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

[TB168 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Rifampicin 150 mg

Ethambutol hydrochloride 275 mg

Isoniazid 75 mg

Pyrazinamide 400 mg

Excipients with potential clinical effect

Each tablet contains 0.325 mg sunset yellow colorant

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Light buff coloured biconvex capsule shaped film-coated tablets, with plain surface on both sides.

The tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB168 trade name] is a combination medicine for the initial treatment of tuberculosis due to *Mycobacterium tuberculosis*.

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

4.2 Posology and method of administration

For oral use.

Posology

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

Typical recommended doses for initial (intensive phase) treatment in adults and children weighing more than 25 kg:

Patients' weight	**Dose**
25–29.9 kg	2 tablets once daily
30–34.9 kg	3 tablets once daily
35–64.9 kg	4 tablets once daily
65 kg and over	5 tablets once daily

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

Initial (intensive phase) treatment with [TB168 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.

[TB168 trade name] should not be used for intermittent treatment regimens.

[TB168 trade name] should be taken 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.

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 (ethambutol, isoniazid, pyrazinamide, and rifampicin) should be used.

Supplementation with pyridoxine (vitamin B_6) 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 ethambutol, 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. [TB168 trade name] must not be used in patients with a history of acute liver disease (see section 4.3).

Children, adolescents and patients weighing less than 25 kg

[TB168 trade name] is not suitable for patients with a body weight below 25 kg, since appropriate dose adjustments cannot be made. Alternative formulations should be used.

Elderly

No special dosage regimen is necessary, but hepatic or renal insufficiency should be considered. Supplementation of pyridoxine (vitamin B_6) may be useful.

Interruption of treatment

If treatment with [TB168 trade name] is interrupted for any reason including non-adherence, the product should **not** be used for resuming treatment. Ethambutol, 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.

4.3 Contraindications

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

A history of drug induced hepatitis and acute liver disease, regardless of its cause.

Porphyria.

Acute gouty arthritis.

Severe renal impairment (creatinine clearance less than 30 mL/minute) (see section 4.4).

Concomitant use with voriconazole or with protease inhibitors for HIV or hepatitis C virus infection (see section 4.5).

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 four 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. [TB168 trade name] should be withdrawn immediately if severe acute hypersensitivity reactions occur. Patients who develop such reactions must never again be treated with rifampicin.

[TB168 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.

Because of the ethambutol component, [TB168 trade name] should be used with care in patients with visual defects. Ocular examinations including acuity, colour discrimination and visual field are recommended before starting treatment and periodically during treatment, especially if high doses are used. Patients should be questioned at every visit about their vision and advised to stop taking [TB168 trade name] if a visual disturbance arises until a clinical evaluation is possible.

[TB168 trade name] is not suitable for use in the treatment of patients with a body weight of less than 25 kg, since appropriate dose adjustments cannot be made. Other formulations should be used that allow suitable doses to be given.

Precautions

The precautions for the use of [TB168 trade name] are the same as those that apply for the administration of rifampicin, isoniazid, pyrazinamide and ethambutol 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, pyrazinamide and ethambutol 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, [TB168 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, [TB168 trade name], should be replaced by individual component formulations of rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride in order to facilitate treatment in these clinical circumstances.

Withdrawing rifampicin, pyrazinamide and ethambutol is recommended if liver function does not return to normal or transaminases exceed 5 times the ULN. The fixed drug combination, [TB168 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 [TB168 trade name] in these patients may cause a more severe form of liver damage.

[TB168 trade name]is not suitable for patients with chronic liver disease, or in chronic alcoholics and undernourished patients, if the dosage of rifampicin, isoniazid, pyrazinamide and ethambutol needs to be adjusted separately.

For undernourished or elderly patients, supplementation with pyridoxine (vitamin B_6) 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, pyrazinamide and ethambutol can be delayed, leading to a higher systemic exposure and a potential increase in adverse events. [TB168 trade name] should be used with caution in patients with moderate renal impairment (creatinine clearance 30–60 mL/minute).

Gout

Pyrazinamide and ethambutol should be used with caution in patients with a history of gout. Regular monitoring of serum uric acid should be undertaken. [TB168 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 [TB168 trade name] because of the neurotoxic effects of isoniazid and ethambutol hydrochloride.

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_6) 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.

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 [TB168 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. Ocular examination is recommended during treatment with ethambutol hydrochloride.

