.

[TB068 trade name] should be taken on an empty stomach (at least one hour prior to or two hours after a meal). Bioavailability may be impaired if [TB068 trade name] is taken with food to improve gastrointestinal tolerance.

For situations where it is necessary to stop or reduce the dose of one of the active substances of this medicine, separate preparations of rifampicin and/or isoniazid should be used.

*Adolescents and children younger than 10 years or weighing less than 25 kg*

[TB068 trade name] is not recommended for patients younger than 10 years or with a body weight below 25 kg, since appropriate dose adjustments cannot be made.
For these patients other formulations are available.

***Renal impairment:***

No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to 2/3 of the normal daily dose may be considered in slow acetylators with severe renal failure (ClCr <25 ml/min) or in those with signs of isoniazid toxicity. If so, separate preparations of rifampicin and isoniazid should be administered (see section 4.4).

***Hepatic impairment:***

Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. [TB068 trade name] must not be used in patients with severe liver disease (see section 4.3).

***Missed doses***

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB068 trade name] and reduce its effectiveness.

In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be omitted.

***Method of administration***

[TB068 trade name] is administered orally, and should be taken on an empty stomach (at least 1 hour prior to or 2 hours after a meal). Bioavalability may be impaired if [TB068 trade name] is taken with food to improve gastrointestinal tolerance.

## 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 [TB068 trade name] with voriconazole, any HIV protease inhibitor, elvitegravir/cobicistat or any direct acting antiviral for chronic Hepatitis C is contraindicated (see section 4.5).

## 4.4 Special warnings and precautions for use

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

Whenever possible, the use of [TB068 trade name]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 [TB068 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),
- 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, [TB068 trade name]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 [TB068 trade name]and periodically throughout treatment.

Increased liver function tests are common during therapy with [TB068 trade name]. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin or isoniazid. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within three months, even with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of [TB068 trade name]should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until symptoms and laboratory abnormalities have subsided. In case of rechallenge, [TB068 trade name]should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents should be used.

*Hypersensitivity*: Rifampicin may cause a hypersensitivity syndrome including ‘flu-like’ symptoms and/or organ manifestation. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity do appear (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure). Then, [TB068 trade name]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, [TB068 trade name]should not be used.

*Cross-sensitivity*: Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid.

*Peripheral neuropathy:* This is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely with [TB068 trade name]at doses of 10 mg per day to prevent and at doses of 50-75 mg daily to treat peripheral neuropathy.

*Epilepsy and psychotic disorders*: [TB068 trade name]should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

*Haematological toxicity*: Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with [TB068 trade name]. In case of severe haematological disturbances [TB068 trade name]must be discontinued.

Renal impairment: Patients with renal impairment, particularly those who are slow acetylators (see sections 4.2 and 5.2) may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

*Nephrotoxicity*: [TB068 trade name]should be discontinued in case of clinical signs of nephrotoxicity.

*Diabetes Mellitus*: Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

*Drug interactions*: Rifampicin is a strong inducer of hepatic drug metabolism. Therefore [TB068 trade name]may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

*Contraception*: Oral contraceptives do not provide adequate protection against conception when co-administered with [TB068 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.

*Treatment with corticosteroids*: [TB068 trade name]may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

*Porphyria*: [TB068 trade name]should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

*Discolouration of body fluids*: [TB068 trade name]may cause a reddish-orange discolouration of body fluids such as urine, sputum and tears. This is due to rifampicin, and does not require medical attention.

*Laboratory monitoring*: Full blood count and liver function should be monitored prior to and at regular intervals during treatment with [TB068 trade name].

## 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 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 cotreating 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 [TB068 trade name].

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus it may increase exposure to drugs mainly eliminated through either of these pathways. However, when co-treating with rifampicin, as when using [TB068 trade name], these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. Insofar as it has been investigated, the net effect of rifampicin and isoniazid on drug clearance will be an increase due to rifampicin rather than a decrease due to isoniazid.
Concurrent use of isoniazid with other hepatotoxic or neurotoxic medications may increase the hepatotoxicity and neurotoxicity of isoniazid, and should be avoided.

Mainly due to rifampicin, [TB068 trade name]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 [TB068 trade name], the possibility of a drug-drug interaction should be considered. The

following list of drug interactions with [TB068 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.

