WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

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

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

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

1. NAME OF THE MEDICINAL PRODUCT

[TB302 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 50 mg isoniazid and 75 mg rifampicin.

Excipients with potential clinical effect

Each dispersible tablet contains 3.13 mg aspartame

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible tablet

Mottled brick-red, round, uncoated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have score line on one side and are plain on the other side.

The score line can be used to break the tablet for ease of swallowing but not to divide it into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB302 trade name] is indicated in children weighing less than 25 kg, for the treatment of tuberculosis due to *Mycobacterium tuberculosis*.

It is also indicated for the prevention of tuberculosis in children at risk.

Regimens for treatment and prophylaxis should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

This medicine is for use in children. However, information from its use in adults is also included to give a fuller picture of the medicine's effects.

4.2 Posology and method of administration

Patients should be advised to take [TB302 trade name] exactly as prescribed and to complete the full course.

Posology

Treatment of drug-susceptible tuberculosis

For the initial, two-month intensive phase of treatment, isoniazid and rifampicin should be combined with pyrazinamide and, where appropriate, ethambutol; a fixed-dose combination containing all the active substances should be preferred if available. For the subsequent continuation phase of treatment, [TB302 trade name] is used alone.

[TB302 trade name] is taken **once daily** in the following doses:

Patient's weight	**Daily dose of isoniazid/rifampicin**	**Number of [TB302 trade name] tablets**
4 to less than 8 kg	50 mg/75 mg	1
8 to less than 12 kg	100 mg/150 mg	2

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

12 to less than 16 kg	150 mg/225 mg	3
16 to less than 25 kg	200 mg/300 mg	4

Treatment is normally given for a total of 4 or 6 months, depending on the regimen.

For situations where one of the active agents of this medicine needs to be withdrawn, or dose reduction is necessary, separate preparations of rifampicin and/or isoniazid should be used.

Children weighing 25 kg or more

For children weighing at least 25 kg, a different formulation supplying adult doses of isoniazid and rifampicin is recommended.

Prevention of tuberculosis

For prevention of tuberculosis in persons considered at risk, [TB302 trade name] is taken alone **once daily** for 3 months. Doses are the same as those for treatment, above.

Special populations

Renal impairment:

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

Hepatic impairment:

Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. [TB302 trade name] must not be used in patients with severe liver disease (see section 4.3).

Missed doses

It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to [TB302 trade name] and reduce its effectiveness.

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

A dose may be repeated if a patient vomits within 1 hour of taking it.

Method of administration

[TB302 trade name] is for oral use and should be taken on an empty stomach (at least one hour before or two hours after a meal). If taken with food to improve gastrointestinal tolerance, bioavailability may be impaired. The recipient or carer should be advised on how the medicine is taken, as follows.

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL.

1) The required amount of drinking water should be placed in a small, 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 taken immediately
3) The cup should be rinsed with an additional 10 mL of water, which should also be drunk to ensure the entire dose is taken.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

A history of drug-induced hepatic disease, or previous severe adverse reactions such as drug fever, chills or arthritis with isoniazid.

Co-administration of [TB302 trade name] with certain other medicines whose therapeutic effect or adverse effects may be significantly affected by rifampicin, notably the following (see also section 4.5):

- voriconazole
- HIV protease inhibitors
- nevirapine, rilpivirine, doravirine and etravirine
- direct-acting antivirals for hepatitis C
- lurasidone

4.4 Special warnings and precautions for use

Liver toxicity

Rifampicin and isoniazid may both cause hepatotoxicity (see section 4.8).

Severe and sometimes fatal liver injury has been reported. Isoniazid-related hepatitis is thought to be caused by the metabolite diacetylhydrazine, while the mechanism of rifampicin-induced liver injury may be either an immuno-allergic mechanism or direct toxicity of metabolic products. The majority of cases occur within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

Patients especially at risk for developing hepatitis include:

- those aged 35 years or older (hepatotoxicity is rare in those below 20 years of age and commonest in those aged over 50 years)
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
- patients with active chronic liver disease ([TB302 trade name] is contraindicated in those with a history of acute liver disease, see section 4.3)
- individuals with a history of drug misuse by injection.