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 [TB168 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.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Excipients

This medicinal product contains a colorant (sunset yellow) which may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interaction

Influence of other medicinal products on [TB168 trade name]

Antacids reduce the bioavailability of rifampicin, isoniazid and ethambutol. To avoid this interaction, [TB168 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 [TB168 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 [TB168 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 [TB168 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 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.

Ethambutol has fewer significant pharmacokinetic or pharmacodynamic interactions with other medicines, but particular care may be needed if used with other medicines that also affect visual function.

Thus, mainly due to rifampicin, [TB168 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 [TB168 trade name], the possibility of a drug-drug interaction should be considered. The following list of drug interactions with [TB168 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
INFECTION		
Antiretrovirals		
Nucleoside analogues **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.
Didanosine **Emtricitabine** **Lamivudine** **Stavudine**	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.	Co-administration 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 **Efavirenz** / rifampicin	Efavirenz AUC ↓ 26%	When co-treating with [TB168 trade name], increasing the efavirenz dose to 800 mg daily may be considered
Nevirapine / rifampicin	Nevirapine: AUC ↓ 58%	Concomitant use of [TB168 trade name] and nevirapine is not recommended since appropriate doses of nevirapine when given concomitantly with rifampicin have not been established and the safety of the combination is unknown,

Drugs	Interaction	Recommendations on co-administration
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of [TB168 trade name] and etravirine should be avoided.
Protease inhibitors **Atazanavir /** rifampicin **Boceprevir** **Darunavir** **Fosamprenavir** **Indinavir** **Lopinavir** **Ritonavir** **Saquinavir** **Tipranavir**	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.	[TB168 trade name] must not be co-administered with protease inhibitors for treating HIV or hepatitis C virus infections (see section 4.3).
Others **Raltegravir** / rifampicin	Raltegravir AUC ↓ 40%	Co-treatment should be avoided. If deemed necessary, consider increasing the raltegravir dose to 600 mg twice daily
Dolutegravir / rifampicin	Dolutegravir AUC ↓ 54%	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with [TB168 trade name] in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
Elvitegravir/cobicistat/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.
Maraviroc / rifampicin	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg twice daily.
Antivirals for hepatitis C infection		
Daclatasvir **Elbasvir/Grazoprevir** **Glecaprevir/Pibrentasvir** **Ledipasvir/Sofosbuvir** **Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)** **Simeprevir** **Sofosbuvir (with or without velpatasvir with or without voxilaprevir) /**	*Rifampicin:* 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. *Isoniazid:*	Co-administration of [TB168 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
Rifampicin Isoniazid	Co-administration has not been studied. Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal hepatitis associated with isoniazid 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/tuberculosis medicines		
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.
Doxycycline / rifampicin	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole / rifampicin	Metronidazole AUC i.v.↓ 33%	The clinical relevance of the interaction is unknown. Dose adjustment is not routinely recommended. Efficacy should be monitored.
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.

Drugs	Interaction	Recommendations on co-administration
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% 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% Dihydroarthemisinin AUC ↓ 85%	Co-administration should be avoided.
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 metabolite of codeine, are likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary.
Paracetamol (acetaminophen) / 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 with isoniazid may increase hepatotoxicity.	Co-administration of [TB168 trade name] and paracetamol should be avoided.
Etoricoxib / 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.

Drugs	Interaction	Recommendations on co-administration
ANTIEPILEPTICS		
Carbamazepine / 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 [TB168 trade name] and carbamazepine should be avoided.
Phenobarbital / 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 [TB168 trade name] and phenobarbital should be undertaken with caution, and the patient monitored for clinical effects and, if possible, plasma drug concentrations.
Phenytoin / 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 [TB168 trade name] should be avoided.
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.
IMMUNOSUPPRESSANTS		
Ciclosporin / 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).
Tacrolimus / rifampicin **Sirolimus** **Everolimus**	Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 6870% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of [TB168 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		
ACE inhibitors		
Enalapril / rifampicin	No interaction expected	No dose adjustment required.

Drugs	Interaction	Recommendations on co-administration
Antiarrhythmics		
Lidocaine / rifampicin	Lidocaine CLi.v. ↑ 15%	No dose adjustment required
Verapamil / rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	[TB168 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.
Anticoagulants		
Warfarin and other coumarin anticoagulants / 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.
Beta blockers		
Atenolol / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Calcium-channel blockers		
Amlodipine / 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.
Cardiac glycosides		
Digoxin / rifampicin	AUC p.o ↓ 30%	When co-administering [TB168 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Statins		
Simvastatin / rifampicin	Simvastatin AUC ↓ 87% 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.