Use of isoniazid should be carefully monitored with patients with current chronic liver disease. Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment.

| **Drugs by Therapeutic Area** | **Interaction** | **Recommendations concerning co-administration** |
|---|---|---|
| **INFECTION**<br>*Antiretrovirals* | | |
| *Nucleoside analogues*<br>**Zidovudine** / rifampicin | 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**<br>**Didanosine**<br>**Lamivudine**<br>**Emtricitabine** | No interaction expected | No dose adjustment required. |
| **Tenofovir alafenamide/ emtricitabine/ rifampicin** | Interaction not studied. Co-administration of rifampicin, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance. | Coadministration is not recommended. |
| **Tenofovir disoproxil** / rifampicin | Tenofovir AUC ↓ 13% | No dose adjustment required. |
| **Abacavir /** rifampicin | Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation. | Efficacy of abacavir should be closely monitored in co-treatment. |
| *Non-nucleoside analogues*<br>**Efavirenz** / rifampicin | Efavirenz AUC ↓ 26% | When co-treating with [TB068 trade name], it may be considered to increase the efavirenz dose to 800 mg q.d. |
| **Nevirapine** / rifampicin | nevirapine: AUC ↓ 58% | Since neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established, concomitant use of [TB068 trade name]and nevirapine is not recommended. |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| **Etravirine /** rifampicin | Rifampicin is likely to significantly reduce exposure to etravirine. | Co-treatment of [TB068 trade name]and etravirine should be avoided. |
| *Protease inhibitors*<br>**Fosamprenavir /** rifampicin<br>**Saquinavir**<br>**Indinavir**<br>**Ritonavir**<br>**Lopinavir**<br>**Atazanavir**<br>**Tipranavir**<br>**Darunavir**<br>**Boceprevir** | Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to dose adjust by increased doses, or an increase in ritonavir-boosting, have been ineffective or ill-tolerated with a high rate of hepatotoxicity. | [TB068 trade name]must not be co-administered with HIV or HCV protease inhibitors (see section 4.3). |
| *Others* | | |
| **Raltegravir** / rifampicin | Raltegravir AUC ↓ 40% | Co-treatment should be avoided. If deemed necessary, consider an increase of the raltegravir dose to 600 mg b.i.d. |
| **Dolutegravir / rifampicin** | Dolutegravir AUC ↓ 54% | A dose adjustment of dolutegravir to 50 mg twice daily is recommended when coadministered with [TB068 trade name]in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided. |
| **Elvitegravir/cobicistat/**rifampicin | Coadministration has not been studied. Rifampicin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect. | Coadministration is contraindicated. |
| **Maraviroc** / rifampicin | Maraviroc AUC ↓ 63% | Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d. |
| *Antivirals Hepatitis C-infection* | | |
| **Daclatasvir**<br>**Elbasvir/Grazoprevir**<br>**Glecaprevir/Pibrentasvir**<br>**Ledipasvir/Sofosbuvir**<br>**Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)**<br>**Simeprevir** | <u>Rifampicin</u>:<br>Coadministration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifampicin and hence to | Coadministration of [TB068 trade name] with these antivirals is contraindicated (for further details see Summary of product characteristics of the drugs for therapy of HCV). |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| **Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/**<br><br>Rifampicin<br>Isoniazid | reduce their therapeutic effect.<br><br><u>Isoniazid:</u><br>Coadministration has not been studied. Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal hepatitis associated with isoniazid therapy may develop even after many months of treatment. | |
| *Antifungals* | | |
| **Ketoconazole** / rifampicin | Ketoconazole AUC ↓ 80% | Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required. |
| **Fluconazole** / rifampicin | Fluconazole AUC ↓ 23% | Monitor therapeutic effect.. An increased dose of fluconazole may be required. |
| **Itraconazole** / rifampicin | Itraconazole AUC ↓ >64-88% | Co-administration should be avoided. |
| **Voriconazole /** rifampicin | Voriconazole AUC ↓ 96% | Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin. |
| *Antibacterials/Antituberculotics* | | |
| **Clarithromycin /** rifampicin | Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged. | Co-administration should be avoided. |
| **Chloramphenicol /** rifampicin | Case reports indicate >60-80% reduction of chloramphenicol exposure. | Co-administration should be avoided. |
| **Ciprofloxacin /** rifampicin | No significant interaction | No dose adjustment required. |
| **Doxycyclin** / rifampicin | Doxycyclin AUC ↓ 50-60% | If co-treatment is considered necessary, the dose of doxycyclin should be doubled. |
| **Metronidazole** / rifampicin | Metronidazole AUC i.v.↓ 33% | The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored. |

