

## 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.*

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\*[https://extranet.who.int/prequal/sites/default/files/document\\_files/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[TB309 trade name]<sup>†</sup>

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 50 mg isoniazid, 150 mg pyrazinamide and 75 mg rifampicin

*Excipients with potential clinical effect*

Each tablet contains 3.13 mg aspartame.

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Brick-red, mottled, circular, uncoated biconvex tablets having a deep score on one side and a plain surface on the other side.

The score line is not intended for breaking the tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[TB309 trade name] is indicated in children weighing less than 25 kg, for the initial treatment of non-severe tuberculosis (TB) due to drug-susceptible *Mycobacterium tuberculosis*.

Non-severe TB is peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.

[TB309 trade name] is also indicated in combination with other medicine(s), in infants and children weighing less than 25 kg, for the initial treatment of drug-susceptible *M. tuberculosis* tuberculosis that does not meet the criteria for non-severe TB.

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

This product is intended for use in children. Nonetheless, safety information is provided for adult health issues such as liver disease, pregnancy and breast-feeding, to allow full access to all relevant information.

### 4.2 Posology and method of administration

#### *Posology*

Recommended doses for initial (intensive phase) treatment in children weighing less than 25 kg:

Patients' weight	Dose
4 to less than 8 kg	1 tablet once daily
8 to less than 12 kg	2 tablet once daily
12 to less than 16 kg	3 tablets once daily
16 to less than 25 kg	4 tablets once daily
25 kg or more	Adult dosages recommended

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

Initial (intensive phase) treatment with [TB309 trade name] is normally given for 2 months, which is generally followed by treatment with isoniazid and rifampicin (continuation phase). The duration of treatment depends on the regimen selected.

[TB309 trade name] should not be used for intermittent treatment regimens.

Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants.

If one of the active ingredients of this medicine needs to be discontinued or if the dose needs to be reduced, then separate preparations of the ingredients (isoniazid, pyrazinamide, and rifampicin) should be used.

Supplementation with pyridoxine (vitamin B<sub>6</sub>) may be considered, especially in malnourished individuals, children and those living with HIV (see section 4.4).

#### *Renal impairment*

Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance  $\leq 50$  mL/minute), it is recommended that separate preparations of isoniazid, pyrazinamide, and rifampicin be used (see section 4.4).

#### *Hepatic impairment*

Limited data indicate that the pharmacokinetics of isoniazid and rifampicin are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. [TB309 trade name] must not be used in patients with a history of acute liver disease (see section 4.3).

#### *Children, adolescents and patients weighing 25 kg or more*

For these patients, alternative formulations containing higher amounts of isoniazid, pyrazinamide and rifampicin are more suitable and should be used.

#### *Elderly*

No special dosage regimen is necessary, but hepatic or renal insufficiency should be considered.

Supplementation of pyridoxine (vitamin B<sub>6</sub>) may be useful.

#### ***Interruption of treatment***

If treatment with [TB309 trade name] is interrupted for any reason including non-adherence, the product should **not** be used for resuming treatment. Isoniazid, pyrazinamide and rifampicin must be administered separately for the resumption of treatment because rifampicin needs to be reintroduced at a lower dose. Official guidance should be consulted on the resumption of treatment with tuberculosis medicines.

#### ***Method of administration***

For oral use.

[TB309 trade name] should be given as a single daily dose on an empty stomach (at least 1 hour before or 2 hours after a meal). Absorption may be reduced if taken with food e.g., to improve gastrointestinal tolerance.

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in 10 mL of water.

#### *Instructions for use*

1. The required amount of drinking water should be taken in a small and clean cup and the required number of tablets should be added.
2. The cup should be gently swirled until tablets disperse, and the entire mixture should be given immediately by syringe.
3. The cup should be rinsed with a little additional water, and this should be drunk by the patient to ensure the entire dose is taken.

### **4.3 Contraindications**

Hypersensitivity to rifamycins, isoniazid, pyrazinamide or any of the excipients listed in section 6.1.

- Acute liver disease
- A history of drug-induced liver disease caused by rifampicin or isoniazid
- Porphyria
- Gouty arthritis or hyperuricemia
- Severe renal impairment (creatinine clearance less than 30 mL/minute). See section 4.4.
- Co-administration of [TB309 trade name] with HIV protease inhibitors, elvitegravir/cobicistat, nevirapine, rilpivirine, etravirine, doravirine, bicitgravir, emtricitabine/tenofovir alafenamide, artemisinin & its derivatives, or direct-acting antivirals for chronic hepatitis C or voriconazole. (See section 4.4).

#### 4.4 Special warnings and precautions for use

##### **Warnings**

Where the patient's acetylation phenotype is known, patients with extremely fast or extremely slow acetylating capability should receive the three components separately in order to facilitate dose adjustment of isoniazid.

In exceptional cases, rifampicin may provoke severe hypersensitivity reactions such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock or renal failure. [TB309 trade name] should be withdrawn immediately if severe acute hypersensitivity reactions occur. Patients who develop such reactions must never again be treated with rifampicin.

[TB309 trade name] should also be withdrawn if other signs of hypersensitivity appear, such as fever or skin reactions. For safety reasons, treatment should not be continued or resumed with rifampicin.

##### **Precautions**

The precautions for the use of [TB309 trade name] are the same as those that apply for the administration of rifampicin, isoniazid and pyrazinamide as individual medicinal products.

Patients should be advised against interrupting treatment except as indicated by their health care provider (e.g., pending clinical evaluation if visual disturbances occur).

##### *Impaired liver function, undernourishment, alcoholism*

Rifampicin, isoniazid and pyrazinamide are metabolised in the liver. Elevated transaminase levels, above the upper limit of normal (ULN), commonly occur. Liver dysfunction that may occur in the first few weeks of treatment usually returns to the normal range spontaneously, without interruption of treatment, and usually by the third month of treatment.