Drugs	Interaction	Recommendations on co-administration
Antacids / 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 [TB168 trade name] is necessary. [TB168 trade name] should be taken at least 1 hour before the antacid.
PSYCHOTHERAPEUTIC MEDICINES		
Anxiolytics and hypnotics		
Diazepam / rifampicin / isoniazid **Midazolam** **Triazolam** **Alprazolam** **Nitrazepam**	Diazepam AUC ↓ > 70% Midazolam AUC ↓ 98% Triazolam AUC ↓ 95% Alprazolam AUC ↓ 88% Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals.
Zolpidem / rifampicin **Zopiclone** / rifampicin	Zolpidem AUC ↓73% Zopiclone AUC ↓82%	Co-administration should be avoided.
Antipsychotics		
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 **Clozapine**	Haloperidol clearance is substantially increased by rifampicin; theoretical considerations imply that same applies to clozapine.	If co-treatment of [TB168 trade name] with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Tricyclic antidepressants		
Amitriptyline / rifampicin **Nortriptyline**	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases clearance of tricyclic antidepressants.	Co-treatment should be avoided. If necessary, monitor for clinical response, side effects, and, if possible, plasma concentrations.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Corticosteroids		
Prednisolone **Other systemically administered corticosteroids /** rifampicin	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of [TB168 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
Antidiabetics		
Glibenclamide / rifampicin **Glimepiride** **Repaglinide**	Glibenclamide AUC ↓ 39% Glimepiride AUC ↓ 34% Repaglinide AUC ↓ 57%	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
Insulin	No interaction expected.	No dose adjustment required.
Thyroid hormones		
Levothyroxine / rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored.
Hormonal contraceptives		
Ethinylestradiol / rifampicin	Ethinylestradiol AUC ↓ 66%	Co-administration with [TB168 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
Norethisterone (norethindrone) / rifampicin	Norethisterone AUC ↓ 51%	Co-administration with [TB168 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
OTHERS		
Disulfiram / 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 [TB168 trade name].
Enflurane / isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB168 trade name] with enflurane should be avoided.
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)..
Praziquantel / rifampicin	Praziquantel AUC ↓ 80-99%	Co-treatment with [TB168 trade name] should be avoided.
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.
Typhoid vaccine, oral / pyrazinamide	Antibiotics may inactivate oral typhoid vaccine	Avoid concomitant administration oral typhoid vaccine with [TB168 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_{12}) 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, ethambutol 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.

[TB168 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 [TB168 trade name] is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Supplemental pyridoxine (vitamin B_6) may be advised in pregnant adolescents (see section 4.4)..

Breastfeeding

Rifampicin, isoniazid, pyrazinamide and ethambutol 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.

[TB168 trade name] can be used during breast-feeding.

Fertility

No human data on the effect of [TB168 trade name] on fertility are available. Animal studies indicate that co-administration of ethambutol, rifampicin, isoniazid, and pyrazinamide has effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[TB168 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 [TB168 trade name] should be borne in mind when considering the patient's ability to drive or operate machinery. In particular, undesirable effects of ethambutol, such as confusion, disorientation, hallucinations, dizziness, malaise and visual disturbances (blurred vision, red-green colour blindness, loss of vision), and 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 [TB168 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.

The most important adverse reaction of *ethambutol* is retrobulbar neuritis with reduced visual acuity.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 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	
Common	Tiredness, drowsiness, headache, light-headedness, dizziness
Rare	Ataxia, muscular weakness, myopathy
Psychiatric disorders	
Rare	Mental confusion, psychosis
Gastrointestinal disorders	
Common	Anorexia, nausea, abdominal pain, bloatedness
Rare	Vomiting, diarrhoea, isolated occurrences of erosive gastritis and pseudomembranous colitis, pancreatitis
Hepatobiliary disorders	
Common	Asymptomatic increase in liver enzymes
Rare	Hepatitis or jaundice, induction of porphyria
Renal and urinary disorders	
Rare	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.
Endocrine disorders	
Not known	Adrenal insufficiency, induction of crisis in Addison patients
Metabolism and nutritional disorders	
Unknown	Decreased appetite
General disorders	
Very common	Pyrexia, chills
Common	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).
Not known	Collapse, shock, oedema
Blood and lymphatic system disorders	
Rare	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
Not known	Disseminated intravascular coagulation has also been reported.
Skin and subcutaneous tissue disorders	
Common	Flushing, itching with or without skin rash, urticaria
Rare	Severe skin reactions such as Stevens-Johnson syndrome and generalised hypersensitivity reactions, e.g. exfoliative dermatitis, Lyell syndrome and pemphigoid reactions
Immune System Disorders	
Not known	Anaphylaxis
Musculoskeletal disorders	
Not known	Muscle weakness, myopathy, bone pain
Eye disorders	
Common	Reddening of the eyes, permanent discoloration of soft contact lenses
Rare	Visual disturbances, exudative conjunctivitis
Reproductive system and breast disorders	
Rare	Menstrual disturbances (in extreme cases, amenorrhoea);
Vascular disorders	
Not known	Shock, flushing, vasculitis, bleeding
Investigations	
Common	Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased

[TB168 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 (≥ 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	
Very common	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).
Uncommon	Seizures, toxic encephalopathy
Not known	Polyneuritis, presenting as muscle weakness, loss of tendon reflexes

Hyperreflexia may be troublesome with doses of 10 mg/kg

Psychiatric disorders

Uncommon Memory impairment, toxic psychosis

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, leucopenia (allergic), neutropenia with 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

Gastrointestinal disorders

Common	Nausea, vomiting
Not known	Abdominal cramps, anorexia

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	Anaemia, thrombocytopenia, neutropenia

Musculoskeletal disorders

Very common	Arthralgia
Unknown	Gouty arthritis

Vascular disorders

Not known	Hypertension

Undesirable effects of ethambutol

Nervous system disorders

Rare	Peripheral neuritis, peripheral neuropathy, paraesthesia (especially in the extremities), numbness
Very rare	Disorientation, dizziness, headache

Psychiatric disorders

Very rare	Mental confusion and hallucination

Gastrointestinal disorders

Not known	Nausea, vomiting, anorexia, flatulence, abdominal pain, diarrhoea

Hepatobiliary disorders

Very rare	Hepatic failure
Not known	Hepatitis, jaundice, increase in liver enzymes

Renal and urinary disorders

Very rare	Nephrotoxicity including interstitial nephritis

Eye disorders

Uncommon	Optic neuritis (decreased visual acuity, loss of vision, scotoma, colour blindness, visual disturbance, visual field defect, eye pain)

Blood and lymphatic systems disorders

Rare	Thrombocytopenia,
Very rare	Leucopenia, neutropenia

Respiratory, thoracic and mediastinal disorders

Very rare	Pneumonitis, pulmonary infiltrates, with or without eosinophilia

Metabolism and nutrition disorders

Uncommon	Hyperuricaemia
Very rare	Gout

Immune system disorders

Very rare	Hypersensitivity, anaphylactoid reactions (see also “Skin and subcutaneous tissue disorders”)

Skin and subcutaneous tissue disorders

Rare	Rash, pruritus, urticaria
Very rare	Photosensitive lichenoid eruptions, bullous dermatitis, Stevens-Johnson syndrome, epidermal necrolysis

Musculoskeletal and connective tissue disorders

Very rare	Joint pains

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 lLiver 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.

Ethambutol

Loss of appetite, gastro-intestinal disturbances, fever, headache, dizziness, confusion, hallucinations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J04A M06.

Rifampicin is a rifamycin antibiotic. Isoniazid, pyrazinamide and ethambutol 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).

Ethambutol: The mechanism of action is not fully known. It diffuses into mycobacteria and appears to suppress multiplication by interfering with RNA synthesis. It is effective only against mycobacteria that are actively dividing.

5.2 Pharmacokinetic properties

The absorption characteristics of [TB168 trade name] have been determined after administration of 1 tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value ± standard deviation**			
	Ethambutol	**Isoniazid**	**Pyrazinamide**	**Rifampicin**
Maximum concentration (C_{max})µg/ml	3.27 ± 1.09	5.69 ± 1.56	31.40 ± 2.55	9.83 ± 1.70
Area under the curve (AUC_{0-t}), a measure of the extent of absorption µg.hour/ml	19.34 ± 3.35	32.26 ± 15.19	515.4 ± 61.8	65.07 ± 13.35
Time to attain maximum concentration (t_{max}) hour	3.02 ± 0.58	1.37 ± 0.62	1.98 ± 0.63	1.92 ± 0.62