| **Drugs by Therapeutic Area** | **Interaction** | **Recommendations concerning co-administration** |
|---|---|---|
| **Sulfamethoxazole** / rifampicin | Sulfamethoxazole AUC ↓ 23% | Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored. |
| **Trimethoprim** / rifampicin | Trimethoprim AUC ↓ 47% | A dose increase of trimethoprim may be required. Efficacy should be monitored. |
| **Ethionamide /** rifampicin | | Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity. |
| *Antimalarials* | | |
| **Chloroquine /** rifampicin | | Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. Co-administration should be avoided. |
| **Atovaquone** / rifampicin | Atovaquone AUC ↓ 50%<br>Rifampicin AUC ↑ 30% | Co-administration should be avoided. |
| **Mefloquine** / rifampicin | Mefloquine AUC ↓ 68% | Co-administration should be avoided. |
| **Amodiaquine /** rifampicin | 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 /** rifampicin | Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates. | Co-administration should be avoided. If co-administration is deemed necessary, an increased dose of quinine should be considered. |
| **Lumefantrine** / rifampicin | Lumefantrine AUC ↓ 68% | Co-administration should be avoided. |
| **Artemisinin and its derivatives /** rifampicin | Artemether AUC ↓ 89%<br>Dihydroarthemisinin AUC ↓ 85% | Co-administration should be avoided. |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| **ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS** | | |
| **Morphine /** rifampicin | Morphine AUC p.o ↓ 30%, loss of analgesic effect. | Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased. |
| **Codeine /** rifampicin | Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced. | Efficacy should be monitored and codeine dose increased if necessary. |
| **Methadone /** rifampicin | Methadone AUC ↓ 33-66% | Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).. |
| **Acetaminophen (paracetamol)** / rifampicin / isoniazid | 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. Concurrent use with isoniazid may increase hepatotoxicity. | Co-administration of [TB068 trade name]and acetaminophen (paracetamol) should be avoided. |
| **ANTICONVULSANTS** | | |
| **Carbamazepine /** rifampicin / isoniazid | Rifampicin is expected to decrease the serum concentration of carbamazepine whereas isoniazid may increase them. Neurological side effects and the. risk of hepatotoxicity increase when co-treating with carbamazepine. | Co-administration of [TB068 trade name]and carbamazepine should be avoided. |
| **Phenobarbital** / rifampicin / isoniazid | Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isonazid may increase the risk of hepatotoxicity. | Co-administration of [TB068 trade name]and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations. |
| **Phenytoin** / rifampicin isoniazid | Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid | Co-treatment with phenytoin and [TB068 trade name]should be avoided. |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| | may result in an increased risk of hepatotoxicity. | |
| **Valproic acid** / rifampicin | 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. | Co-treatment should be avoided. If deemed necessary, efficacy and, if possible, also plasma concentrations of valproic acid, should be carefully monitored. |
| **Lamotrigine /** rifampicin | Lamotrigine AUC ↓ 45% | Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate. |
| **IMMUNOSUPPRESSIVES** | | |
| **Cyclosporine /** rifampicin | Several studies and case reports have shown substantially increased cyclosporine clearance when co-administered with rifampicin. | Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required). |
| **Tacrolimus /** rifampicin<br>**Sirolimus**<br>**Everolimus** | Tacrolimus AUC i.v. ↓ 35%;<br>AUC p.o ↓ 6870%<br>Sirolimus AUC ↓ 82%<br>Everolimus AUC ↓ 63% | Co-administration of [TB068 trade name] and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored, and the dose increased as appropriate. |
| **CARDIOVASCULAR MEDICINES** | | |
| **Warfarin /** rifampicin /isoniazid | Warfarin AUC ↓ 85%<br>Isoniazid may inhibit hepatic metabolism of warfarin. | Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifampicin treatment. |