With rifampicin, although slight elevations of liver enzymes are common, clinical jaundice or evidence of hepatitis are rare. In patients taking both isoniazid and rifampicin, a cholestatic pattern with elevated alkaline phosphatase suggests that rifampicin is the cause, whereas a rise in transaminases may be caused by isoniazid, or rifampicin, or pyrazinamide, or the combination of the three.

Patients with impaired liver function should be treated with caution and under strict medical supervision.

In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT/ALAT) and serum glutamic oxaloacetic transaminase (SGOT/ASAT) should be carried out prior to therapy and repeated weekly or fortnightly during therapy. If signs of hepatocellular damage occur, [TB309 trade name] should be withdrawn.

A moderate rise in bilirubin and/or transaminase levels is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating these liver function tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Interrupting isoniazid treatment is recommended when there is clinical jaundice or transaminases exceeding 3 times the ULN. The fixed drug combination, [TB309 trade name], should be replaced by individual component formulations of rifampicin, isoniazid and pyrazinamide in order to facilitate treatment in these clinical circumstances.

Withdrawing rifampicin and pyrazinamide is recommended if liver function does not return to normal or transaminases exceed 5 times the ULN. The fixed drug combination, [TB309 trade name], should be replaced by individual component formulations in order to facilitate treatment in these clinical circumstances.

Use of isoniazid should be carefully monitored in patients with chronic liver disease. Severe and sometimes fatal hepatitis caused by isoniazid may occur and may develop even after many months of treatment. Hepatotoxicity associated with isoniazid therapy (thought to be caused by the metabolite diacetylhydrazine) is rare in patients up to 20 years of age, but more common with increasing age and affecting up to 3% of patients aged over 50 years. The incidence of severe hepatotoxicity can be minimised by careful monitoring of liver function. Patients should be monitored for prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs of hepatic damage are detected, treatment should be discontinued promptly. Continued use of [TB309 trade name] in these patients may cause a more severe form of liver damage.

[TB309 trade name] is not suitable for patients with chronic liver disease, or in chronic alcoholics and undernourished patients, if the dosage of rifampicin, isoniazid and pyrazinamide needs to be adjusted separately.

For undernourished or elderly patients, supplementation with pyridoxine (vitamin B<sub>6</sub>) may be useful, because isoniazid in high doses can lead to pyridoxine deficiency. Pyridoxine supplementation is recommended in malnourished children and adolescents, in those who are pregnant and those living with HIV, at a dosage of 0.5–1 mg/kg daily, increased to 2–5 mg/kg daily if peripheral neuropathy develops.

#### *Impaired renal function*

In severe renal insufficiency, the elimination of isoniazid and pyrazinamide can be delayed, leading to a higher systemic exposure and a potential increase in adverse events. [TB309 trade name] should be used with caution in patients with moderate renal impairment (creatinine clearance 30–60 mL/minute).

#### *Gout*

Pyrazinamide should be used with caution in patients with a history of gout. Regular monitoring of serum uric acid should be undertaken. [TB309 trade name] treatment should be stopped in gouty arthritis.

#### *Haematology*

Full blood count should be monitored during prolonged treatment and in patients with hepatic disorders. Rifampicin should be withdrawn permanently if thrombocytopenia or purpura occur. The possibility of pyrazinamide having an undesirable effect on blood clotting time or vascular integrity should be borne in mind in patients with haemoptysis.

#### *Diabetes mellitus*

Increased difficulty has been reported in controlling diabetes mellitus when such patients are given isoniazid.

#### *Epilepsy*

Patients suffering from convulsive disorders must be kept under special observation during treatment with [TB309 trade name] because of the neurotoxic effects of isoniazid.

#### *Neuropathy*

Caution should be exercised in subjects with peripheral or optic neuritis. Regular neurological examination is necessary, with special care in patients with a history of alcohol abuse. Use of pyridoxine (vitamin B<sub>6</sub>) may prevent or diminish neuropathy due to isoniazid treatment especially in elderly and in malnourished patients, and patients living with HIV. Pyridoxine should be given in line with official guidelines.

#### *Psychosis*

Isoniazid-containing medicines should be used with caution in patients with a history of psychosis.

#### *Contraception*

Additional non-hormonal means of contraception must be employed to prevent the possibility of pregnancy during treatment with rifampicin (see section 4.5).

### *Alcohol*

Patients should abstain from alcohol while receiving treatment with [TB309 trade name].

### *Laboratory tests*

Full blood counts, liver function tests (SGPT/ALAT, SGOT/ASAT), renal function tests and monitoring serum uric acid should be performed before treatment and at regular intervals during treatment.

### *Discolouration of body fluids*

[TB309 trade name] may cause a reddish-orange discolouration of body fluids and/or fluids, e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid. This is due to rifampicin, and does not require medical attention. In addition, contact lenses or dentures may be permanently stained red-orange.

### *Concomitant medications*

Rifampicin is a potent inducer of the cytochrome P450 system and may increase the metabolism of concomitantly administered drugs resulting in subtherapeutic plasma levels and a lack of effect. Drugs that are eliminated by hepatic metabolism should only be used concomitantly with [TB309 trade name] if the plasma level or clinical response and undesirable effects can be monitored and the dose can be adequately adjusted (see section 4.5).

Rifampicin has enzyme inducing properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

### *Excipients*

[TB309 trade name] contains a small amount of aspartame. Aspartame is a source of phenylalanine. It may be harmful if the patient has phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

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**

### ***Influence of other medicinal products on [TB309 trade name]***

Antacids reduce the bioavailability of rifampicin and isoniazid. To avoid this interaction, [TB309 trade name] should be taken at least 1 hour before antacids. Corticosteroids can reduce the plasma levels of isoniazid, by increasing its metabolic and/or renal clearance.

### ***Influence of [TB309 trade name] on other medicinal products***

**Rifampicin** is a very potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system (especially the CYP3A and CYP2C subfamilies). Rifampicin is likely to *accelerate elimination* of co-administered drugs that undergo biotransformation through these metabolic pathways. Rifampicin also induces UDP-glucuronyltransferase, another enzyme involved in the metabolism of several drugs. This can result in subtherapeutic plasma levels of co-administered drugs, with a decreased or even a loss of effect.

