SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RIFAPENTINE/ISONIAZID 300/300 ADCO film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each RIFAPENTINE/ISONIAZID 300/300 ADCO film coated tablet contains 300 mg rifapentine and 300 mg isoniazid.
RIFAPENTINE/ISONIAZID 300/300 ADCO tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet.
Brown coloured, circular, biconvex, film coated tablets, score line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RIFAPENTINE/ISONIAZID 300/300 ADCO is indicated for prevention of active tuberculosis in adults and children 2 years of age and older presenting with:
1. latent tuberculosis infection (LTBI) caused by Mycobacterium tuberculosis who are at high risk of progression to tuberculosis disease (including those in close contact with active tuberculosis patients, recent conversion to a positive tuberculin skin test).
2. HIV-infected patients not receiving antiretroviral therapy (ART),
3. patients with pulmonary fibrosis on radiograph with no signs and symptoms of TB regardless of HIV status.

Active tuberculosis disease should be ruled out before initiating treatment with RIFAPENTINE/ISONIAZID 300/300 ADCO.

4.2 Posology and method of administration

Posology:

RIFAPENTINE/ISONIAZID 300/300 ADCO is to be administered once-weekly for 12 weeks as directly observed therapy (DOT).

Adults and children 12 years and older:

The recommended dose of rifapentine should be determined based on weight of the patient up to a maximum of 900 mg once-weekly for 12 weeks (see Table 1).
The recommended dose of isoniazid is 15 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a to a maximum of 900 mg once-weekly for 12 weeks (see Table 1).

Children 2 to 11 years:

The recommended dose of rifapentine should be determined based on weight of the patient up to a maximum of 900 mg once-weekly (see Table 1).
The recommended dose of isoniazid is 25 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a maximum of 900 mg once-weekly for 12 weeks.

Table 1: Weight-based dose of RIFAPENTINE/ISONIAZID 300/300 ADCO in the prophylactic treatment of latent tuberculosis infection in adults and children 2 years and older at high risk of progression to tuberculosis disease:

Weight range	**Rifapentine dose**	**Isoniazid dose**	**Number of RIFAPENTINE/ISONIAZID 300/300 ADCO tablets once a week for 12 weeks**
10 – 14 kg	300 mg	300 mg	**1**
14,1 – 25 kg	450 mg	450 mg	**1 + half**
25,1 – 32 kg	600 mg	600 mg	**2**
32,1 – 50 kg	750 mg	750 mg	**2 + half**
> 50 kg	900 mg	900 mg	**3**

Special populations

Elderly patients (65 years of age and older):

No dose adjustment is required, but caution should be exercised due to the possible decrease in renal and hepatic function.

Hepatic impairment:

No dose adjustment required.

However, in the presence of hepatic insufficiency, the half-life of isoniazid may be prolonged, and therefore RIFAPENTINE/ISONIAZID 300/300 ADCO should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.3 and 4.4).

Renal impairment:

No dose adjustment required when given to patients with mild renal failure. However, RIFAPENTINE/ISONIAZID 300/300 ADCO is contraindicated in patients with severe renal failure (glomerular filtration rate of less than 10 mL/minute) (creatinine clearance <30 mL/min). (see sections 4.3 and 4.4).

Paediatric population

No data are available for patients below 2 years old.

Method of administration

For oral use.

To ensure effective treatment, the strict adherence to the treatment regimen of RIFAPENTINE/ISONIAZID 300/300 ADCO and other medicines, as well as the importance of not missing any doses, should be stressed
to the patient.

RIFAPENTINE/ISONIAZID 300/300 ADCO should be given with food.

For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food, all of which should be consumed immediately (see section 5.2).

Interaction with antacids has not been studied. RIFAPENTINE/ISONIAZID 300/300 ADCO should therefore be taken/administered at least 1 hour before or 2 hours after taking antacids.