| **Atenolol /** rifampicin | Atenolol AUC ↓ 19% | No dose adjustment required. |
| **Verapamil /** rifampicin | S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold | [TB068 trade name]and verapamil per-orally should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required. |
| **Digoxin** / rifampicin | AUC p.o ↓ 30% | When co-administering [TB068 trade name]with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required. |
| **Lidocaine**. / rifampicin | Lidocaine CLi.v. ↑ 15% | No dose adjustment required |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| **Amlodipine /** rifampicin | Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin. | Efficacy should be monitored. |
| **Enalapril** / rifampicin | No interaction expected | No dose adjustment required. |
| **Simvastatin /** rifampicin | Simvastatin AUC ↓ 87%<br>Simvastatin acid AUC ↓ 93% | Co-administration is not recommended. |
| **Atorvastatin / rifampicin** | Atorvastatin AUC ↓ 80% | Co-administration is not recommended |
| **GASTROINTESTINAL MEDICINES** | | |
| **Ranitidine /** rifampicin | Ranitidine AUC ↓ 52% | Efficacy should be monitored, and ranitidine dose increased if necessary. |
| **Antacids** / isoniazid / rifampicin | Antacids may reduce the bioavailability of rifampicin by up to one third.<br><br>Aluminium hydroxide impairs the absorption of isoniazid. | The clinical importance is unknown.<br><br>Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used, if co-treatment with [TB068 trade name]is necessary. |
| **PSYCHOTHERAPEUTIC MEDICINES** | | |
| **Diazepam /** rifampicin / isoniazid<br>**Midazolam**<br>**Triazolam**<br>**Alprazolam**<br>**Nitrazepam** | Diazepam AUC ↓ >70%<br>Midazolam AUC ↓ 98%<br>Triazolam AUC ↓ 95%<br>Alprazolam AUC ↓ 88%<br>Reduced nitrazepam through concentrations, increased clearance. | Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals. |
| **Zolpidem** / rifampicin<br>**Zopiclone** /rifampicin | Zolpidem AUC ↓73%<br>Zopiclone AUC ↓82% | Co-administration should be avoided. |
| **Chlorpromazine /** rifampicin / isoniazid | Rifampicin may reduce chlorpromazine exposure. Also, concomitant use of chlorpromazine with isoniazid may impair the metabolism of isoniazid. | Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity. |
| **Haloperidol /** rifampicin<br>**Clozapine** | Haloperidol clearance is substantially increased by rifampicin, theoretical considerations imply that same applies to clozapine. | If co-treatment of [TB068 trade name]with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required. |
| **Amitriptyline /** rifampicin<br>**Nortriptyline** | Case reports (supported by theoretical considerations) | Co-treatment should be avoided. If necessary, monitor for clinical |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| | suggest that rifampicin considerably increases clearance of tricyclic antidepressants.. | response, side effects, and, if possible, plasma concentrations.. |
| **HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES** | | |
| **Prednisolone /** rifampicin **And other systemically administered corticosteroids** | Prednisolone AUC ↓ 66%<br><br>Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin. | Co-administration of [TB068 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** / rifampicin **Glimepiride** **Repaglinide** | Glibenclamide AUC ↓ 39%<br>Glimepiride AUC ↓ 34%<br>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 /** rifampicin | Case reports indicate that rifampicin may decrease the effect of levothyroxine. | TSH levels should be monitored. |
| **Ethinylestradiol** / rifampicin | Ethinylestradiol AUC ↓ 66% | Co-adminstration with [TB068 trade name]may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used. |
| **Norethindrone /** rifampicin | Norethindrone AUC ↓ 51% | Co-administration with [TB068 trade name]may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used. |
| **OTHERS** | | |
| **Praziquantel** / rifampicin | Praziquantel AUC ↓ 80-99% | Co-treatment with [TB068 trade name]should be avoided. |
| **Disulfiram /** isoniazid | Concurrent use of disulfiram together with isoniazid may result in increased incidence of adverse effects on the central nervous system. | Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB068 trade name]. |