These effects approach their maximum after about 10 days of treatment, and gradually return to normal in 2 or more weeks after discontinuation. This must be taken into account when co-administering other drugs. To maintain optimum therapeutic blood levels, doses of drugs metabolised by these enzymes may require adjustment when starting or stopping the concomitant administration of [TB309 trade name].

In vitro, **isoniazid** inhibits CYP2C19 and CYP3A4. Thus, it may *reduce elimination* and increase blood levels of drugs mainly eliminated through either of these pathways. However, when given with rifampicin, as when using [TB309 trade name], these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. The net effect on drugs affected in opposite ways by rifampicin and isoniazid (such as phenytoin, warfarin and theophylline) is hard to predict and may change over time.

Concurrent use of isoniazid with other hepatotoxic or neurotoxic medicines may increase the hepatotoxicity and neurotoxicity of isoniazid and should be avoided.

**Pyrazinamide** may also potentiate the hepatotoxicity of other medicines given concomitantly. Use with probenecid and sulfinpyrazone should preferably be avoided, due to complex pharmacokinetic and pharmacodynamic interactions that may affect both medicines. Pyrazinamide inhibits urate elimination, and also antagonises the effect of allopurinol and sulfinpyrazone.

Thus, mainly due to rifampicin, [TB309 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 medicines, no interaction data with rifampicin are available. However, clinically significant reductions in drug exposure may occur.

Whenever co-prescribing any drug together with [TB309 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with [TB309 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	Interaction	Recommendations on co-administration
<b>INFECTION</b>		
<i>Antiretrovirals</i>		
<i>Nucleoside analogues</i> <b>Zidovudine</b> / 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.
<b>Didanosine</b> <b>Emtricitabine</b> <b>Lamivudine</b>	No interaction expected	No dose adjustment required.
<b>Stavudine</b> / isoniazid	There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine.	Co-administration is not recommended.
<b>Tenofovir alafenamide/emtricitabine</b> /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.	Co-administration is not recommended.
<b>Tenofovir disoproxil</b> / rifampicin	Tenofovir AUC ↓ 13%	No dose adjustment required.
<b>Abacavir</b> / 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.
<i>Non-nucleoside analogues</i> <b>Efavirenz</b> / rifampicin	Efavirenz AUC ↓ 26%	When co-treating with [TB309 trade name], increasing the efavirenz dose to 800 mg daily may be considered
<b>Nevirapine</b> / rifampicin	Nevirapine: AUC ↓ 58%	Concomitant use of [TB309 trade name] and nevirapine is contraindicated.
<b>Etravirine</b> / rifampicin	Rifampicin is likely to significantly reduce exposure	Co-treatment of [TB309 trade name] and etravirine is contraindicated.

Drugs	Interaction	Recommendations on co-administration
	to etravirine.	
<i>Protease inhibitors</i> <b>Atazanavir</b> / rifampicin <b>Darunavir</b> <b>Fosamprenavir</b> <b>Indinavir</b> <b>Lopinavir</b> <b>Ritonavir</b> <b>Tipranavir</b>	Protease inhibitors exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Increasing doses, or an increase in ritonavir-boosting, have been ineffective or ill-tolerated with a high rate of hepatotoxicity.	[TB309 trade name] must not be co-administered with protease inhibitors for treating HIV or hepatitis C virus infections (see section 4.3).
<i>Others</i> <b>Raltegravir</b> / rifampicin	Raltegravir AUC ↓ 40%	Co-treatment should be avoided. If deemed necessary, consider increasing the raltegravir dose to 600 mg twice daily
<b>Dolutegravir</b> / rifampicin	Dolutegravir AUC ↓ 54%	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with [TB309 trade name] in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
<b>Elvitegravir/cobicistat</b> /rifampicin	Co-administration 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.	Co-administration is contraindicated.
<b>Maraviroc</b> / rifampicin	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg twice daily.
<b>Antivirals for hepatitis C infection</b>		
<b>Daclatasvir</b> <b>Elbasvir/Grazoprevir</b> <b>Glecaprevir/Pibrentasvir</b> <b>Ledipasvir/Sofosbuvir</b> <b>Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)</b> <b>Simeprevir</b> <b>Sofosbuvir (with or without velpatasvir with or without voxilaprevir) /</b>  Rifampicin Isoniazid	<u><b>Rifampicin:</b></u> Co-administration has not been studied but is expected to decrease concentrations of these hepatitis C virus antivirals due to induction of CYP3A4 by rifampicin and hence to reduce their therapeutic effect.  <u><b>Isoniazid:</b></u> Co-administration has not been studied. Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal hepatitis	Co-administration of [TB309 trade name] with these antivirals is contraindicated (for further details see summary of product characteristics of antivirals for treating hepatitis C virus infection).



Drugs	Interaction	Recommendations on co-administration
	associated with isoniazid may develop even after many months of treatment.	
<b>Antifungals</b>		
<b>Ketoconazole</b> / rifampicin /isoniazid	Ketoconazole AUC ↓ 80%	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
<b>Fluconazole</b> / rifampicin	Fluconazole AUC ↓ 23%	Monitor therapeutic effect. An increased dose of fluconazole may be required.
<b>Itraconazole</b> / rifampicin /isoniazid	Itraconazole AUC ↓ 64–88%	Co-administration should be avoided.
<b>Voriconazole</b> / rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
<b>Antibacterials/tuberculosis medicines</b>		
<b>Clarithromycin</b> / rifampicin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
<b>Chloramphenicol</b> / rifampicin	Case reports indicate 60–80% reduction of chloramphenicol exposure.	Co-administration should be avoided.
<b>Ciprofloxacin</b> / rifampicin	No significant interaction	No dose adjustment required.
<b>Dapsone</b> / rifampicin	Rifampicin increases dapsone clearance and the production of the hydroxylamine metabolite of dapsone which could increase the risk of methaemoglobinaemia, haemolytic anaemia, agranulocytosis, and haemolysis.	Co-administration should be avoided.
<b>Ethionamide</b> / rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
<b>Doxycycline</b> / rifampicin	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
<b>Metronidazole</b> / rifampicin	Metronidazole AUC i.v. ↓ 33%	The clinical relevance of the interaction is unknown. Dose adjustment is not routinely recommended. Efficacy should be monitored.
<b>Paraminosalicylic acid</b> / isoniazid / rifampicin	Tissue concentration of isoniazid may be enhanced, and adverse effects are more likely to appear.	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.