4.3 Contraindications

- hypersensitivity to rifapentine, other rifamycins (e.g. rifampicin, rifabutin), isoniazid, ethionamide, pyrazinamide, niacin, or other chemically-related medicines or to any of the ingredients of RIFAPENTINE/ISONIAZID 300/300 ADCO (see section 6.1)
- porphyria. Based on experience with rifampicin, it may be assumed that rifapentine can also induce delta-aminolevulinic acid synthetase and therefore cause an acute attack of porphyria
- in patients with acute or chronic liver disease including medicine-induced liver disease.
- Alcoholism
- in patients with severe renal failure
- in patients with uncontrolled seizures
- pregnancy and lactation
- HIV-infected patients on antiretroviral therapy because of potential interactions leading to loss of efficacy with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (see section 4.5).

4.4 Special warnings and precautions for use

Hepatotoxicity

RIFAPENTINE/ISONIAZID 300/300 ADCO may cause serious hepatic disease/injury including severe and sometimes fatal hepatitis.

Advanced age, female gender, slow acetylators, malnutrition, HIV infection, pre-existing liver disease, and extra-pulmonary tuberculosis were identified as risk factors for isoniazid-induced hepatotoxicity.

Patients with abnormal liver tests and/or liver disease should only be prescribed RIFAPENTINE/ISONIAZID 300/300 ADCO if no safer alternative is available, and then with caution and under strict medical supervision (see section 4.3).

All patients should have baseline liver function tests performed and careful monitoring of liver parameters (especially serum transaminases and bilirubin) carried out prior to therapy and then every 2 to 4 weeks during therapy. In the event of any indication of a liver reaction or of the hepatic condition worsening, RIFAPENTINE/ISONIAZID 300/300 ADCO should be discontinued.

Hypersensitivity and related reactions

Hypersensitivity reactions may occur in patients taking RIFAPENTINE/ISONIAZID 300/300 ADCO.

Signs and symptoms of hypersensitivity may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations) (see section 4.8).

Patients taking RIFAPENTINE/ISONIAZID 300/300 ADCO should be monitored for signs and/or symptoms of hypersensitivity reactions.

If these symptoms occur, administer supportive measures, and discontinue RIFAPENTINE/ISONIAZID 300/300 ADCO.

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Cases of severe cutaneous adverse reactions including Stevens- Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with fatal outcome, have been reported with the use of antituberculosis therapy, such as RIFAPENTINE/ISONIAZID 300/300 ADCO (see section 4.8). Patients should be advised of these signs and symptoms and closely monitored for skin reactions. The patient should be advised that if signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develop, they should consult their doctor immediately.

RIFAPENTINE/ISONIAZID 300/300 ADCO should be permanently discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity, and if an alternative etiology for these signs and symptoms cannot be established.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during antituberculosis therapy such as RIFAPENTINE/ISONIAZID 300/300 ADCO (see section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy, or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult their doctor immediately.

RIFAPENTINE/ISONIAZID 300/300 ADCO should be permanently discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity, and if an alternative etiology for these signs and symptoms cannot be established.

Clostridium difficile-associated diarrhoea

Pseudomembranous colitis has been reported to occur with rifamycins such as RIFAPENTINE/ISONIAZID 300/300 ADCO. Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, RIFAPENTINE/ISONIAZID 300/300 ADCO should be stopped immediately, and the patient treated appropriately without delay. Medicines inhibiting the peristalsis are contraindicated in this clinical situation.

Concomitant medicine interactions

As RIFAPENTINE/ISONIAZID 300/300 ADCO is an inducer of CYP3A4 and CYP2C8/9, concomitant use with other medicines metabolised by these enzymes, (such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception) may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these medicines (see sections 4.5 and 5.2).

RIFAPENTINE/ISONIAZID 300/300 ADCO has also been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (a P-gp substrate with narrow therapeutic index). Appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with RIFAPENTINE/ISONIAZID 300/300 ADCO (see sections 4.5 and 5.2).

Discolouration of body fluids

Patients should be warned that RIFAPENTINE/ISONIAZID 300/300 ADCO may produce a predominantly red-orange discolouration of body tissues and/or fluids (e.g. skin, teeth, tongue, urine, faeces, saliva, sputum, tears, sweat and cerebrospinal fluid).