Pharmacokinetics of rifampicin, isoniazid, pyrazinamide and ethambutol

	Rifampicin	**Isoniazid**	**Pyrazinamide**	**Ethambutol**
Absorption				
Absolute bioavailability	90−95%	NA*	> 90%	NA*
Oral bioavailability	> 90%	> 80%	NA*	70–80%
Food effect	No effect on extent of absorption. Rate of absorption is reduced.	Reduced.	None	None
Distribution				
Volume of distribution (mean)	55 L	43 L	40 L	20 L
Plasma protein binding *in vitro*	60−90%	< 10%	10–20%	10–40%
Tissue distribution	CSF concentrations are of the same order of magnitude as the unbound concentrations in plasma. Concentrations in liver, spleen, kidneys and lung tissue are higher than serum concentrations. Penetrates into vaginal and cervical tissue and into cervicovaginal fluid. Passes into the placenta; serum concentration in fetus is about ⅓ of those in mother.	Diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). Crosses the placenta and passes into milk.	Widely distributed into body tissues and fluids including the liver, lungs, and CSF. In CSF concentrations are approximately equal to plasma concentrations.	*CSF*: Relatively low concentrations distributed to CSF
Metabolism				
	Primarily hepatic, rapidly deacetylated.	Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid	Hepatic	Hepatic
Active metabolite(s)	25-o-deacetyl rifampicin	Nicotinoyl-NAD adduct	Pyrazinoic acid	NA*
Elimination				
Elimination half life	3−5 hours Decreases to 2−3 hours after repeated	1.2 hours: rapid acetylators 3.5 hours: Slow	9 − 10 hours	3–4 hours

	administration	acetylators		
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	41 L/hour
% of dose excreted in urine	30%	75−95%	70–90%	60–80%
% of dose excreted in faeces	60−65%	< 10%	< 10%	20%
Pharmacokinetic linearity	Non linear	NA*	NA*	NA*
Drug interactions *(in vitro*)	Rifampicin induces hepatic enzymes	Isoniazid is CYP450 inducer and inhibitor. Isoniazid is a arylamine n-acetyltransferase 2 substrate and inhibitor	Pyrazinamide is a xanthine dehydrogenase/oxidase substrate and aldehyde oxidase substrate	NA*
Transporters	Solute carrier transporters (SLC) ATP Binding Cassette transporters (ABC) P-glycoprotein 1	NA*	NA*	NA*
Metabolizing enzymes	CYP450	CYP450: 2C19, 3A4	Deamination followed by xanthine oxidase	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.

Ethambutol

Half is increased up to 8 hours in cases of renal impairment. Ethambutol is not removed from the blood by haemodialysis.

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.

Ethambutol

Toxicological studies on high prolonged doses produced evidence of myocardial damage and heart failure, and depigmentation of the tapetum lucidum of the eyes in the dog. Degenerative changes in the central nervous system, apparently not dose-related, have also been noted in dogs over a prolonged period. In the rhesus monkey, neurological signs appeared after treatment with high doses given daily over several months.

These were correlated with specific serum levels of ethambutol and with definite neuroanatomical changes in the central nervous system.

Conflicting results are available on genotoxicity (negative Ames test, negative in human lymphocyte cell cultures, positive in mouse micronucleus).

Cleft palate, exencephaly and vertebral column abnormalities have been observed with high doses in studies in mice. Studies in rats and rabbits have shown that ethambutol in high doses causes minor abnormalities of the cervical vertebrae, limb reduction defects, hare lip and cleft palate in the offspring. Ethambutol decreases testosterone concentrations, spermatogenesis, and male fertility in high doses in rats when administered over 60 days.

A study in male rats determined that co-administration of four antituberculosis drugs, including ethambutol, rifampicin, isoniazid, and pyrazinamide, produced a range of adverse effects on the testes and in sperm, as well as an increase in pre- and post-implantation embryo lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Calcium stearate
Colloidal silicon dioxide,
Croscarmellose sodium,
Crospovidone,
Disodium edetate,
Maize starch,
Povidone,
Purified talc,
Shellac.

Seal coating: *Hypromellose*

Film coating: Copovidone,
Polyvinyl alcohol
Titanium dioxide,
Talc,
Lecithin,
Xanthan gum
Colour Lake of sunset yellow

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

36 months

Alu/PVC/PVDC blister pack: 24 months

Alu/PVC/PE/PVDC blister pack: 36 months

Alu/Alu Strip pack: 36 months

HDPE Bulk Pack: 24 months

6.4 Special precautions for storage

Blister pack: Stored in a dry place below 25°C and protect from light.

Strip Pack: Stored in a dry place below 30°C and protect from light.

For bulk HDPE bottle pack: Store at a temperature not exceeding 25° C in a dry place and protect from light.

6.5 Nature and contents of container

Transparent LDPE bag, containing 500 or 1000 tablets, packed in a triple laminated aluminium sachet which is further packed in an HDPE bottle along with a leaflet. Each bottle is sealed with an aluminium tagger and closed with a screw cap.

Alu/PVC/PVDC blister of 10 and 7 tablets. Such 10 blisters per box. Pack size: 100 (10 x 10) tablets and 70 (10 x 7) tablets.

Alu/PVC/PVDC blister of 10 tablets. Such 10 blisters per box. Pack size: 100 tablets.

Alu/PVC/PVDC blister of 28 tablets. Such 3 or 24 blisters per box. Pack sizes: 84 (28 x 3) and 672 (28 x 24) tablets.

Alu/Alu strip of 10 tablets. Such 10 strips in a carton. Pack sizes: 100 (10 x 10) tablets.

Alu/Alu strip of 12 tablets. Such 14 strips in a carton. Pack sizes: 168 (12 x 14) tablets.

Alu/Alu strip of 28 tablets. Such 3 or 24 strips in a carton. Pack sizes: 84 (3 x 28) and 672 (24 x 28) tablets.

Alu/PVC/PE/PVDC blister of 7 tablets. Such 10 blister per box. Pack size: 70 tablets (7 x 10)

Alu/PVC/PE/PVDC blister of 10 tablets. Such 10 blisters per box. Pack size: 100 tablets.

Alu/PVC/PE/PVDC blister of 28 tablets. Such 3, 6 or 24 blisters per box. Pack sizes: 84 (28 x 3), 168 (28 x 6) and 672 (28 x 24) 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

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB168

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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References

WHO, Geneva, 2003: Treatment of Tuberculosis: Guidelines for national programmes

WHO, Geneva, 2006: Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children.

WHO consolidated guidelines on tuberculosis, Module 4: Treatment Drug-susceptible tuberculosis treatment (2022). Available at https://www.who.int/publications/i/item/9789240048126

WHO operational handbook on tuberculosis: Module 4: treatment: Drug-susceptible tuberculosis treatment (2022). Available at https://www.who.int/publications/i/item/9789240050761

WHO, Geneva, 2022. WHO consolidated guidelines on tuberculosis, Module 5: management of tuberculosis in children and adolescent. Available at: https://apps.who.int/iris/rest/bitstreams/1414329/retrieve

WHO, Geneva, 2022. WHO operational handbook on tuberculosis, Module 5: management of tuberculosis in children and adolescents. Available at: https://apps.who.int/iris/rest/bitstreams/1414333/retrieve

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

Fixed-dose combination tablets for the treatment of tuberculosis Report of an informal meeting held in Geneva Tuesday, 27 April 1999, World Health Organization Communicable Diseases Cluster 1999

Rimstar SPC. Available at: https://www.medicines.org.uk/emc/product/2999/smpc [accessed 26/11/2019]

Stockley's Drug Interactions. Available at: www.medicinescomplete.com.

University of Liverpool HIV drug interactions site: hiv-druginteractions.org

Schaefer C, Peters P, Miller RK (eds). Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment, 3rd edn. Amsterdam: Academic Press, 2015. Available at: https://doi.org/10.1016/B978-0-12-408078-2.01001-5.

Kovalenko VM, Bondarenko LB, Byshovetz TF et al: Pyrazinamide Effects On Male Rat's Reproductive Function. Toxicol Lett 2005;158(Suppl 1):S123.

Adebayo OA, Adesanoye OA, Abolaji OA, Kehinde AO, Adaramoye OA. First-line antituberculosis drugs disrupt endocrine balance and induce ovarian and uterine oxidative stress in rats. J Basic Clin Physiol Pharmacol. 2018 Mar 28;29(2):131-140. doi: 10.1515/jbcpp-2017-0087. PubMed PMID: 29116933.

Shayakhmetova GM, Bondarenko LB, Voronina AK, Matvienko AV, Kitam V, Kovalenko VM. 2017. Repeated administration of ethambutol in therapeuetic dose causes testes alteration and spermatogenesis disruption in Wistar rats. Hum Exp Toxicol 36(5): 520-533.

Shayakhmetova GM, Bondarenko LB, Kovalenko VM. 2012. Damage of testicular cell macromolecules and reproductive capacity of male rats following co-administration of ethambutol, rifampicin, isoniazid and pyrazinamide. Interdiscip Toxicol 5(1): 9-14.

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