Drugs	Interaction	Recommendations on co-administration
<b>Sulfamethoxazole</b> / rifampicin	Sulfamethoxazole AUC ↓ 23%	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
<b>Trimethoprim</b> / rifampicin	Trimethoprim AUC ↓ 47%	A dose increase of trimethoprim may be required. Efficacy should be monitored.
<b>Antimalarials</b>		
<b>Chloroquine</b> / 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.
<b>Atovaquone</b> / rifampicin	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Co-administration should be avoided.
<b>Mefloquine</b> / rifampicin	Mefloquine AUC ↓ 68%	Co-administration should be avoided.
<b>Amodiaquine</b> / 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.
<b>Quinine</b> / 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.
<b>Lumefantrine</b> / rifampicin	Lumefantrine AUC ↓ 68%	Co-administration should be avoided.
<b>Artemisinin and its derivatives</b> / rifampicin	Artemether AUC ↓ 89% Dihydroarthemisinin AUC ↓ 85%	Co-administration is contraindicated.
<b>ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS</b>		
<b>Morphine</b> / 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.
<b>Codeine</b> / rifampicin	Plasma levels of morphine, the active metabolite of codeine, are likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary.
<b>Paracetamol (acetaminophen)</b> / rifampicin  / isoniazid	Rifampicin may increase the glucuronidation of paracetamol and decrease its efficacy. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive. Concurrent use	Co-administration of [TB309 trade name] and paracetamol should be avoided.

Drugs	Interaction	Recommendations on co-administration
	with isoniazid may increase hepatotoxicity.	
<b>Etoricoxib</b> / rifampicin	Rifampicin has been reported to produce a 65% decrease in etoricoxib plasma concentrations when given concomitantly.	Patients should be monitored for possible loss of analgesic effect; however, evidence to support an increase in analgesic dose is lacking.
<b>ANTIEPILEPTICS</b>		
<b>Carbamazepine</b> / rifampicin / isoniazid	Rifampicin is expected to decrease serum concentrations of carbamazepine whereas isoniazid may increase them. Neurological side effects and the risk of hepatotoxicity increase when co-treating with carbamazepine.	Co-administration of [TB309 trade name] and carbamazepine should be avoided.
<b>Phenobarbital</b> / rifampicin / isoniazid	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isoniazid may increase the risk of hepatotoxicity.	Co-administration of [TB309 trade name] and phenobarbital should be undertaken with caution, and the patient monitored for clinical effects and, if possible, plasma drug concentrations.
<b>Phenytoin</b> / rifampicin isoniazid	Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and [TB309 trade name] should be avoided.
<b>Valproic acid</b> / 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.
<b>Lamotrigine</b> / rifampicin	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
<b>IMMUNOSUPPRESSANTS</b>		
<b>Ciclosporin</b> / rifampicin	Several studies and case reports have shown substantially increased ciclosporin clearance when co-administered with rifampicin.	Co-administration should be avoided. If deemed necessary, plasma concentrations of ciclosporin should be monitored and doses adapted accordingly (3- to 5-fold increases in ciclosporin dose have been required).
<b>Tacrolimus</b> / rifampicin <b>Sirolimus</b> <b>Everolimus</b>	Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 70% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of [TB309 trade name] and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored,

Drugs	Interaction	Recommendations on co-administration
		and the dose increased as appropriate.
<b>CARDIOVASCULAR MEDICINES</b>		
<i>ACE inhibitors</i>		
<b>Enalapril</b> / rifampicin	No interaction expected	No dose adjustment required.
<i>Antiarrhythmics</i>		
<b>Lidocaine</b> / rifampicin	Lidocaine CL <sub>i.v.</sub> ↑ 15%	No dose adjustment required
<b>Verapamil</b> / rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	[TB309 trade name] and oral forms of verapamil should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required.
<b>Levodopa</b> /isoniazid	Isoniazid may reduce the therapeutic effects of levodopa	
<i>Anticoagulants</i>		
<b>Warfarin and other coumarin anticoagulants</b> / rifampicin /isoniazid	Warfarin AUC ↓ 85% Isoniazid may inhibit hepatic metabolism of warfarin.	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifampicin treatment.
<i>Beta blockers</i>		
<b>Atenolol</b> / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
<i>Calcium-channel blockers</i>		
<b>Amlodipine</b> / rifampicin	Amlodipine is metabolised by CYP3A; lower exposure of amlodipine and potentially other calcium- channel blockers is expected when co-treating with rifampicin.	Efficacy should be monitored.
<i>Cardiac glycosides</i>		
<b>Digoxin</b> / rifampicin	AUC p.o ↓ 30%	When co-administering [TB309 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
<i>Statins</i>		
<b>Simvastatin</b> / rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended.
<b>Atorvastatin</b> / rifampicin	Atorvastatin AUC ↓ 80%	Co-administration is not recommended
<b>GASTROINTESTINAL MEDICINES</b>		
<b>Ranitidine</b> / rifampicin	Ranitidine AUC ↓ 52%	Efficacy should be monitored, and ranitidine dose increased if necessary.

Drugs	Interaction	Recommendations on co-administration
<b>Antacids</b> / isoniazid / rifampicin	Antacids may reduce the bioavailability of rifampicin, isoniazid and ethambutol, in the former case by up to a third.  Aluminium hydroxide impairs the absorption of isoniazid.	Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used if co-treatment with [TB309 trade name] is necessary. [TB309 trade name] should be taken at least 1 hour before the antacid.
<b>PSYCHOTHERAPEUTIC MEDICINES</b>		
<i>Anxiolytics and hypnotics</i>		
<b>Diazepam</b> / rifampicin / isoniazid <b>Midazolam</b> <b>Triazolam</b> <b>Alprazolam</b> <b>Nitrazepam</b>	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.
<b>Zolpidem</b> / rifampicin <b>Zopiclone</b> / rifampicin	Zolpidem AUC ↓ 73% Zopiclone AUC ↓ 82%	Co-administration should be avoided.
<i>Antipsychotics</i>		
<b>Chlorpromazine</b> / 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.
<b>Haloperidol</b> / rifampicin <b>Clozapine</b>	Haloperidol clearance is substantially increased by rifampicin; theoretical considerations imply that same applies to clozapine.	If co-treatment of [TB309 trade name] with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
<i>Tricyclic antidepressants</i>		
<b>Amitriptyline</b> / rifampicin <b>Nortriptyline</b>	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.
<b>HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES</b>		
<i>Corticosteroids</i>		
<b>Prednisolone</b> <b>Other systemically administered corticosteroids</b> / rifampicin	Prednisolone AUC ↓ 66%  Also, for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of [TB309 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.

Drugs	Interaction	Recommendations on co-administration
<b>Antidiabetics</b>		
<b>Glibenclamide</b> / rifampicin <b>Gliclazide</b> <b>Glimepiride</b> <b>Repaglinide</b>	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.
<b>Insulin</b>	No interaction expected.	No dose adjustment required.
<b>Thyroid hormones</b>		
<b>Levothyroxine</b> / rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored.
<b>Hormonal contraceptives</b>		
<b>Ethinylestradiol</b> / rifampicin / pyrazinamide	Ethinylestradiol AUC ↓ 66%	Co-administration with [TB309 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
<b>Norethisterone (norethindrone)</b> / rifampicin	Norethisterone AUC ↓ 51%	Co-administration with [TB309 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
<b>OTHERS</b>		
<b>Disulfiram</b> / isoniazid	Concurrent use of disulfiram together with isoniazid may increase incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB309 trade name].
<b>Enflurane</b> / isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB309 trade name] with enflurane should be avoided.
<b>Methadone</b> / rifampicin	Methadone AUC ↓ 33-66%	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold)..
<b>Praziquantel</b> / rifampicin	Praziquantel AUC ↓ 80-99%	Co-treatment with [TB309 trade name] should be avoided.
<b>Theophylline</b> / 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.
<b>Typhoid vaccine, oral</b> / pyrazinamide	Antibiotics may inactivate oral typhoid vaccine	Avoid concomitant administration oral typhoid vaccine with [TB309 trade name]

### ***Interactions with food***

Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), which can reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, and hypotension. Patients should therefore be advised against ingesting foods rich in tyramine and/or histamine, such as cured meat, some cheeses (e.g., matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).

### ***Interactions with diagnostic tests***

Rifampicin can delay the biliary excretion of contrast media during gallbladder radiographic examination.

Microbiological methods used to determinate folic acid and cyanocobalamin (vitamin B<sub>12</sub>) plasma concentrations cannot be used during rifampicin treatment as rifampicin is in competition with bilirubin and BSP. To avoid false positive reactions, BSP test should be carried out the morning before rifampicin administration.

## **4.6 Fertility, pregnancy and breastfeeding**

### ***Pregnancy***

There are no or limited amount of data from the use of rifampicin in pregnant women. Studies on rifampicin in animals have shown reproductive toxicity (see section 5.3).

No adverse effects of isoniazid or pyrazinamide on the fetus have been reported. Use of rifampicin in the third trimester has been associated with postnatal haemorrhages in the mother and infant.

[TB309 trade name] can be used in pregnancy if the benefits are considered to outweigh the risks. The treatment of TB in pregnant women is the same as for non-pregnant women. As maternal TB increases the risk of vertical transmission of HIV, TB treatment must be started promptly to prevent transmission.

If [TB309 trade name] is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Supplemental pyridoxine (vitamin B<sub>6</sub>) may be advised in pregnant adolescents (see section 4.4).

### ***Breastfeeding***

Rifampicin, isoniazid and pyrazinamide appear in human milk. 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 effects on the breastfed newborns/infants are anticipated.

[TB309 trade name] can be used during breast-feeding.

### ***Fertility***

No human data on the effect of [TB309 trade name] on fertility are available. Animal studies indicate that co-administration of rifampicin, isoniazid and pyrazinamide has effects on fertility (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

[TB309 trade name] has minor to moderate influence on the ability to drive and use machines.

The clinical status of the patient and the adverse reaction profile of [TB309 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery. In particular, neurotoxicity associated with isoniazid, may impair the patient's ability to drive or operate machinery.

## **4.8 Undesirable effects**

The most important adverse reactions of [TB309 trade name] are hepatotoxicity, neurotoxicity and effects on vision, due to the components of the fixed-dose combination.

The most important adverse reactions caused by *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.

The most important adverse effect of *pyrazinamide* is liver damage, ranging from asymptomatic increases of serum transaminases to symptomatic liver dysfunction, and in rare cases also fatal liver failure.

Various cardiorespiratory adverse events have been reported with the use of the triple combination of isoniazid / pyrazinamide / rifampicin. These include tightness in chest, coughing, diffuse chest pain, haemoptysis, angina, palpitation and total pneumothorax.

#### *Tabulated list of adverse reactions*

In the tables below, ADRs are listed under system organ class (SOC) and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10\,000$  to  $< 1/1000$ ), very rare ( $< 1/10\,000$ ), not known (cannot be estimated from the available data). The table in this section is for adult patients only. Tables have been included for each of the components of the fixed dose combination

### **Undesirable effects of rifampicin daily therapy**

#### **Nervous system disorders**

<i>Common</i>	Tiredness, drowsiness, headache, light-headedness, dizziness
<i>Rare</i>	Ataxia, muscular weakness, myopathy

#### **Psychiatric disorders**

<i>Rare</i>	Mental confusion, psychosis
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#### **Gastrointestinal disorders**

<i>Common</i>	Anorexia, nausea, abdominal pain, bloatedness
<i>Rare</i>	Vomiting, diarrhoea, isolated occurrences of erosive gastritis and pseudomembranous colitis, pancreatitis

#### **Hepatobiliary disorders**

<i>Common</i>	Asymptomatic increase in liver enzymes
<i>Rare</i>	Hepatitis or jaundice, induction of porphyria

#### **Renal and urinary disorders**

<i>Rare</i>	Elevations of blood urea nitrogen and serum uric acid. Acute renal failure due to haemoglobinuria, haematuria, interstitial nephritis, glomerulonephritis and tubular necrosis have been reported.
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#### **Endocrine disorders**

<i>Not known</i>	Adrenal insufficiency, induction of crisis in Addison patients
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#### **Metabolism and nutritional disorders**

<i>Unknown</i>	Decreased appetite
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#### **General disorders**

<i>Very common</i>	Pyrexia, chills
<i>Common</i>	Reddish discoloration of body fluids and secretions such as e.g. urine, sputum, lacrimal fluid, faeces, saliva and sweat; paradoxical drug reaction (appearance of new tuberculosis symptoms despite adherence and absence of resistance).
<i>Not known</i>	Collapse, shock, oedema



### Blood and lymphatic system disorders

<i>Rare</i>	Transient leucopenia, eosinophilia, agranulocytosis. 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. Haemolysis, haemolytic anaemia
<i>Not known</i>	Disseminated intravascular coagulation has also been reported.

### Skin and subcutaneous tissue disorders

<i>Common</i>	Flushing, itching with or without skin rash, urticaria
<i>Rare</i>	Severe skin reactions such as Stevens-Johnson syndrome and generalised hypersensitivity reactions, e.g., exfoliative dermatitis, Lyell syndrome and pemphigoid reactions

### Immune System Disorders

<i>Not known</i>	Anaphylaxis
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### Musculoskeletal disorders

<i>Not known</i>	Muscle weakness, myopathy, bone pain
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### Eye disorders

<i>Common</i>	Reddening of the eyes, permanent discoloration of soft contact lenses
<i>Rare</i>	Visual disturbances, exudative conjunctivitis

### Reproductive system and breast disorders

<i>Rare</i>	Menstrual disturbances (in extreme cases, amenorrhoea);
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### Vascular disorders

<i>Not known</i>	Shock, flushing, vasculitis, bleeding
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### Investigations

<i>Common</i>	Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased
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[TB309 trade name] should **not** be used for intermittent treatment regimens. In patients taking rifampicin other than on a daily basis or in those resuming treatment after a temporary interruption, an influenza-like syndrome may occur, this being very probably of immunopathological origin. It is characterised by fever, shivering and possibly headache, dizziness and musculoskeletal pain. In rare cases this flu-like syndrome may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, shock and acute renal failure. These serious complications may, however, also set in suddenly without preceding flu-like syndrome, mainly when treatment is resumed after a temporary interruption or when rifampicin is given only once a week in high doses ( $\geq 25$  mg/kg). When rifampicin is given in lower doses (600 mg) 2–3 times a week, the syndrome is less common, the incidence then being comparable to that observed during daily medication.

### Undesirable effects of isoniazid

#### Nervous system disorders

<i>Very common</i>	Peripheral neuropathy, usually preceded by paraesthesia 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).
<i>Uncommon</i>	Seizures, toxic encephalopathy
<i>Not known</i>	Polyneuritis, presenting as muscle weakness, loss of tendon reflexes Hyperreflexia may be troublesome with doses of 10 mg/kg

#### Psychiatric disorders

<i>Uncommon</i>	Memory impairment, toxic psychosis
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*Not known*      Elevated mood, psychotic disorder  
Although isoniazid usually has a mood-elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are usually reversed on withdrawal of the drug

#### **Gastrointestinal disorders**

*Not known*      nausea, vomiting, anorexia, dry mouth, epigastric distress, constipation, pancreatitis  
acute

#### **Hepatobiliary disorders**

*Very common*      Transient elevation of serum transaminases

*Uncommon*      Hepatitis

*Not known*      Acute hepatic failure, liver injury, jaundice  
The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.

#### **Renal and urinary disorders**

*Not known*      Dysuria

#### **Metabolic and nutritional disorders**

*Not known*      Hyperglycaemia, metabolic acidosis, pellagra, pyridoxine deficiency, nicotinic acid deficiency  
Nicotinic acid deficiency may be related to isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

#### **General disorders**

*Not known*      Pyrexia

#### **Respiratory, thoracic and mediastinal disorders**

*Not known*      Pneumonitis (allergic), interstitial lung disease

#### **Blood and lymphatic system disorders**

*Not known*      Anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, eosinophilia, agranulocytosis, lymphadenopathy

#### **Skin and subcutaneous tissue disorders**

*Rare*      Toxic epidermal necrolysis, eosinophilia systemic symptoms

*Not known*      Erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, rash, acne

#### **Immune System Disorders**

*Not known*      Anaphylactic reactions

#### **Musculoskeletal disorders**

*Not known*      Arthritis, systemic lupus erythematosus, lupus-like syndrome, rheumatic syndrome

#### **Eye disorders**

*Uncommon*      Optic atrophy or neuritis

#### **Ear and labyrinth disorders**

*Not known*      Deafness, tinnitus, vertigo  
These have been reported in patients with end-stage renal impairment

#### **Reproductive system and breast disorders**

*Not known*      Gynaecomastia

#### **Vascular disorders**

*Not known*      Vasculitis

#### **Investigations**

*Not known*      Anti-nuclear bodies

#### **Miscellaneous**

Withdrawal symptoms, which may occur on cessation of treatment, include headache, insomnia, excessive dreaming,

irritability and nervousness.

## Undesirable effects of pyrazinamide

### Nervous system disorders

*Not known* Headache, dizziness, nervousness, insomnia, aggravation of peptic ulcer

### Gastrointestinal disorders

*Common* Nausea, vomiting

*Not known* Abdominal cramps, anorexia, aggravation of peptic ulcer

### Hepatobiliary disorders

*Very common* Increased liver enzymes

*Uncommon* Jaundice

*Rare* Liver failure

### Metabolism and nutrition disorders

*Very common* Hyperuricaemia

*Very rare* Pellagra, aggravated porphyria

### Renal and urinary disorders

*Not known* Interstitial nephritis

### Skin and subcutaneous tissue disorders

*Rare* Rash, photosensitivity reaction, urticaria

### General disorders

*Very common* Flushing

*Not known* Malaise, fever, weight loss, allergic reactions

### Blood and lymphatic systems disorders

*Not known* Sideroblastic anemia,, thrombocytopenia

### Musculoskeletal disorders

*Very common* Arthralgia, myalgia

*Unknown* Gouty arthritis

### Vascular disorders

*Not known* Hypertension

## 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

### Rifampicin

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 and/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 children. 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 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

### *Management*

Intensive supportive measures should be instituted, and individual symptoms treated as they arise. The instillation of activated charcoal slurry into the stomach shortly after overdose may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients

### *Isoniazid*

Typical symptoms are seizures and metabolic acidosis, ketonuria, hyperglycaemia. In addition, there may be periorbital myoclonus, dizziness, tinnitus, tremor, hyperreflexia, paraesthesia, hallucinations, impaired consciousness, respiratory depression, apnoea, tachycardia, arrhythmias, hypotension, nausea, vomiting, fever, rhabdomyolysis, disseminated intravascular coagulation, hyperglycaemia, hyperkalaemia and liver involvement.

Doses of isoniazid exceeding 10 mg/kg may adversely affect the nervous system, e.g., in the form of peripheral neuropathy, and thus impair the patient's ability to drive or operate machinery.

Isoniazid toxicity is potentiated by alcohol. Lethal dose is thought to be 80–150 mg/kg bodyweight. Administration of 3 g to a 5-year-old and 5–7.5 g to adults resulted in extremely severe intoxication. A 5-g dose in a 15-year-old resulted in lethal intoxication. A dose of 900 mg in an 8-year-old has resulted in moderate intoxication and 2–3 g to a 3-year-old resulted in severe intoxication.

### *Management*

Where considered appropriate, evacuation of the stomach (provided the patient is not experiencing seizures) and administration of activated charcoal can reduce absorption if instituted within a few hours of ingestion. Blood samples must be collected for immediate determination of blood gases, electrolytes, BUN, glucose etc. Subsequently, pyridoxine is given (intravenous bolus on a gram-per-gram basis, equal to the isoniazid dose; if the isoniazid dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered). Pyridoxine should be diluted to reduce vascular irritation and is administered for 30 minutes via infusion pump or syringe pump. The dose is repeated if necessary.

Intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring and support of ventilation and correction of metabolic acidosis. There is no specific antidote.

### *Pyrazinamide*

Abnormal liver function tests, hyperuricaemia.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

*Pharmacotherapeutic group:* Combinations of drugs for treatment of tuberculosis (rifampicin, pyrazinamide and isoniazid).

ATC code: J04AM05.

Rifampicin is a rifamycin antibiotic. Isoniazid and pyrazinamide are bactericidal antituberculous agents.

## Mechanism of action

*Rifampicin* exerts, both *in vitro* and *in vivo* bactericidal effects on *Mycobacterium tuberculosis*. It also exhibits variable activity against other atypical species of *Mycobacterium*.

*In vivo* rifampicin exerts its antibacterial effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, but without affecting the host enzymatic systems.

*Isoniazid* exerts a bactericidal effect mainly on rapidly growing populations of *Mycobacterium tuberculosis*. Its mechanism of action is probably based chiefly on inhibition of mycolic acid synthesis, mycolic acids being important constituents of the mycobacterial cell wall.

*Pyrazinamide*: The exact mechanism of action is unknown. *In vitro* and *in vivo* studies have demonstrated that pyrazinamide is only active at a slightly acidic pH (pH 5.5).

## 5.2 Pharmacokinetic properties

The absorption characteristics of [TB309 trade name] have been determined after administration of a single dose tablet of [TB309 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Arithmetic mean value $\pm$ standard deviation		
	Isoniazid	Pyrazinamide	Rifampicin
Maximum concentration ( $C_{\max}$ ) ng/mL	4649 $\pm$ 1767	16740 $\pm$ 3746	4949 $\pm$ 1182
Area under the curve ( $AUC_{0-\infty}$ ), a measure of the extent of absorption ng.h/mL	16544 $\pm$ 7846	194531 $\pm$ 32857	29111 $\pm$ 7621
Time to attain maximum concentration ( $t_{\max}$ ) h	0.57 $\pm$ 0.45	0.69 $\pm$ 0.50	1.41 $\pm$ 0.78

	Rifampicin	Isoniazid	Pyrazinamide
<b>Absorption</b>			
Absolute bioavailability	90–95%	NA*	> 90%
Oral bioavailability	> 90%	> 80%	NA*
Food effect	No effect on extent of absorption. Rate of absorption is reduced.	Reduced.	None
<b>Distribution</b>			
Volume of distribution (mean)	55 L	43 L	40 L
Plasma protein binding <i>in vitro</i>	60–90%	< 10%	10–20%
Tissue distribution	CSF concentrations are of the same order of magnitude as the unbound concentrations	Diffuses readily into all body fluids (cerebrospinal, pleural and ascitic	Widely distributed into body tissues and fluids including the liver, lungs, and CSF.

	<p>in plasma.</p> <p>Concentrations in liver, spleen, kidneys and lung tissue are higher than serum concentrations. Penetrates into vaginal and cervical tissue and into cervicovaginal fluid.</p> <p>Passes into the placenta; serum concentration in fetus is about <math>\frac{1}{3}</math> of those in mother.</p>	<p>fluids), tissues, organs and excreta (saliva, sputum and faeces). Crosses the placenta and passes into milk.</p>	<p>In CSF concentrations are approximately equal to plasma concentrations.</p>
<b>Metabolism</b>			
	Primarily hepatic, rapidly deacetylated.	Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid	Hepatic
Active metabolite(s)	25-o-deacetyl rifampicin	Nicotinoyl-NAD adduct	Pyrazinoic acid
<b>Elimination</b>			
Elimination half life	3–5 hours Decreases to 2–3 hours after repeated administration	1.2 hours: rapid acetylators 3.5 hours: Slow acetylators	9 – 10 hours
Mean systemic clearance (Cl/F)	5.7–9.0 L/hour	15.5 L/hour: slow NAT2 genotype  26.1 L/hour: rapid/intermediate NAT2 genotype	3.3 L/hour
% of dose excreted in urine	30%	75–95%	70–90%
% of dose excreted in faeces	60–65%	< 10%	< 10%
<b>Pharmacokinetic linearity</b>	Non-linear	NA*	NA*
<b>Drug interactions (<i>in vitro</i>)</b>	Rifampicin induces hepatic enzymes	<p>Isoniazid is CYP450 inducer and inhibitor.</p> <p>Isoniazid is a arylamine n-acetyltransferase 2 substrate and inhibitor</p>	Pyrazinamide is a xanthine dehydrogenase/oxidase substrate and aldehyde oxidase substrate
Transporters	Solute carrier transporters (SLC)	NA*	NA*

	ATP Binding Cassette transporters (ABC) P-glycoprotein 1		
Metabolizing enzymes	CYP450	CYP450: 2C19, 3A4	Deamination followed by xanthine oxidase

\*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 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, pediatric patients 6 to 58 months old were given rifampicin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of  $10.7 \pm 3.7$  and  $11.5 \pm 5.1$  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  $t_{1/2}$  of rifampicin 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.

### *Pyrazinamide*

The plasma half-life may be prolonged in patients with impaired renal function. Pyrazinamide is removed from blood by haemodialysis.

Patients with hepatic cirrhotic insufficiency exhibit a marked reduction of the pyrazinamide clearance and an increase in half-life. The area under the curve of pyrazinoic acid (the main metabolite) is increased three-fold.

## 5.3 Preclinical safety data

### *Rifampicin*

After oral administration of 100 mg/kg 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. There is limited evidence for the carcinogenicity of rifampicin in mice. The available studies on mutagenicity indicate an absence of a mutagenic effect.

An increased incidence of congenital malformations (principally spina bifida and cleft palate) has been reported in the offspring of mice and rats given rifampicin in a dose of 150–250 mg/kg daily during pregnancy. Defective osteogenesis and embryotoxicity occurred when rifampicin doses up to 20 times the usual daily human dose were used in pregnant rabbits.

Fertility and reproductive performance were not affected by oral administration of rifampicin to male and female rats at doses of up to one-third of the human dose.

### ***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.

### ***Pyrazinamide***

Pyrazinamide was not mutagenic in the Ames test. Pyrazinamide induced chromosomal aberrations in human lymphocyte cell cultures. Pyrazinamide was not carcinogenic in rats or male mice when administered in daily doses of approximately 10–40 times the maximum recommended human dose; results in female mice could not be determined because of insufficient numbers of surviving mice in the control group.

Studies in rats with pyrazinamide showed reduced concentrations of follicle-stimulating and luteinizing hormones, oestrogen, and prolactin. In mice, oral dose levels of pyrazinamide approximately 12 times those used therapeutically did not have adverse effects on sperm production. High dose level studies in rats also demonstrated decreased sperm production.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

microcrystalline cellulose

crospovidone

povidone

bleached shellac

croscarmellose sodium

aspartame

strawberry flavour

magnesium stearate

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per tablet.

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

#### ***Bottle pack***

Do not store above 25°C. Store in a dry place. Protect from light.  
Once the bottle is opened, use within 120 days.

#### ***Strip pack***

Do not store above 30°C. Store in dry place. Protect from light.

### **6.5 Nature and contents of container**

#### ***Bottle pack***



100 tablets packed in a self-sealing LDPE bag, plain triple laminated (LDPE/AL/PET) sachet and then in a

round, wide mouth, opaque, milky white HDPE container with a HDPE screw thread cap along with the leaflet.

#### *Strip pack*

Alu/Alu strip pack of 10 tablets, such 10 strips are packed in a carton along with the package insert.

Alu/Alu strip pack of 28 tablets, such 3 strips are packed in a carton along with the package insert.

### **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**

Macleods Pharmaceuticals Limited  
304 Atlanta Arcade  
Marol Church Road  
Andheri (East)  
Mumbai 400 059  
India

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

TB309

## **9. DATE OF PREQUALIFICATION**

12 December 2017

## **10. DATE OF REVISION OF THE TEXT**

December 2024  
Section 6 was updated in April 2025.

### ***References***

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WHO, Geneva, 2010. Rapid Advice Treatment of tuberculosis in children. Available at: <https://iris.who.int/handle/10665/44444>

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US FDA labelling Rifater® (isoniazid/pyrazinamide/rifampicin)

Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/050705s0111bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050705s0111bl.pdf)

Isoniazid tablets UK SmPC

Available at: <https://www.medicines.org.uk/emc/product/9138/smpc#gref>

Isoniazid tablets US FDA labelling

Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/008678s0281bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008678s0281bl.pdf)

Zinamide® UK SmPC (pyrazinamide)

Available at: <https://www.medicines.org.uk/emc/product/5273/smpc#gref>

Rifampicin tablets UK SmPC

Available at: <https://www.medicines.org.uk/emc/product/8789/smpc#gref>

Rifadin® US FDA labelling (rifampicin capsules)

Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/050420s087,050627s0301bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050420s087,050627s0301bl.pdf)

*Detailed information on this medicine is available on the World Health Organization (WHO) website:*  
<https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>