Contact lenses or dentures may become permanently stained.

In patients suffering from convulsive disorders and diabetes mellitus, and patients with a history of psychosis, RIFAPENTINE/ISONIAZID 300/300 ADCO should be prescribed with caution.

RIFAPENTINE/ISONIAZID 300/300 ADCO should be used with caution in patients with mild to moderate hepatic or renal impairment (see section 4.2) or patients taking other potentially hepatotoxic medicines. Should symptoms of hepatitis deteriorate in this patient group, RIFAPENTINE/ISONIAZID 300/300 ADCO should be discontinued immediately.

Pyridoxine

In order to prevent or minimise symptoms of peripheral neuritis in high-risk groups such as in patients who are diabetic, alcoholic, malnourished, uraemic, pregnant or infected with HIV (currently not on antiretroviral therapy), the administration of pyridoxine daily is recommended.

Pyridoxine, in a dose of 10 mg daily, during treatment with RIFAPENTINE/ISONIAZID 300/300 ADCO, is recommended in patients who are at risk of neuropathy or pyridoxine deficiency, including those in the abovementioned high risk groups.

Periodic eye examinations during treatment are recommended as isoniazid in combination with other anti-tuberculosis medicines, such as RIFAPENTINE/ISONIAZID 300/300 ADCO, causes optic neuritis which can lead to optic atrophy and blindness (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

RIFAPENTINE/ISONIAZID 300/300 ADCO

Food Interaction

Isoniazid, as in RIFAPENTINE/ISONIAZID 300/300 ADCO, is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), may therefore reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, conjunctival irritation, tachycardia, tachypnoea and hypotension.

Patients should be advised against ingesting foods rich in tyramine and/or histamine during treatment with RIFAPENTINE/ISONIAZID 300/300 ADCO, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).

RIFAPENTINE

Effect of rifapentine on other medicines

Cytochrome P450 substrates:

In vitro, rifapentine and its metabolite (25-desacetyl-rifapentine) are potent inducers of CYP3A4. In vivo in humans, rifapentine has also been shown to be a potent CYP3A4 inducer: rifapentine daily (from 5 mg/kg) decreased midazolam exposure by 90 %;

rifapentine 600 mg twice-weekly dosing reduced indinavir (protease inhibitor substrate of CYP3A4) exposure by 70 %. There are no clinical data evaluating the interaction between CYP3A substrate and rifapentine at the dosing regimen recommended for latent tuberculosis infection (LTBI) (900 mg weekly dosing). However, rifapentine is also predicted a potent inducer at this dosing regimen.
In vitro, rifapentine is an inducer of CYP2C8 and CYP2C9 and its metabolite (25-desacetyl-rifapentine) is a potential inhibitor of CYP2C8. No clinical interaction study was performed to assess in vivo potential of rifapentine to interact with medicines metabolised by CYP2C8/C9, but the risk of interaction is likely. The in vivo net effect, resulting from induction and inhibition of CYP2C8, was not evaluated but a higher impact of induction can be predicted.
In vitro studies showed that rifapentine and its metabolite (25- desacetyl-rifapentine) are inducers of CYP2B6 and that rifapentine is an inhibitor of CYP2B6. Interactions with CYP2B6 substrate was evaluated in one clinical study with efavirenz which is known as a very sensitive CYP2B6 substrate. After a single and repeated weekly administration of rifapentine 900 mg, no or minor modification (+ 15 %) of steady-state exposure of efavirenz was observed.
In vitro, rifapentine and its metabolite are not inducers of CYP1A2. Based on *in vitro* data, it is predicted that rifapentine and its metabolite have no potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1, *in vivo* in humans.