| Drugs by Therapeutic Area | Interaction | Recommendations concerning co-administration |
|---|---|---|
| **Theophylline** / Isoniazid / Rifampicin | Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of combination are unknown. | Theophylline dose adjustment may be needed. |
| **Enflurane /** Isoniazid | Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane. | Coadministration of [TB068 trade name] with enflurane should be avoided. |

*Interactions with food and drink*:

Alcohol: concurrent daily use of alcohol may result in an increased incidence of isoniazid induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages (see section 4.4).

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.

*Interactions with laboratory tests*:

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

## 4.6 Fertility, pregnancy and breastfeeding

Pregnancy:

At very high doses in animals rifampicin has been shown to have teratogenic effects. There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, [TB068 trade name] should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. When [TB068 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.

Lactation

Rifampicin and isoniazid are excreted into the breast milk of lactating mothers. However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants. No adverse effects in the baby have been reported.

Fertility

There are no data on the effects [TB068 trade name]on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility. Animal studies indicate no effects of rifampicin on fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of [TB068 trade name], especially the potential neurotoxicity of isoniazid, should be borne in mind when considering the patient's ability to drive or operate 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.

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects, and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. The majority of cases have occurred within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

Adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomized controlled trials, but on published literature data, generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Nervous system disorders
Very common: Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4),
Uncommon: headache, lethargia, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy,
Not known: tremor, vertigo, insomnia, hyperreflexia.

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

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

Hepatobiliary disorders:
Very common: Transient increases of serum transaminases,
Uncommon: Increases of serum bilirubin and alkaline phosphatases, hepatitis.

Renal and urinary disorders
Rare: acute renal failure, interstitial nephritis,
Not known: urinary retention.

Metabolic and nutrition disorders
Very rare: aggravated porphyria,
Not known: hyperglycaemia, metabolic acidosis, pellagra, decreased appetite.

General disorders
Very common: Flushing,
Common: Reddish discolouration of body fluids and –secretions, such as urine, sputum, tears, saliva and sweat,
Not known: allergic reactions with skin manifestations, pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome, hypotension, shock.

Blood and lymphatic systems disorders
Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis.

Musculoskeletal disorders
Not known: Arthralgia, myalgia.

Skin and subcutaneous tissue disorders:
Common: Erythema, exanthema, pruritus with or without rash, urticaria.
Rare: photosensitivity reaction, exfoliative dermatitis, pemphigoid reactions, purpura.
Not known: Lyell's Syndrome, Stevens-Johnson Syndrome, sweat discoloration.

Eye disorders:
Common: Ocular redness, permanent discolouration of soft contact lenses,
Rare: Exudative conjunctivitis,
Not known: Optic atrophy or neuritis, tear discoloration.

Reproductive system and breast disorders
Common: Disturbances of the menstrual cycle.
Not known: Gynaecomastia

Vascular disorders:
Not known: Shock, flushing, vasculitis

Investigations:
Common: Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased
Not known: Blood pressure decreased, blood creatinine increased, hepatic enzyme increased

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

## 4.9 Overdose

Symptoms:
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances have occurred within 30 minutes to 3 hours after ingestion of isoniazid. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

When overdosed, rifampicin may cause a reddish-orange discolouration of the skin ('red man syndrome'). Further symptoms include facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14 g has caused cardiopulmonary arrest.

Treatment:
Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram per gram basis, equal to the isoniazid dose, if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. There is no

specific antidote. Treatment is symptomatic and supportive with special attention to monitoring/support of ventilation and correction of metabolic acidosis.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis
ATC Code: J04AM02.

*Mechanism of action*

In vitro, rifampicin is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis.* The mode of action is by inhibition of DNA-dependent RNA polymerase, inhibiting transcription. In tuberculosis, rifampicin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance may occur, and is a result of alterations in the target enzyme (RNA polymerase).

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids, which are unique constituents of the mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

## 5.2 Pharmacokinetic properties

The absorption characteristics of [TB068 trade name] have been determined after administration of tablets of [TB068 trade name] in healthy volunteers in the fasting state as follows:

| **Pharmacokinetic variable** | **Mean value ± standard deviation** (*) | |
|---|---|---|
| | **Rifampicin** | **Isoniazid** |
| Maximum concentration ($C_{max}$) ng/ml | 12232 ± 3129 (11866) | 4649 ± 1713 (4313) |
| Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.hour/ml | 91952 ± 22974 (89462) | 15719 ± 7973 (13539) |
| Time to attain maximum concentration ($t_{max}$) hour | 3.60 ± 0.93 | 0.68 ± 0.55 |

*geometric mean

| | **Rifampicin** | **Isoniazid** |
|---|---|---|
| **Absorption** | | |
| Absolute bioavailability | 90 − 95% | NA* |
| Oral bioavailability | > 90% | > 80% |
| Food effect | No effect on extent of absorption. Rate of absorption is reduced. | Reduced. |
| **Distribution** | | |
| Volume of distribution (mean) | 55 L | 43 L |
| Plasma proteinbinding *in vitro* | 60 − 90% | < 10% |
| Tissue distribution | CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma.<br><br>Concentrations in liver, spleen, kidneys and lung tissue are higher than serum concentrations.<br><br>Penetrates into vaginal and cervical tissue and into cervicovaginal fluid.<br><br>Passes the placenta; serum concentration in fetes are about 1/3 of those in mother. | It diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). It crosses the placenta and is secreted in the milk. |
| **Metabolism** | | |
| General | Primarily hepatic, rapidly deacetylated. | Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid |
| Active metabolite(s) | 25-o-deacetyl rifampicin | Nicotinoyl-NAD adduct |
| **Elimination** | | |
| Elimination half life | 3 − 5 hours<br>Decreases to 2 − 3 hours after repeated administration | 1.2 hours: rapid acetylators<br>3.5 hours: Slow acetylators |
| Mean systemic clearance (Cl/F) | 5.7 − 9 .0 L/hour | 15.5 L/hour: slow NAT2 genotype<br><br>26.1 L/hour: rapid/intermediate NAT2 genotype |
| % of dose excreted in urine | 30% | 75 − 95% |
| % of dose excreted in faeces | 60 − 65% | <10% |
| **Pharmacokinetic linearity** | Non linear | NA* |
| **Drug interactions *(in vitro*)** | Rifampicin induces hepatic enzymes | Isoniazid is CYP450 inducer and inhibitor.<br><br>Isoniazid is a arylamine n-acetyltransferase 2 substrate and inhibitor |
| Transporters | Solute carrier transporters (SLC)<br>ATP Binding Cassette transporters (ABC)<br>P-glycoprotein 1 | NA* |