Careful monitoring is also advised in malnourished or HIV-infected patients, those known to be slow acetylators, during pregnancy and immediately post-partum, and in those taking other long-term therapy with potentially hepatotoxic medicines (see also section 4.5).

Whenever possible, the use of [TB302 trade name] should be avoided in patients with existing hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with [TB302 trade name].

Patients should be instructed to immediately report signs or symptoms consistent with liver damage. These include any of the following: unexplained anorexia, nausea, vomiting, persistent fatigue or rash, together with abdominal tenderness, especially in the right upper quadrant, pruritus, icterus, dark urine or abnormally pale stools. If these symptoms appear or if other signs suggestive of hepatic damage are detected, [TB302 trade name] should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured when feasible before patients start therapy with [TB302 trade name] and periodically throughout treatment.

Increased liver function tests are common during therapy with [TB302 trade name]. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin or isoniazid. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even with continued therapy. However, if liver enzyme values exceed 3 to 5

times the upper limit of normal, or if bilirubin values trend upwards consistently, discontinuation of [TB302 trade name] should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until symptoms and laboratory abnormalities have subsided. In case of rechallenge, [TB302 trade name] should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents should be used.

Hypersensitivity

Rifampicin may cause a hypersensitivity syndrome including 'flu-like' symptoms and/or organ manifestations. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity appear (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure), [TB302 trade name] should immediately be discontinued. Such patients should not be rechallenged with rifampicin. If therapy is temporarily discontinued, rifampicin should be restarted carefully at a reduced dose, and with close monitoring. In this situation, [TB302 trade name] should not be used.

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

At the time of prescription patients should be informed of the signs and symptoms and advised to inform their health care provider immediately should they occur. Patients must be monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, [TB302 trade name] should be withdrawn immediately, and an alternative treatment considered (as appropriate).

Cross-sensitivity

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

Peripheral neuropathy

Peripheral neuropathy is the most common toxic effect of isoniazid (see also section 4.8). The frequency depends on the dose and on predisposing conditions such as

- malnutrition,
- chronic alcohol dependence,
- HIV infection,
- renal failure
- diabetes
- pregnancy or breastfeeding.

[TB302 trade name] should therefore be used with careful monitoring in patients with neuropathy or conditions that may predispose to it. Patients should be encouraged to report signs such as persistent paraesthesia of the hands and feet.

Pyridoxine (vitamin B6) considerably reduces the risk of developing peripheral neuropathy. Individuals with conditions that predispose them to peripheral neuropathy (see above) should receive preventative **pyridoxine supplementation** when taking isoniazid. Treatment doses of pyridoxine may also be used for management if signs of peripheral neuropathy develop.

For doses of pyridoxine in the prevention and management of isoniazid toxicity, the product information of relevant pyridoxine products should be consulted.

Other neurological conditions

[TB302 trade name] should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

Haematological toxicity

Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be performed before starting treatment and monitored regularly throughout therapy with [TB302 trade name]. In case of severe haematological disturbances, [TB302 trade name] must be discontinued. Vitamin K supplementation may be considered in patients at risk of vitamin-K-dependent coagulopathy.

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with rifampicin use. If laboratory or clinical findings associated with TMA occur in a patient receiving [TB302 trade name], treatment should be discontinued and thorough evaluation for TMA performed. Treatment with [TB302 trade name] should not be resumed in patients who develop TMA and patients should be treated accordingly (consider plasma exchange).

Respiratory effects

After initial improvement of tuberculosis under therapy with [TB302 trade name], the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions or the development of new lesions have been detected. Such paradoxical reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

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

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

There have also been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving rifampicin for treatment of tuberculosis (see section 4.8). [TB302 trade name] should be permanently discontinued if this occurs.

Malaria

The rifampicin content of [TB302 trade name] may reduce exposure, and potentially clinical efficacy, of some antimalarials (see section 4.5).

If a person has diagnosed malaria but has not yet begun treatment with [TB302 trade name], the episode of malaria should be prioritised and treated first. If TB treatment has already begun, malaria treatment should be started concomitantly and monitored clinically according to national guidelines to ensure that the malaria is cured. There is insufficient evidence to indicate that the doses of either TB treatment or artemisinin-based combination therapy should be adjusted.

Diabetes mellitus

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

Renal impairment

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

Drug interactions

Rifampicin is a strong inducer of hepatic drug metabolism. Therefore [TB302 trade name] may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, corticosteroids, hormonal contraceptives, immunosuppressants and coumarin derivatives (see section 4.5).

Contraception

Hormonal contraceptives may not provide adequate protection against conception when co-administered with [TB302 trade name] (see also section 4.5). Barrier or other non-hormonal methods of contraception should be used if contraception is needed.

Porphyria

[TB302 trade name] should be used with caution in patients with porphyria, since enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids

[TB302 trade name] may cause a reddish-orange discolouration of body fluids such as urine, sputum and tears. This is due to rifampicin, and does not require medical attention. Contact lenses or dentures may be permanently stained.

Excipients

[TB302 trade name] contains aspartame, which is a source of phenylalanine and may be harmful for people with 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

Rifampicin is a very potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as of glucuronidation and the P-glycoprotein transport system**.** Administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be taken into account when cotreating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping concomitant treatment with [TB302 trade name].

In vitro, *isoniazid* acts as an inhibitor of CYP2C19 and CYP3A4. Thus, it may increase exposure to drugs mainly eliminated through either of these pathways. However, when given with rifampicin, as when using [TB302 trade name], these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. Insofar as it has been investigated, the net effect of rifampicin and isoniazid on drug clearance will be an increase due to rifampicin rather than a decrease due to isoniazid.

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

Mainly due to rifampicin, [TB302 trade name] may interact with a very large number of other drugs, primarily by reducing the exposure to co-administered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic agents, no interaction data with rifampicin are available. However, clinically significant reductions in drug exposure may occur. Whenever co-prescribing any drug together with [TB302 trade name], the possibility of a drug-drug interaction should be considered.

Some combinations are contra-indicated: in particular, [TB302 trade name] must not be given with HIV protease inhibitors and nevirapine, rilpivirine, doravirine or etravirine, direct-acting antivirals for hepatitis C therapy, the antipsychotic lurasidone or the antifungal voriconazole. For more information on these and other combinations that should be avoided, see the table below.

The following list of drug interactions with [TB302 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 by Therapeutic Area	Interaction	Recommendations concerning 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.
Lamivudine **Emtricitabine** /rifampicin	No interaction expected	No dose adjustment required.
Tenofovir alafenamide/ emtricitabine/ rifampicin	Interaction not studied. Co-administration of rifampicin, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Coadministration is not recommended.
Tenofovir disoproxil / rifampicin	Tenofovir AUC ↓ 13%	No dose adjustment required.
Abacavir / rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.
Non-nucleoside analogues **Efavirenz** / rifampicin	Efavirenz AUC ↓ 26%	No dose adjustment required; monitor virological response
Nevirapine / rifampicin	nevirapine: AUC ↓ 58%	[TB302 trade name] must not be co-administered with nevirapine (see section 4.3).
Doravirine / rifampicin	Doravirine AUC ↓ 88% Cmax ↓ 57%	[TB302 trade name] must not be co-administered with doravirine
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	[TB302 trade name] must not be co-administered with etravirine .
Rilpivirine / rifampicin	Rilpivirine AUC ↓ 80%	[TB302 trade name] must not be co-administered with rilpivirine

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Protease inhibitors **Fosamprenavir /** rifampicin **Indinavir** **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir**	Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to dose adjust by increased doses, or an increase in ritonavir-boosting, have been ineffective or ill-tolerated with a high rate of hepatotoxicity.	[TB302 trade name] must not be co-administered with HIV or HCV protease inhibitors (see section 4.3).
Other antiretrovirals		
Raltegravir / rifampicin	Raltegravir AUC ↓ 40%	Co-treatment should be avoided. If deemed necessary, consider an increase of the raltegravir dose to 600 mg b.i.d.
Dolutegravir / rifampicin	Dolutegravir AUC ↓ 54%	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with [TB302 trade name] in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
Elvitegravir/cobicistat/rifampicin	Coadministration has not been studied. Rifampicin is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect.	Co-treatment should be avoided.
Maraviroc / rifampicin	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d.
Antivirals for hepatitis C-infection		
Daclatasvir **Elbasvir/Grazoprevir** **Glecaprevir/Pibrentasvir** **Ledipasvir/Sofosbuvir** **Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)** **Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/** rifampicin isoniazid	Rifampicin: Coadministration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifampicin and hence to reduce their therapeutic effect.	Coadministration of [TB302 trade name] with these antivirals is contraindicated (for further details see Summary of product characteristics of the drugs for therapy of HCV).

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Isoniazid: Coadministration has not been studied. Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal hepatitis associated with isoniazid therapy may develop even after many months of treatment.	
Antifungals		
Ketoconazole / rifampicin	Ketoconazole AUC ↓ 80%	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Fluconazole / rifampicin	Fluconazole AUC ↓ 23%	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Itraconazole / rifampicin	Itraconazole AUC ↓ >64-88%	Co-administration should be avoided.
Voriconazole / rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials/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. No dose adjustment is 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

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		required. Efficacy should be monitored.
Ethionamide / rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
Antimalarials		
Chloroquine / rifampicin		Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy. If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Atovaquone / rifampicin	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Mefloquine / rifampicin	Mefloquine AUC ↓ 68%	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Amodiaquine / rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Quinine / rifampicin	Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates.	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Lumefantrine / rifampicin	Lumefantrine AUC ↓ 68%	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
Artemisinin and its derivatives / rifampicin	Artemether AUC ↓ 89% Dihydroarthemisinin AUC ↓ 85%	If coadministration cannot be avoided,careful monitoring of efficacy is recommended (see section 4.4).
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	Efficacy should be monitored and codeine dose increased if

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	moiety of codeine, are likely to be substantially reduced.	necessary.
Methadone / rifampicin	Methadone AUC ↓ 33-66%	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
Paracetamol (acetaminophen) / rifampicin / isoniazid	Rifampicin may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive. Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of [TB302 trade name] and paracetamol should be avoided.
ANTICONVULSANTS		
Carbamazepine / rifampicin / isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine whereas isoniazid may increase them. Neurological side effects and the. risk of hepatotoxicity increase when co-treating with carbamazepine.	Co-administration of [TB302 trade name] and carbamazepine should be avoided.
Phenobarbital / rifampicin / isoniazid	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isonazid may increase the risk of hepatotoxicity.	Co-administration of [TB302 trade name] and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin / rifampicin isoniazid	Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and [TB302 trade name] should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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 (3-5 fold increases in cyclosporine 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 [TB302 trade name] and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Warfarin / rifampicin /isoniazid	Warfarin AUC ↓ 85% Isoniazid may inhibit hepatic metabolism of warfarin.	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifampicin treatment.
Atenolol / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Verapamil / rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	[TB302 trade name] and verapamil per-orally should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required.
Digoxin / rifampicin	AUC p.o ↓ 30%	When co-administering [TB302 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine. / rifampicin	Lidocaine CLi.v. ↑ 15%	No dose adjustment required.
Amlodipine / rifampicin	Amlodipine, like other calcium channel blockers, is metabolised	Efficacy should be monitored.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	by CYP3A; lower exposure is expected when co-treating with rifampicin.	
Enalapril / rifampicin	Decrease in exposure to the active metabolite of enalapril	Dose adjustment of enalapril should be made if required by the patient's clinical condition.
Simvastatin / rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended.
Atorvastatin / rifampicin	Atorvastatin AUC ↓ 80%	Co-administration is not recommended.
Clopidogrel / rifampicin	Induction of CYP2C19, results in an increased level of clopidogrel active metabolite and enhanced platelet inhibition, which may potentiate the risk of bleeding.	Co-administration is not recommended.
GASTROINTESTINAL MEDICINES		
Ranitidine / rifampicin	Ranitidine AUC ↓ 52%	Efficacy should be monitored, and ranitidine dose increased if necessary.
Antacids / isoniazid / rifampicin	Antacids may reduce the bioavailability of rifampicin by up to one third. Aluminium hydroxide impairs the absorption of isoniazid.	The clinical importance is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used, if co-treatment with [TB302 trade name] is necessary.
PSYCHOTHERAPEUTIC MEDICINES		
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.
Chlorpromazine / rifampicin / isoniazid	Rifampicin may reduce chlorpromazine exposure. Also, concomitant use of chlorpromazine with	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	isoniazid may impair the metabolism of isoniazid.	
Haloperidol / rifampicin **Clozapine**	Haloperidol clearance is substantially increased by rifampicin, theoretical considerations imply that same applies to clozapine.	If co-treatment of [TB302 trade name] with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Lurasidone	Rifampicin 600mg was shown to decrease lurasidone AUC by 81%. Therefore, markedly reduced exposure of lurasidone can be expected when lurasidone is given concomitantly.	Co-administration of [TB302 trade name] with lurasidone is contraindicated (see section 4.3).
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		
Prednisolone / rifampicin **And other systemically administered corticosteroids** /isoniazid	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin. Concomitant use with isoniazid may moderately decrease isoniazid exposure	Co-administration of [TB302 trade name] with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.
Glibenclamide / rifampicin **Glimepiride** **Repaglinide**	Glibenclamide AUC ↓ 39% Glimepiride AUC ↓ 34% Repaglinide AUC ↓ 57%	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
Insulin	No interaction expected.	No dose adjustment required.
Levothyroxine / rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored.
Ethinylestradiol / rifampicin	Ethinylestradiol AUC ↓ 66%	Co-adminstration with [TB302 trade name] may be associated with decreased

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Norethindrone / rifampicin	Norethindrone AUC ↓ 51%	Co-administration with [TB302 trade name] may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Mifepristone / rifampicin	Rifampicin was shown to decrease mifepristone AUC by 6.3-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone by 20-fold and 5.9-fold, respectivel	Co-administration with [TB302 trade name] may be associated with decreased efficacy and should be avoided.
OTHER MEDICINES		
Praziquantel / rifampicin	Praziquantel AUC ↓ 80-99%	Co-treatment with [TB302 trade name] should be avoided.
Dapsone / 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.	Monitor patients for haematological adverse effects
Disulfiram / isoniazid	Concurrent use of disulfiram together with isoniazid may result in increased incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB302 trade name].
Levodopa / isoniazid	Isoniazid may reduce the therapeutic effects of levodopa.	Patients should be monitored for an increase in parkinsonian symptoms.
Theophylline / Isoniazid / Rifampicin	Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of combination are unknown.	Theophylline dose adjustment may be needed.
Enflurane / Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Co-administration of [TB302 trade name] with enflurane should be avoided.

Interactions with food and drink:

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

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

Interactions with laboratory tests:

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B_{12}. Alternative assay methods should be considered.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

This medicine may be used during pregnancy, including for prophylaxis. Isoniazid and rifampicin cross the placenta but are not considered to pose any additional risks to the patient or fetus. Tuberculosis can be particularly dangerous during pregnancy and should be managed with effective treatment. Close monitoring during pregnancy will allow any concerns to be managed promptly (see section 4.4) and pyridoxine supplementation is recommended. When [TB302 trade name] is administered during the last few weeks of pregnancy it may cause post-natal haemorrhage in the mother and infant for which treatment with vitamin K may be indicated.

Breast-feeding

Rifampicin and isoniazid pass into the breast milk of breast-feeding mothers in low concentrations. Rifampicin may result in discoloration of the milk. No adverse effects in the baby have been reported, and breast-feeding should not be discouraged. Because of the theoretical risk associated with isoniazid, breast-fed infants whose mothers are taking [TB302 trade name] should be monitored for any signs of vitamin B6 deficiency; pyridoxine supplementation should be given to both the mother and infant.

Concentrations in breast milk are too low to be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

Fertility

There are no data on the effects of [TB302 trade name] on human fertility. Studies in rats with isoniazid have shown slight reductions in fertility. Animal studies indicate no effects of rifampicin on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[TB302 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

The most important adverse reactions of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage, but occasionally causes hepatocellular injury. It can also potentiate the hepatotoxicity of the other anti-tuberculosis medications.

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects (especially peripheral neuropathy), and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. The majority of cases have occurred within the first 3 months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

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

.Infections and infestations

Frequency not known	Pseudomembranous colitis, influenza

Blood and lymphatic system disorders

Common	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, reversible if treatment is discontinued as soon as purpura occurs.
Uncommon	Leukopenia
Not known	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome; disseminated intravascular coagulation; eosinophilia; agranulocytosis, haemolytic anaemia, vitamin K-dependent coagulation defect; aplastic anaemia, sideroblastic anaemia, lymphadenopathy

Immune system disorders

Not known	Anaphylactic reaction

Endocrine disorders

Not known	Adrenal insufficiency in patients with compromised adrenal function; gynaecomastia

Metabolism and nutrition disorders

Not known	Decreased appetite; hyperglycaemia, pellagra

Psychiatric disorders

Uncommon	Toxic psychosis

Nervous system disorders

Common	Headache, dizziness
Uncommon	Convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment
Not known	Vertigo, increased seizure frequency in patients with epilepsy. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura. Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on isoniazid 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), Cerebellar syndrome (including cerebellar ataxia, ataxia, dysdiadochokinesis, balance disorders, nystagmus, dysmetria) mainly in patients with chronic kidney disease

Vascular disorders

Not known	Shock, flushing, vasculitis, bleeding

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

Common	Nausea, vomiting
Uncommon	Diarrhoea

Not known	Abdominal discomfort, tooth discoloration (may be permanent); constipation, dry mouth, pancreatitis

Hepatobiliary disorders

Uncommon	Severe, sometimes fatal hepatitis
Not known	Drug-induced liver injury (including fatal cases especially when used in combination with other tuberculosis medicines)

Skin and subcutaneous tissue disorders

Not known	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), pruritus, pruritic rash, urticaria, allergic dermatitis, pemphigoid, sweat discoloration; acne, exfoliative dermatitis, pemphigus, alopecia

Musculoskeletal and connective tissue disorders

Not known	Muscle weakness, myopathy, bone pain; systemic lupus-like syndrome

Renal and urinary disorders

Not known	Acute kidney injury, usually due to renal tubular necrosis or tubulointerstitial nephritis; chromaturia

Pregnancy, puerperium and perinatal conditions

Not known	Post-partum haemorrhage, fetal-maternal haemorrhage

Reproductive system and breast disorders

Not known	Menstrual disorders

Congenital, familial and genetic disorders

Not known	Porphyria

General disorders and administration site conditions

Very common	Pyrexia, chills
Common	Paradoxical drug reaction (recurrence or appearance of new symptoms or physical/radiological signs of tuberculosis in a patient who had previously shown improvement with appropriate treatment)
Not known	Oedema

Investigations

Common	Increases in blood bilirubin, aspartate aminotransferase, alanine aminotransferase
Not known	Blood pressure decreased, increases in blood creatinine, hepatic enzymes

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances have occurred within 30 minutes to 3 hours after ingestion of **isoniazid**. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria and hyperglycaemia. The toxicity is potentiated by alcohol. Lethal doses have been reported to range between 80 and 150 mg/kg.

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy are expected within a short time after acute ingestion of **rifampicin**; 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. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases. Non-fatal acute overdoses in adults have been reported with doses ranging from 9–12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14–60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and non-fatal reports. Non-fatal overdoses in paediatric patients ages 1–4 years old of 100 mg/kg for one to two doses have been reported.

Treatment

There is no specific antidote and management is largely symptomatic. Evacuation of the stomach and administration of activated charcoal may be considered if within a short time of ingestion and the patient is not experiencing seizures.

In the event of seizures and metabolic acidosis, pyridoxine is given intravenously at 1 g per g of isoniazid; if the isoniazid dose is unknown, 5 g pyridoxine is given. In the absence of seizures, 2 to 3 g pyridoxine is given intravenously for prophylaxis. Pyridoxine should be diluted to reduce vascular irritation and it is infused for 30 minutes via infusion pump or syringe pump. The dose is repeated if necessary.

Diazepam potentiates the effect of pyridoxine. A high dose of diazepam can also be tried to combat seizures if pyridoxine is unavailable. In severe cases, respiratory therapy should be instituted.

Metabolic acidosis and electrolyte disturbances should be corrected and good diuresis ensured. Haemodialysis or haemoperfusion has been used in the event of extremely severe intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

In vitro, **rifampicin** is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. It inhibits bacterial DNA-dependent RNA polymerase, preventing transcription. In tuberculosis, rifampicin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance may occur, as a result of alterations in the target enzyme (RNA polymerase).

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

5.2 Pharmacokinetic properties

The absorption characteristics of [TB302 trade name] have been determined after administration of tablets of [TB302 trade name] in healthy volunteers under fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean value ± standard deviation**	
	Isoniazid	**Rifampicin**
Maximum concentration (C_{max}) ng/mL	2043 ± 739	2160 ± 516
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption ng.h/mL	7653 ± 3889	10950 ± 2180
Time to attain maximum concentration (t_{max}) h	0.57 ± 0.34	1.20 ± 0.50

	Rifampicin	Isoniazid
Absorption		
Absolute bioavailability	90 −95%	NA*
Oral bioavailability	> 90%	>80%
Food effect	No effect on extent of absorption. Rate of absorption is reduced.	Reduced.
Distribution		
Volume of distribution (mean)	55 L	43 L
Plasma proteinbinding *in vitro*	60 −90%	< 10%
Tissue distribution	CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Concentrations in liver, spleen, kidneys and lung tissue are higher than serum concentrations. Penetrates into vaginal and cervical tissue and into cervicovaginal fluid. Passes the placenta; serum concentration in fetus are about 1/3 of those in mother.	It diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). It crosses the placenta and is secreted in the milk.
Metabolism		
General	Primarily hepatic, rapidly deacetylated while undergoing enterohepatic recirculation.	Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid.
Active metabolite(s)	25-o-deacetyl rifampicin	Nicotinoyl-NAD adduct
Elimination		
Elimination half life	3−5 hours Decreases to 2−3 hours after repeated administration	1.2 hours: rapid acetylators 3.5 hours: Slow 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
% of dose excreted in urine	30%	75−95%
% of dose excreted in faeces	60−65%	<10%
Pharmacokinetic linearity	Non linear	NA*
Drug interactions *(in vitro*)	Rifampicin induces hepatic enzymes	Isoniazid is CYP450 inducer and inhibitor. Isoniazid is an arylamine n-acetyltransferase 2 substrate and inhibitor
Transporters	Solute carrier transporters (SLC) ATP Binding Cassette transporters (ABC) P-glycoprotein 1	NA*
Metabolising enzymes	CYP450	CYP450: 2C19, 3A4

Pharmacokinetics of rifampicin and isoniazid

*NA information not available

Special populations

Rifampicin

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

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

In one study, **paediatric patients** 6 to 58 months old were given rifampicin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 µg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the $t_{½}$ of rifampicin averaged 2.9 hours. It should be noted that in other studies in paediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 µ/mL to 15 µ/mL have been reported.

Isoniazid

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

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

5.3 Preclinical safety data

Rifampicin

After oral administration of 100 mg/kg bodyweight 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 occurred with multiple doses of 105 mg/kg/day.

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

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

Rifampicin concentrations in cord blood reach 12–33% of maternal blood concentrations.

Teratogenic effects were noted in rodents treated with high doses. 100 to 150 mg/kg daily in rodents have been reported to cause cleft palate and spina bifida.

In rats, neither fertility nor peri- or postnatal development was impaired.

Malformation and death were reported at the same frequency in infants born to mothers exposed to rifampicin as in the general population.

Isoniazid

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Treatment of pregnant rats with isoniazid resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis was impaired in treated rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose

crospovidone

povidone

bleached shellac

croscarmellose sodium

aspartame

trusil raspberry 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 packs

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

Strip packs

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

6.5 Nature and contents of container

Bottle pack

[TB302 trade name] are packed in an LDPE bag put in a triple laminated sachet kept in an HPDE bottle (round milky white container with screw thread cap), finally sealed with a tagger seal along with pack insert.

Pack size: 100 tablets

Strip pack

Alu/alu strip pack, each containing 10 or 28 tablets. Available in cartons of 10 x 10 tablets or 3 x 28 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)

TB302

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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