RIFAPENTINE/ISONIAZID 300/300 ADCO may increase the metabolism of other co-administered medicines that are metabolised by these enzymes.
Appropriate monitoring and dosage adjustment may be necessary if medicines metabolised by CYP3A4 or CYP2C8/9 are co-administered with RIFAPENTINE/ISONIAZID 300/300 ADCO.
Induction of enzyme activities by rifapentine occurred after the first dose of rifapentine. Enzyme activities returned to baseline levels, in general, 14 days after discontinuing rifapentine.
Examples of such medicines include:

- antiretroviral medicines:
    - protease inhibitors: indinavir, darunavir, lopinavir, saquinavir, ritonavir
    - non-nucleoside reverse transcriptase inhibitors: rilpivirine
    - nucleoside reverse transcriptase inhibitor: zidovudine
- antifungals (itraconazole, ketoconazole, voriconazole)
- narcotic analgesics (methadone, alfentanil, buprenorphine)

- hypoglycaemic medicines (repaglinide)
- calcium channel blockers (felodipine, diltiazem, verapamil, nifedipine)
- alpha/beta adrenergic antagonists (alfuzosin, propranolol)
- ergot alkaloid derivatives (ergotamine)
- oral anti-vitamin K anticoagulant (warfarin)
- hormonal contraceptives (oral, transdermal and implant)
- immunosuppressants (ciclosporin, tacrolimus, sirolimus)
- benzodiazepines (midazolam).

Transporter substrates

In vitro, rifapentine has been shown to inhibit several transporters (P- gp, BCRP and OATP1B1/B3, OCT1). However, the risk of clinically significant interaction resulting from inhibition of BCRP and/or OATP1B1/B3, evaluated using a mechanistic static approach, was considered as minimal. Moreover, rifamycins are known to induce some of these transporters (such as P-gp, OATP1B1/OATP1B3) via activation of PXR and could balance the inhibition effect. For P-gp, interactions have been evaluated in humans with 2 substrates of P-gp, raltegravir and tenofovir, suggesting a limited effect.
In vitro, rifapentine has been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (P-gp substrate).
Because of the narrow therapeutic index of digoxin, appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with RIFAPENTINE/ISONIAZID 300/300 ADCO.

Antiretroviral medicines

- ***Protease inhibitors and certain reverse transcriptase inhibitors***:

Concomitant use of rifapentine, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, with protease inhibitors and certain reverse transcriptase inhibitors, metabolised by CYP3A4 or CYP2C8/9, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these medicines.

- ***Fixed dose combination of efavirenz, emtricitabine and tenofovir:***

Once-weekly co-administration of 900 mg rifapentine as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO with the antiretroviral fixed dose combination of 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxyl fumarate in HIV-

infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine and tenofovir.
No clinically significant change in CD4 cell counts or viral loads were noted.
Co-administration of a fixed dose combination of efavirenz, emtricitabine and tenofovir with RIFAPENTINE/ISONIAZID 300/300 ADCO 900 mg once-weekly requires no dose adjustment.

- ***Raltegravir:***

Once-weekly co-administration of 900 mg rifapentine, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, with raltegravir resulted in a 71 % mean increase in raltegravir AUC0-12, and an 89 % increase in Cmax. No need for dose adjustment of raltegravir, if co-administered with RIFAPENTINE/ISONIAZID 300/300 ADCO 900 mg once-weekly.

Hormonal contraceptives
Rifapentine may reduce the effectiveness of hormonal contraceptives.
Women taking oral contraception, using a transdermal patch, or other systemic hormonal contraceptives who need RIFAPENTINE/ISONIAZID 300/300 ADCO therapy should discuss the use of an additional non- hormonal means of contraception or the change of their contraceptive pill with their medical practitioner.

Effect of other medicines on rifapentine:
Rifapentine is metabolised by esterases and its main metabolite, 25-desacetyl-rifapentine, is not metabolised. There is a lack of risk of interaction with CYP450 inducer and as well as inhibitor medicines (such as triazole antifungal agents frequently co-administered in HIV-infected patients).
Similarly, taking into account the high passive diffusion component in the hepatocyte uptake or the good intestinal permeability, potential interaction with transporters inhibitor/inducer medicines are not expected.
Since rifapentine, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, is highly bound to albumin, medicine displacement interactions with non-steroidal anti-inflammatory drugs (NSAIDs), sulfonylureas and oral anticoagulants may also occur.

Interferences with laboratory and diagnostic tests
Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}.

Similar interferences should be considered for rifapentine, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO. Therefore, alternative assay methods should be considered.

ISONIAZID

Inhibition of CYP450

Isoniazid, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, primidone, and phenytoin, the benzodiazepines diazepam and triazolam, and others such as warfarin and theophylline.

Concomitant administration of benzodiazepines (such as diazepam/carbamazepine) and isoniazid, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, has been reported to result in benzodiazepine toxicity (with symptoms such as sedation, respiratory depression, etc.).

Other interactions

Administration of isoniazid, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, may lead to a higher risk of hepatotoxicity. Increased central nervous system adverse effects have occurred when isoniazid is given with potentially neurotoxic medicines such as cycloserine or disulfiram.

Hepatotoxic reactions have been reported when paracetamol is given concurrently with isoniazid, while chronic alcoholism increases the risk of isoniazid induced hepatitis.

When isoniazid, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, is given to patients receiving para-aminosalicyclic acid concurrently, the plasma concentrations of isoniazid may be increased, and adverse effects are more likely to occur.
Prednisolone may increase hepatic metabolism and/or excretion of isoniazid (as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO).
Aluminium-containing antacids may delay and decrease absorption and serum concentration of isoniazid.
It is therefore recommended that RIFAPENTINE/ISONIAZID 300/300 ADCO be administered at least 1 hour before taking antacids (see section 4.2).

Isoniazid, as in RIFAPENTINE/ISONIAZID 300/300 ADCO may reduce the therapeutic effects of levodopa.
Concomitant administration of isoniazid, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, with itraconazole or ketoconazole may result in significant decreases in either medicine's serum concentrations, and thus therapeutic failure.
Concurrent use should be well monitored, and dosage increases made if necessary.

Because the clearance of isoniazid, contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, was found to be doubled when zalcitabine was given in HIV-positive patients, concurrent use of isoniazid and zalcitabine should be monitored to ensure isoniazid effectiveness.

4.6 Fertility, pregnancy and lactation
Women of child-bearing potential should be advised to avoid becoming pregnant while on treatment with RIFAPENTINE/ISONIAZID 300/300 ADCO.

Pregnancy
Isoniazid, as in RIFAPENTINE/ISONIAZID 300/300 ADCO, crosses the placenta.
Women who are pregnant should not be treated with RIFAPENTINE/ISONIAZID 300/300 ADCO as safety in pregnancy and lactation has not been established and harm to the embryo/developing foetus cannot be excluded (see section 4.3).

Human data
As rifapentine may have a similar effect to rifampicin (known to cause postnatal haemorrhages in the mother and infant when taken during the last few weeks of pregnancy), appropriate coagulation testing should be performed when pregnant women are inadvertently exposed to RIFAPENTINE/ISONIAZID 300/300 ADCO during late pregnancy. Treatment with vitamin K may be indicated.

Breastfeeding
It is not known whether rifapentine or isoniazid are excreted in human milk, therefore mothers on RIFAPENTINE/ISONIAZID 300/300 ADCO therapy should not breastfeed their babies.
Rifapentine, as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO, may produce a red-orange discolouration of body fluids, including breast milk.

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

RIFAPENTINE/ISONIAZID 300/300 ADCO may influence the ability to drive and use machines. Adverse reactions such as convulsions have been reported in patients receiving isoniazid (as contained in RIFAPENTINE/ISONIAZID 300/300 ADCO).

Patients should be advised not to drive or operate machines if they experience any side effects of RIFAPENTINE/ISONIAZID 300/300 ADCO which could adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

Tabulated summary of adverse reactions

RIFAPENTINE

System Organ Class	Frequency	Side effects
Infections and infestations	Less frequent	Influenza
	Frequency unknown	Pneumonia
Immune system disorders	Frequent	Hypersensitivity
Nervous system disorders	Less frequent	Headache
Gastrointestinal disorders	Less frequent	Nausea, upper abdominal pain
	Frequency unknown	Pancreatitis, oesophageal irritation
Hepatobiliary disorders	Less frequent	Hepatitis
	Less frequent	Skin reaction

Skin and subcutaneous tissue disorders	Frequency unknown	Severe cutaneous adverse reactions (SCARs)* such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see section 4.4)
Musculoskeletal, connective tissue and bone disorders	Less frequent	Myalgia
General disorders and administrative site conditions	Less frequent	Influenza-like illness, fatigue, chills, pyrexia, asthenia

ISONIAZID

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Haematological effects (various anaemias, agranulocytosis, thrombocytopenia and eosinophilia).
Immune system disorders	Less frequent	Hypersensitivity reactions (fever, skin rashes, joint pain)
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, metabolic acidosis
Psychiatric disorders	Less frequent	Neurotoxicity (psychotic reactions)
Reproductive system and breast disorders	Less frequent	Gynaecomastia

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
You may also report to Adcock Ingram Limited using the following e-mail address: Adcock.AEReports@adcock.com.

4.9 OVERDOSE

Signs and symptoms

RIFAPENTINE

An overdose may precipitate side effects and increase the severity thereof.

ISONIAZID

Symptoms of isoniazid overdose include slurred speech, metabolic acidosis, hyperglycaemia, hallucinations, respiratory and CNS depression, convulsions and coma.

Management of overdose:

RIFAPENTINE

Treatment should be symptomatic and supportive.
Rifapentine and 25-desacetyl rifapentine are highly plasma protein bound and have limited urinary excretion.
Therefore, neither haemodialysis nor forced diuresis is expected to enhance the systemic elimination.

ISONIAZID

Treatment for significant overdose consists of symptomatic and supportive therapy. This includes use of large doses of pyridoxine (1:1) to prevent and/or control convulsions, and sodium bicarbonate for metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterial
ATC code: J04AC01
Category and class: A 20.2.3 Tuberculostatics

Mechanism of action

RIFAPENTINE

Rifapentine belongs to the rifamycin class of antibiotics which exert their antibacterial action by selectively inhibiting the DNA-dependent RNA polymerase of susceptible bacteria.

It forms a stable complex with bacterial DNA-dependent RNA polymerase, leading to repression of RNA synthesis and cell death.

Rifapentine and its 25-desacetyl metabolite accumulate in human monocyte-derived macrophages and are bactericidal to both intracellular and extracellular Mycobacterium tuberculosis organisms at concentrations achievable by the recommended oral dosing regimens. 25-Desacetyl rifapentine, the active metabolite, is almost as active as rifapentine.

Resistance

Most organism's resistant to other rifamycins are likely to be resistant to rifapentine. In the treatment of tuberculosis, the small number of resistant bacilli present within large populations of susceptible bacilli can rapidly become predominant. In addition, resistance to rifamycin antibiotics has been determined to occur as a single step mutation of the gene that encodes for the beta subunit of the DNA-dependent RNA polymerase.

However, other mechanisms of rifamycin resistance observed among certain organisms, such as Nocardia and mycobacteria other than *M.tuberculosis*, cannot be ruled out. Appropriate susceptibility tests should be performed in the event of persistently positive cultures.

ISONIAZID

Isoniazid is a synthetic bactericidal antituberculosis medicine, that is active against many mycobacteria, and primarily those that are actively dividing. The mechanism of action is by entering the bacilli through passive diffusion. Isoniazid then inhibits the biosynthesis of mycotic acids which are essential components of the cell wall of Mycobacterium tuberculosis leading to bacterial cell death.

5.2 Pharmacokinetic properties

RIFAPENTINE

When 600 mg oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days (4 doses), mean Ctrough were below the limit of quantification suggesting no accumulation; moreover, single dose AUC(0-∞) of rifapentine

was similar to its AUC_{ss} (0-72 h) values after 4 repeated doses, suggesting no significant auto-induction effect.

Based on the data observed after a single oral dose of 900 mg in healthy subjects, no plasma accumulation of rifapentine and 25-desacetyl rifapentine (active metabolite) is expected after once weekly administration of rifapentine.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine on day 10 following oral administration of 600 mg rifapentine every 72 hours to healthy volunteers are described in Table 2 below:

Table 2: Pharmacokinetics of rifapentine and 25-desacetyl rifapentine in healthy volunteers

Parameter	Rifapentine	25-desacetyl rifapentine
	Mean ± SD	
C_{max} (µg/mL)	15,05 ± 4,62	6,26 ± 2,06
$AUC_{(0-72h)}$ (µg*h/mL)	319,54 ± 91,52	215,88 ± 85,96
$T_{1/2}$ (h)	13,19 ± 1,38	13,35 ± 2,67
T_{max} (h)	4,83 ± 1,80	11,25 ± 2,73
Cl/F (L/H)	2,03 ± 0,60	--

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine following single- dose oral administration of 900 mg rifapentine in combination with 900 mg isoniazid in fed conditions are described in Table 3.

Table 3: Mean ± SD pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine in healthy volunteers when rifapentine is co-administered with isoniazid under fed conditions (N = 16)

Parameter	Rifapentine	25-desacetyl rifapentine
	Mean ± SD	
C_{max} (µg/mL)	25,8 ± 5,83	13,3 ± 4,83
$AUC_{(0-72h)}$ (µg*h/mL)	817 ± 128	601 ± 187
$T_{1/2}$ (h)	16,6 ± 5,02	17,5 ± 7,42
T_{max} (h)**	8 (3 – 10)	24 (10 – 36)
Cl/F (L/H)	1,13 ± 0,174	NA***

**Median (min – max)

***Not applicable

Absorption

RIFAPENTINE

The absolute bioavailability of rifapentine has not been determined. Based on mass balance study, absorption was estimated as almost complete.

Rifapentine bioavailability is affected by food intake. When the tablet is administered with food, the bioavailability of rifapentine and its active metabolite increases by 40 % to 50 %. This increase in bioavailability is not affected by the meal composition including the amount of lipids.

In order to maximise rifapentine and 25-desacetyl rifapentine exposures and reduce inter-subject variability, rifapentine should be taken with food.

ISONIAZID

Isoniazid is readily absorbed from the gastrointestinal tract following oral administration. Absorption and bioavailability are reduced when administered with food.

Distribution

RIFAPENTINE

In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97,7 % and 93,2 % bound to plasma proteins, respectively. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and those with hepatic impairment. Following oral dosing of rifapentine in fed condition, the apparent volume of distribution is 32 litres.

The intrapulmonary distribution was studied in healthy subjects who received a single oral dose of rifapentine (600 mg).

The peak concentrations in plasma, in epithelial lining fluid, and in alveolar cells were 26,2; 3,7 and 5,3 µg/mL, respectively. Although the intrapulmonary rifapentine (RPT) concentrations were less than the plasma RPT concentrations at all time periods, they remained above the RPT and 25-desacetyl rifapentine (25-DRPT) minimum inhibitor concentration (MIC) for the 48-hour observation period.

ISONIAZID

It is widely distributed to all fluids and tissues, including cerebrospinal fluid (CSF), pleural and ascitic fluids, skin, sputum, saliva, lungs, muscle, and caseous tissue. Isoniazid crosses the placenta and is excreted in the breast milk (see section 4.6).

Biotransformation

RIFAPENTINE

Rifapentine was hydrolysed by an esterase enzyme to form a single microbiologically active metabolite 25-desacetyl rifapentine. This metabolite represents 60 % to 70 % of rifapentine AUC.

ISONIAZID

The primary metabolic route is acetylation.

Elimination

RIFAPENTINE

After administration of ^{14}Crifapentine, the majority of the dose is excreted in faeces (70 %), while urine is a minor pathway for excretion (17 %). Plasma clearance after oral administration of rifapentine, is low with values in the range of 1,5 to 2 L/h. The apparent elimination of rifapentine and 25-desacetyl rifapentine is monophasic with a terminal half-life ranging from 13 to 17 hours.

The main elimination pathways are metabolism for rifapentine and biliary excretion in faeces for both rifapentine and its metabolite 25-desacetyl rifapentine. Renal clearance is a minor pathway of excretion for rifapentine and its metabolite.

ISONIAZID

The plasma half-life for isoniazid ranges from about 1 to 4 hours. Approximately 75 to 95 % is excreted by the kidneys within 24 hours, mainly as metabolites. Small amounts are excreted in the faeces.

Pharmacokinetics in special patient groups

RIFAPENTINE

Elderly patients

In elderly patients (≥ 65 years), following single oral administration of 600 mg, mean rifapentine and 25-desacetyl-rifapentine exposures were increased (41 % for rifapentine AUC, 58 % for 25-desacetyl-rifapentine) compared to healthy young subjects (historical comparison). However, no dose adjustments were recommended for elderly subjects based on safety results in elderly healthy subjects and elderly patients with LTBI.

Hepatic impairment

Following oral administration of a single 600 mg dose of rifapentine to mild to severe hepatically impaired patients, the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment.

In comparison to healthy subjects, rifapentine and 25-desacetyl- rifapentine exposure (AUC) were increased in subjects with hepatic impairment by 19 % to 25 % and 77 % to 99 %, respectively.

Renal impairment

The pharmacokinetics of rifapentine have not been evaluated in renally impaired patients. However, the risk of an impact of impaired renal function on PK is considered as minimal; only about 17 % of an administered dose is excreted via the kidneys. The clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Asymptomatic HIV-infected volunteers

In asymptomatic HIV-infected subjects, rifapentine and 25-desacetyl metabolite PK profiles were not significantly different from those observed in healthy subjects. The safety and PK results indicated that no dose adjustment for rifapentine is necessary for asymptomatic HIV-infected patients.

Paediatric population - Rifapentine

In healthy adolescents, rifapentine and 25-desacetyl-rifapentine PK were not different from those observed in healthy adults.

In paediatric patients (younger than 12 years old), a significant correlation was observed between clearance and age: clearance adjusted to body weight increased with decreasing age.

Based on these findings, a weight band dosing (Table 1) was selected for rifapentine in children with LTBI and validated with PK and safety data in this population.

In children (2 – 12 years of age) receiving doses based on weight, while the mean rifapentine dosages in mg/kg were 2-fold higher than in adults (23 versus 11 mg/kg), exposures were higher than in adults for rifapentine and 25-desacetyl-rifapentine, respectively, exposures that in adults have been associated with successful treatment of LTBI. Among children, exposure was lower in those who could not swallow the whole tablets and received crushed tablets, but still higher than in adults.

Despite the generally increased exposure observed in children, higher mg/kg rifapentine doses were well tolerated.

Despite the generally increased exposure observed in children, higher mg/kg rifapentine doses were well tolerated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium Stearate

Colloidal Silicon Dioxide

Dewaxed Shellac

Disodium Edetate

Hydroxypropyl Cellulose

Microcrystalline Cellulose

Pregelatinized Starch

Sodium Ascorbate

Sodium Lauryl Sulphate

Sodium Starch Glycolate

Tablet coating (WT-MPAQ-01266P brown):

Polyvinyl Alcohol

Red Iron Oxide

Soya Lecithin

Talcum

Titanium Dioxide

Xanthum Gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25 °C. Protect from excessive heat and moisture.

6.5 Nature and contents of container

Aluminium strips of either 10, 12 or 14 tablets per strip.

Alu-Alu blister packs of either 10, 12 or 14 tablets per blister.

Blisters and strips are packed into printed outer carton with a leaflet.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special precautions.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER

59/20.2.3/0601

9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

25 March 2025