| | | |
|---|---|---|
| Metabolizing enzymes | CYP450 | CYP450: 2C19, 3A4 |

*Pharmacokinetics of Rifampicin and Isoniazid*

*NA information not available

**Special populations**

*Rifampicin*

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 rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900 mg oral dose of rifampin 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, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 mcg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the t1/2 of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

*Isoniazid*

In slow acetylators with severely impaired renal function, accumulation of isoniazid may occur.

An impaired liver function prolongs the elimination half-life of isoniazid.

## 5.3 Preclinical safety data

*Rifampicin*

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

Because of only limited evidence available for the carcinogenicity of rifampicin in mice and the absence of epidemiological studies, no evaluation of the carcinogenicity of rifampicin to humans can be made.

The available studies on mutagenicity indicate an absence of a mutagenic effect.

Rifampicin concentrations in cord blood reach 12-33% of maternal blood concentrations.
Teratogenic effects were noted in rodents treated with high doses. 100 to 150 mg/kg bw daily in rodents have been reported to cause cleft palate and spina bifida.
In rats neither fertility nor peri- or postnatal development was impaired.
Malformation and death in infants born to mothers exposed to rifampicin, were reported at the same frequency as in the general population.

*Isoniazid*

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Treatment of pregnant rats with isoniazid resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis impairment was observed in treated rats.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Core tablet:* Microcrystalline cellulose
Crospovidone
Pregelatinized starch
Ascorbic acid
Colloidal silicon dioxide
Magnesium stearate

*Film coat*: Hypromellose
Polyethylene glycol
Talc
Titanium dioxide
Colour iron oxide red
Simethicone

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

36 months

## 6.4 Special precautions for storage

**PVC/ PVDC Aluminum Blister pack and HDPE container** Store below 25°C, protected from excessive humidity. Protect from light.

**Cold form Alu/Alu Blister pack:** Store below 30°C, protected from excessive humidity. Protect from light.

## 6.5 Nature and contents of container

*Blister packs*

The primary packs are blister cards of 6 tablets (comprised of orange PVC/PVDC foil sealed with aluminium foi1 lid). Such 15 blister cards are packed in a carton with one pack insert.

Pack size: 15 x 6 Tablets.

The primary packs are blister cards of 28 tablets (comprised of green PVC/PVDC foil sealed with aluminium foil lid). Such 24 interlocked blister cards are packed in a carton with one partition after 12 cards and one insert in each partition.

Pack size: 24 x 28 Tablets.

Cold form Alu/Alu blister pack (Laminated aluminium foil, one side bright and shinning, the other side relatively dull for cold forming blister pack).

The primary packs are blister cards of 28 tablets Such 24 blisters kept in a carton with one pack insert.

Pack size: 24 x 28Tablets

The primary packs are blister cards of 28 tablets (comprised of PVC/PE/PVDC foil sealed with aluminium foil lid). Such 24 blister cards are packed in a carton.

Pack size: 24 x 28 Tablets

*Bottle pack*

Tablets are packed in a sealed polypropylene bag, which is packed inside a white HDPE container together with one, a 1 gram silica gel bag with foam on top of the bag and the container is sealed with aluminium tagger. An insert is placed above the container and is shrink wrapped.

Pack size: 1000 Tablets.

### 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

Lupin Ltd
Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
Mumbai 400055
India

## 8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB068

## 9. DATE OF PREQUALIFICATION

19 December 2003

## 10. DATE OF REVISION OF THE TEXT

September 2021

Section 6 was updated in August 2023

**General references**

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*Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines*