SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains:
Rifampicin .....75 mg
Isoniazid .....50 mg
Pyrazinamide .....150 mg
Each tablet also contains: Aspartame 3.13 mg
For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM

Brick-red, mottled, circular, uncoated biconvex tablets having a deep score on one side and a plain surface on the other side.
The score-line is only to facilitate breaking for ease of swallowing and **not** to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is indicated for the initial treatment of tuberculosis in children, caused by drug-susceptible *Mycobacterium tuberculosis*, according to the guidelines of WHO—Treatment of tuberculosis: guidelines 4th edition, WHO, available at:

http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

The 2017 update, Guidelines for treatment of drug-susceptible tuberculosis and patient care, is available at:

http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/ Also, Rapid Advice, Treatment of Tuberculosis in Children, 2010, available at:

http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf

4.2 **Posology and method of administration**

Oral use.

Child's weight	**Dose (single daily dose)**
4–7 kg	1 tablet daily
8–11 kg	2 tablets daily
12–15 kg	3 tablets daily
16–24 kg	4 tablets daily

It is recommended that children weighing over 25 kg receive adult dosage. Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is not suitable for intermittent treatment regimens.

If it is necessary to discontinue or reduce the dose of isoniazid, pyrazinamide or rifampicin then single-component preparations should be used instead of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Renal impairment

Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance less than 30 ml/minute), separate preparations of rifampicin, pyrazinamide and isoniazid are recommended (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. Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be used in patients with severe liver disease (see section 4.3).

Method of administration

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be taken on an empty stomach (at least one hour before or two hours after a meal). Taking with food (e.g. to improve gastrointestinal tolerance) reduces absorption.

The required number of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be dispersed in about 50 ml water and the entire mixture should be swallowed. The mixture (of tablets dispersed in water) should be used within 10 minutes.

4.3 **Contraindications**

Hypersensitivity to the active substances or to any of the excipients. Acute liver disease, icterus or severe liver impairment.

Acute gout

Co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with voriconazole, any HIV protease inhibitor, bictegravir, elvitegravir/cobicistat, etravirine, rilpivirine or with several direct-acting antiviral medicines for treating chronic

hepatitis C is contraindicated (see section 4.5).

4.4 **Special warnings and special precautions for use**

Liver toxicity

Isoniazid, pyrazinamide and rifampicin may cause hepatotoxicity (see section 4.8).

Whenever possible, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be avoided in patients with hepatic impairment (ALT greater than 3 times upper limit of normal) due to the risk of liver toxicity. Patients should be strongly advised to restrict use of alcoholic beverages during treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets. Patient especially at risk for developing hepatitis include:

- age over 35 years;
- daily users of alcohol;
- patients with active chronic liver disease;
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:

- patients taking long-term medication;
- existence of peripheral neuropathy or conditions predisposing to neuropathy;
- pregnant patients;
- HIV-positive patients.

Patients should be instructed to immediately report signs or symptoms suggesting liver damage or other adverse effects. These include: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue or weakness lasting longer than 3 days, and abdominal tenderness especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be discontinued promptly, because continued use may cause severe liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured before starting Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and periodically throughout treatment.

Raised liver enzymes are common during therapy with isoniazid, pyrazinamide and rifampicin. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases are associated with isoniazid, pyrazinamide or rifampicin. These effects on liver enzymes are usually mild to moderate and will most commonly return to normal spontaneously within 3 months, even with continued therapy.

If the concentration of liver enzymes exceeds three to five times the upper limit of normal, discontinuation of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be strongly considered.

If appropriate, component drugs can be reintroduced after intercurrent hepatotoxicity but only after symptoms and laboratory abnormalities have subsided. When restarting the drugs, the component drugs should be given one by one and at gradually increasing doses or alternative drugs should be used; Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should not be used.

Hypersensitivity

Rifampicin may cause a hypersensitivity syndrome including flu-like symptoms. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If case of severe acute signs of rifampicin hypersensitivity (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock, or acute renal failure), Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be discontinued immediately. These patients should not be treated with rifampicin again. If rifampicin is temporarily discontinued, it should be reintroduced carefully at a reduced dose and with close monitoring. In this situation, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should not be used.

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

Peripheral neuropathy

Peripheral neuropathy is the most common toxic effect of isoniazid. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes.

Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine 10 mg daily should be given routinely with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Epilepsy and psychotic disorders

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be used with caution in patients with seizure disorders or a history of psychosis.

Haematological toxicity

Since rifampicin is associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored throughout therapy with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets. In case of severe haematological disturbances Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must be discontinued.

Hyperuricaemia and gout

Pyrazinamide may increase serum levels of uric acid and cause gout. Patients with a history of gout should be carefully monitored. Serum uric acid levels should be determined before starting

therapy with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Renal impairment

In renal insufficiency, the clearance of pyrazinamide and isoniazid is delayed, leading to increased systemic exposure. In case of renal insufficiency, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should not be used, as dose modifications of the active components may be necessary.

Nephrotoxicity

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be discontinued in case of clinical signs of nephrotoxicity.

Diabetes Mellitus

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

Drug interactions

Rifampicin is a strong inducer of hepatic drug metabolism. Therefore Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may reduce efficacy of many medicines, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

Contraception

Oral contraceptives do not provide adequate protection against conception when co- administered with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets. This probably also applies to other forms of hormonal contraceptives (e.g. transdermal patches and transdermal implants). Barrier or other non-hormonal methods of contraception should be used.

Treatment with corticosteroids

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids

Rifampicin in Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears. This does not require medical attention.

Alcohol

Intake of alcohol beverages should be avoided during treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Laboratory monitoring
Full blood count, liver function testing and serum uric acid measurement are required before treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and at regular intervals during treatment.
Excipients
Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets contains aspartame, which is a source of phenylalanine and may be harmful for people with phenylketonuria.

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. Giving rifampicin with drugs that are biotransformed through these metabolic pathways is likely to accelerate elimination of co-administered drugs. These effects approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, doses of drugs metabolised by these enzymes may require adjustment when starting or stopping the concomitant administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets.

Isoniazid can inhibit CYP2C19 and CYP3A4. Thus it may increase exposure to drugs eliminated mainly through either of these pathways. However, when used with rifampicin in Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, these effects are likely to be outweighed by hepatic enzyme induction due to rifampicin. In so far as it has been investigated, the net effect of rifampicin and isoniazid on drug clearance will be an increase due to rifampicin rather than a decrease due to isoniazid.

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

Mainly due to rifampicin, Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets 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. Clinically significant reduction in drug exposure may occur. Whenever prescribing any drug with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, the possibility of a drug–drug interaction should be considered.

The following list of drug interactions with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is not exhaustive. Data on drug interactions is mainly derived from studies in adults.

Drugs by Therapeutic Area	**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 modification of zidovudine in this situation has not been formally evaluated.
Didanosine	Didanosine may reduce metabolism of pyrazinamide	No dose adjustment required but monitor for side effects (e.g. arthralgia)
Emtricitabine **Lamivudine**	No interaction expected	No dose adjustment required
Stavudine	Increased risk of distal sensory neuropathy when isoniazid is used with stavudine	Monitor for side effects when Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is used with stavudine
Emtricitabine with tenofovir alafenamide + rifampicin	Rifampicin may decrease tenofovir alafenamide concentration and can lead to loss of therapeutic effect and possible development of resistance	Concomitant administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with emtricitabine and tenofovir alafenamide is not recommended
Tenofovir disoproxil + rifampicin	Tenofovir AUC □ 13%	No dose adjustment required
Abacavir + rifampicin	Rifampicin may decrease abacavir concentration by inducing	Efficacy of abacavir should be monitored in co-treatment

	glucuronidation	
Antiretrovirals: non-nucleoside analogues		
Efavirenz + rifampicin	Efavirenz AUC □ 26%	When co-treating with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets, consideration may be given to increasing the efavirenz dose (to 800 mg once daily in adults)
Nevirapine + rifampicin	Nevirapine: AUC □ 58%	Since neither the appropriate nevirapine dose when given with rifampicin, nor the safety of the combination has been established, concomitant use of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and nevirapine is not recommended

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Etravirine + rifampicin	Rifampicin is likely to significantly reduce etravirine concentration	Concomitant treatment of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with etravirine should be avoided
Rilpivirine + rifampicin	Rilpivirine AUC □ 80%	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be co-administered with rilpivirine
Antiretrovirals: protease inhibitors		
Atazanavir (also atazanavir with cobicistat) **+** rifampicin **Darunavir** (also darunavir with cobicistat) **Fosamprenavir** **Indinavir** **Lopinavir** **Nelfinavir** **Ritonavir** **Saquinavir** **Tipranavir**	Protease inhibitor exposure will be reduced to sub-therapeutic level due to interaction with rifampicin. Rifampicin also reduces levels of cobicistat (used for boosting atazanavir and darunavir) and can lead to loss of therapeutic effect and possible development of resistance	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be co-administered with protease inhibitors.
Other antiretrovirals		
Bictegravirb + rifampicin	Bictegravir AUC ↓ 75%	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be co-administered with bictegravir
Dolutegravir + rifampicin	Dolutegravir AUC ↓ 54%	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with rifampicin. Children

		should receive the weight-based dose of dolutegravir twice daily
Elvitegravir with cobicistat + rifampicin	Rifampicin significantly reduces levels of elvitegravir and cobicistat and can lead to loss of therapeutic effect and possible development of resistance	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be co-administered with elvitegravir and cobistat
Raltegravir + rifampicin	Raltegravir AUC ↓ 40%	If co-treatment is necessary, increasing the raltegravir dose (to 600 mg twice daily in adults) should be considered
Maraviroc + rifampicin	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If maraviroc is necessary, the dose should be increased (to 600 mg twice daily in adults)

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Antivirals for treating chronic hepatitis C		
Daclatasvir + rifampicin **Dasabuvir** **Elbasvir with grazoprevir** **Elbasvir with grazoprevir** **Glecaprevir with pibrentasvir** **Ledipasvir with sofosbuvir** **Ombitasvir with paritaprevir and ritonavir** **Simeprevir** **Sofosbuvir with velpatasvir** **Sofosbuvir with velpatasvir and voxilaprevir**	Rifampicin can reduce the effectiveness of direct-acting antivirals used for treating chronic hepatitis C	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets must not be co-administered with direct-acting antivirals.
Antifungals		
Ketoconazole + rifampicin	Ketoconazole AUC 80%	Co-administration should be avoided but if necessary, a higher dose of ketoconazole may be required
Fluconazole + rifampicin	Fluconazole AUC ↓ 23%	Efficacy should be monitored. A higher dose of fluconazole may be required
Itraconazole + rifampicin	Itraconazole AUC ↓ 64–88% (or more)	Co-administration should be avoided
Voriconazole + rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials including antituberculosis antibacterials		
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
Ofloxacin + pyrazinamide **Levofloxacin**	Co-treatment with pyrazinamide and either fluoroquinolone increased adverse events (e.g. hepatic, gastrointestinal, musculoskeletal) leading to discontinuation of therapy	Co-treatment of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with either fluoroquinolone is not recommended. However, if co-treatment is necessary, patients should be carefully monitored for adverse effects
Doxycycline + rifampicin	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Metronidazole + rifampicin	Metronidazole AUC (intravenous) ↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is 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 increased risk of hepatotoxicity
Antimalarials		
Chloroquine + rifampicin		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 necessary, a higher dose of quinine should be considered
Lumefantrine + rifampicin	Empirical data are not available. Since lumefantrine is metabolised by CYP3A, lower levels are expected with rifampicin co-treatment.	Co-administration should be avoided
Artemisinin and derivatives + rifampicin	Empirical data are not available. During co-treatment with rifampicin, lower levels of artemisinin and its derivatives may be expected.	Co-administration should be avoided
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine + rifampicin	Morphine AUC (by mouth) □ 30%	If co-administration necessary, efficacy should be monitored and the dose may need to be increased

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Codeine + rifampicin	Plasma level of morphine, an active metabolite of codeine, is likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary
Methadone + rifampicin	Methadone AUC ↓ 33–66%	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate
Paracetamol (acetaminophen) + rifampicin + isoniazid	Rifampicin may increase the glucuronidation of paracetamol and decrease its efficacy Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and paracetamol should be avoided
ANTICONVULSANTS		
Carbamazepine + rifampicin + isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine. Isoniazid may increase risk of hepatotoxicity when co-treating with carbamazepine.	Co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets 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 Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and phenobarbital should be undertaken with caution, with monitoring of clinical effects and, if possible, plasma drug concentrations

Phenytoin + rifampicin + isoniazid	Phenytoin AUC (intravenous) □ 42% Co-treatment with phenytoin and isoniazid may increase risk of hepatotoxicity	Co-treatment with phenytoin and Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be avoided
Valproic acid + rifampicin	Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, rifampicin is likely toreduce plasma level of valproic acid	Co-treatment should be avoided. If necessary, efficacy and, if possible, plasma concentrations of valproic acid, should be monitored
Lamotrigine + rifampicin	Lamotrigine AUC □ 45%	Co-treatment should be avoided but if necessary, lamotrigine dose should be increased.

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
IMMUNOSUPPRESSIVES		
Ciclosporin + rifampicin	Rifampicin can substantially increase ciclosporin clearance	Co-administration should be avoided but if necessary, plasma concentration of ciclosporin should be monitored and doses adapted accordingly (3–5 fold increases in ciclosporin dose have been required).
Tacrolimus + rifampicin	Tacrolimus AUC (intravenous) ↓ 35%; AUC (oral) ↓ 70%	Co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and tacrolimus should be avoided but if necessary, plasma concentrations of tacrolimus should be monitored, and the dose increased as appropriate
CARDIOVASCULAR MEDICINES		
Warfarin + rifampicin	Warfarin AUC ↓ 85%	Co-administration should be avoided
Atenolol + rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required
Verapamil + rifampicin	S-verapamil (oral) CL/F ↑ 32- fold. With (intravenous) S-verapamil, CL ↑ 1.3-fold	Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets and oral verapamil should not be co-administered. If verapamil is given intravenously, the therapeutic effect should be carefully

		monitored; dose adjustment may be required
Digoxin + rifampicin	AUC (oral) ↓ 30%	When co-administering Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required
Lidocaine + rifampicin	Lidocaine CL (intravenous) ↑ 15%	No dose adjustment required
Amlodipine + rifampicin	Amlodipine, like other calcium- channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin	Efficacy should be monitored

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Enalapril + rifampicin	No interaction expected	No dose adjustment required
Simvastatin + rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	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 Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is necessary
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam + rifampicin	Diazepam AUC □ > 70%	Co-treatment is not recommended. If deemed necessary, diazepam doses may need to be increased
Chlorpromazine + rifampicin + isoniazid	Rifampicin may reduce chlorpromazine exposure. Also, chlorpromazine may impair the metabolism of isoniazid	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity
Haloperidol + rifampicin	Rifampicin substantially increases haloperidol clearance	If co-treatment of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with haloperidol is necessary, efficacy of haloperidol should be monitored. A dose

		increase may be required
Amitriptyline + rifampicin	Case reports (and theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance	Co-treatment should be avoided. If necessary, efficacy and, if possible, plasma concentrations of amitriptyline should be monitored.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone and 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 Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets 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 by Therapeutic Area	Interaction	Recommendations on co- administration
Glibenclamide + rifampicin	Glibenclamide AUC ↓ 34%	Blood glucose levels should be closely monitored. The dose of glibenclamide may need to be increased
Insulin		No interaction expected
Levothyroxine + rifampicin	Rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored
Ethinylestradiol + rifampicin	Ethinylestradiol AUC ↓ 66%	Co-administration with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may decrease contraceptive efficacy. Barrier- or other non- hormonal methods of contraception should be used
Norethisterone + rifampicin	Norethisterone AUC ↓ 51%	Co-administration with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets may decrease contraceptive efficacy. Barrier- or other non- hormonal methods of contraception should be used
OTHER MEDICINES		
Praziquantel + rifampicin	Praziquantel AUC □ 80–99%	Co-treatment with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be avoided
Disulfiram + isoniazid	Concurrent use of disulfiram with isoniazid may increase adverse effects on the central nervous system	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg

		Dispersible Tablets
Enflurane + isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane	Co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with enflurane should be avoided.
Probenecid + pyrazinamide	Complex pharmacokinetic and pharmacodynamics two-way interaction occurs between pyrazinamide and probenecid	Recommendations on adjusting the probenecid dose have not been established. Therefore concomitant use with Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be avoided

Drugs by Therapeutic Area	Interaction	Recommendations on co- administration
Allopurinol + pyrazinamide	Pyrazinamide major (active) metabolite pyrazinoic acid ↑ 70% Since pyrazinoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia	Avoid co-administration of Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets with pyrazinamide

Interactions with food and drink

Alcohol: Daily use of alcohol may increase the 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- or diamine-oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. This may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.

Interactions with laboratory tests

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

4.6 **Pregnancy and lactation**

Pregnancy

No adverse effects of isoniazid or pyrazinamide on the human fetus have been reported. At very high doses in animals, rifampicin has teratogenic effects. Rifampicin has been reported to cross the placental barrier and appear in cord blood but the effect of rifampicin, alone or with other antituberculosis drugs, on the human fetus is not known. Use of rifampicin in the third trimester has been associated with postnatal haemorrhage in the mother and infant.

Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K supplements.

Breastfeeding

Isoniazid, pyrazinamide and rifampicin appear in breast 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 adverse effects in the baby have been reported.

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

Isoniazid is associated with vertigo, visual disorders and psychotic reactions (see section 4.8). Patients should be informed of these, and advised that if affected, they should not drive, operate machinery or take part in any activities where these symptoms may put either the patients or others at risk.

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 antituberculosis 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 3 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 increase of serum transaminases to symptomatic liver dysfunction, and in rare cases, fatal liver failure.

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 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1
in 1000), very rare (≤ 1 in 10 000), and 'not known'.

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 Headache, lethargy, ataxia, difficulty concentrating, dizziness, seizures, toxic encephalopathy

Not known Tremor, vertigo, insomnia, hyperreflexia

Psychiatric reactions
Uncommon Memory impairment, toxic psychosis
Not known Confusion, disorientation, hallucination
Gastrointestinal disorders
Common Diarrhoea, abdominal pain, nausea, anorexia, vomiting
Rare Erosive gastritis, pseudomembranous colitis
Not known Dry mouth, metallic taste, flatulence, constipation
Hepatobiliary disorders
Very common Transient increases of serum transaminases
Uncommon Increases of serum bilirubin and alkaline phosphatases, hepatitis
Renal and urinary disorders
Rare Acute renal failure, interstitial nephritis
Not known Urinary retention
Metabolic and nutrition disorders
Very common hyperuricaemia
Very rare Porphyria aggravated
Not known Hyperglycaemia, metabolic acidosis, pellagra
General disorders
Very common Flushing
Common Reddish discoloration of body fluids and secretions, such as urine, sputum, tears, saliva and sweat
Not known Allergic reactions with skin manifestations, pruritus, fever, leucopenia, anaphylaxis, allergic pneumonitis, neutropenia, eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, lupus-like syndrome, hypotension, shock
Blood and lymphatic systems disorders
Not known Anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis
Musculoskeletal disorders
Very common Arthralgia
Not known Gout, myalgia
Skin and subcutaneous tissue disorders
Common Erythema, exanthema, pruritus with or without rash, urticaria
Rare Photosensitivity reactions, exfoliative dermatitis, pemphigoid reactions, purpura
Not known Lyell's syndrome, Stevens-Johnson syndrome
Eye disorders
Common Ocular redness, permanent discolouration of soft contact lenses
Rare Exudative conjunctivitis
Not known Optic atrophy or neuritis
Reproductive system and breast disorders
Common Disturbances of the menstrual cycle

4.9 **Overdose**

Symptoms

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

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

Data on pyrazinamide overdose are scarce. However, liver toxicity and hyperuricaemia may occur.

Treatment

Emesis, gastric lavage and activated charcoal may be of value if started within a few hours of ingestion. Subsequently, pyridoxine (intravenous injection on a gram-per-gram basis, equal to the isoniazid dose, if the dose is not known, an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam or oral midazolam (if seizures not responding to pyridoxine) and haemodialysis may be of value. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring and support of ventilation and correction of metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis. ATC code: J04AM05

Mechanism of action

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

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal 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 develops rapidly if it is used alone in the treatment of mycobacterial infection.

Pyrazinamide is a prodrug that is converted into its active form, pyrazinoic acid, by a mycobacterial enzyme, pyrazinamidase, as

well as through hepatic metabolism. Pyrazinoic acid is bactericidal to *Mycobacterium tuberculosis* at acid pH but not at neutral pH. The precise mechanism of action is unknown. Pyrazinamide is inactive against atypical mycobacteria.
Resistance develops rapidly if pyrazinamide is used as the sole antituberculosis agent.

5.2 **Pharmacokinetic Properties**

Isoniazid

Absorption

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥ 80%, and peak serum concentration reached after 1–2 hours. The rate and extent of absorption are reduced when isoniazid is given with food. Isoniazid undergoes appreciable first-pass metabolism in the wall of small intestine and liver.
Following single-dose administration of 4 × Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets in healthy volunteers, used for comparing the bioavailability of this product with a similar dose of the reference formulation, the mean (SD) isoniazid C_{max} value was 4.65 µg/ml (1.77), and the corresponding value for AUC was 15.8. µg·hour/ml (7.6). The mean (SD) isoniazid t_{max} value was 0.57 (0.45) hours.

Distribution

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57–0.76 litre/kg. Protein binding is very low (0–10%).

Metabolism

Isoniazid undergoes extensive metabolism in the mucosal cells of the small intestine and in the liver. First, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolising enzyme N-acetyl transferase). Different ethnic groups display differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that in slow acetylators.

Excretion

Up to 95% of the ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

Pharmacokinetics in renal impairment

The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged, and exposure is increased, in slow acetylators. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and

slow acetylators.

Pyrazinamide

Absorption

Pyrazinamide is almost completely absorbed from the gastrointestinal tract.

Following single dose administration of 4 × Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets in healthy volunteers, used for comparing the bioavailability of this product with the same dose of the reference formulation, the mean (SD) pyrazinamide C_{max} value was 16.7 µg/ml (3.7), and the corresponding value for AUC was 181.9 µg·hour/ml (33.5). The mean (SD) pyrazinamide t_{max} value was 0.7 (0.5) hours.

Distribution

Pyrazinamide is widely distributed in most fluid compartments and tissues. The volume of distribution has been reported as 0.57–0.84 litre/kg. The plasma protein binding of pyrazinamide is low, approximately 10–20%.

Metabolism

Pyrazinamide is hydrolysed by a microsomal deaminase to the active metabolite pyrazinoic acid, which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid

Elimination

Pyrazinamide is eliminated by the kidneys, mostly in the form of various metabolites. About 3% of a pyrazinamide dose is eliminated unchanged. The half-life of pyrazinamide is approximately 10 hours. The half-life of the active metabolite pyrazinoic acid a single dose is approximately 10–20 hours.

Special populations

Renal impairment: Pyrazinamide is excreted renally, mainly in the form of the active metabolite pyrazinoic acid. Hence, pyrazinamide doses should probably be reduced in patients with renal failure. A single-dose study in haemodialysis patients compared with healthy controls showed an approximately two-fold increase in pyrazinamide AUC and a five-fold increase in the AUC of pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were estimated at 26 and 22 hours, respectively.

Hepatic impairment: A single-dose, parallel-group study comparing the pharmacokinetics of pyrazinamide in patients with severe liver disease (hypoalbuminaemia, increased INR, ascites, in most cases hyperbilirubinaemia) and in healthy volunteers found a 40% reduction in pyrazinamide clearance and a 3-fold increase in the exposure to pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were increased by about 60% and 100%, respectively.

Rifampicin

Absorption

Rifampicin is rapidly absorbed from the gastrointestinal tract. Its bioavailability is 90–95% in adults, but may be lower in children.

Concomitant intake of food delays absorption and reduces the peak concentration, but does not decrease bioavailability.

Following single dose administration of 4 × Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg Dispersible Tablets in healthy volunteers, used for comparing the bioavailability of this product with the same dose of the reference formulation, the mean (SD) rifampicin C_{max} value was 4.95 µg/ml (1.18), and the corresponding value for AUC was 27.9 µg·hour/ml (7.0). The mean (SD) rifampicin t_{max} value was 1.4 (0.8) hours.

Distribution

Rifampicin is 60–90% bound to plasma proteins and has a volume of distribution of approximately 0.9 litre/kg. CSF concentrations are of the same order of magnitude as the unbound concentrations in plasma. Rifampicin readily crosses the placenta.

Metabolism

Rifampicin is metabolised by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetylrifampicin. Rifampicin induces its own metabolism; after repeat doses bioavailability is reduced to approximately 70% and apparent clearance is increased.

Excretion

The half-life of rifampicin after a single dose is approximately three hours. After repeat doses this is reduced to approximately 1–2 hours. Rifampicin and its metabolites are mainly excreted in bile, and rifampicin undergoes enterohepatic recirculation. Approximately 25% of a dose is excreted in the urine.

Special populations

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

5.3 **Preclinical safety data**

Isoniazid and pyrazinamide

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

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 were observed at chronic doses of 105 mg/kg/day.

Only limited evidence is available for the carcinogenicity of rifampicin in mice, and in the absence of epidemiological studies, the carcinogenicity of rifampicin in humans cannot be evaluated.

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 occurred in rodents treated with high doses. 100–150 mg/kg daily in rodents have been reported to cause cleft palate and spina bifida. In rats neither fertility nor perinatal or postnatal development was impaired.

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

6. PHARMACEUTICAL PARTICULARS

6.1 **List of excipients**

Microcrystalline cellulose, crospovidone, povidone, bleached shellac, croscarmellose sodium, aspartame, strawberry flavour, magnesium stearate

6.2 **Incompatibilities**

Not applicable

6.3 **Shelf life**

24 months

6.4 **Special precautions for storage**

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

Once dispersed in water, the mixture should be used within 10 minutes.

6.5 **Nature and contents of container**

Bottle packs

100 tablets packed in a self-sealing LDPE bag, plain triple laminated (LDPE/AL/PET) sachet and then in a round, wide mouth, opaque, milky white HDPE container with a HDPE screw thread cap along with the leaflet.

Strip packs

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

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

6.6 **Instructions for use and handling and disposal**

No special requirements.

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

7. Marketing Authorization Holder

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8. Market Authorization Number
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9. Date of First Authorization/renewal of the authorization
Date of renewal: 15th January 2026

10. DATE OF REVISION OF THE TEXT

15th January 2026