PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

INOZI-CO 300 mg/300 mg (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 300 mg Isoniazid and 300 mg Rifapentine.

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablet

INOZI-CO

Reddish brown coloured, capsule shaped, biconvex, film-coated tablets debossed with "J" and "21" on either side of breakline on one side and plain on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INOZI-CO is indicated for the prevention of active tuberculosis in adults 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),

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(2) HIV-infected patients not receiving protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs) as 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 **INOZI-CO**.

4.2 Posology and method of administration

Posology

INOZI-CO should be administered once-weekly for 12 weeks as directly observed therapy (DOT).

Adults:

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 15 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 INOZI-CO in the prophylactic treatment of latent Tuberculosis Infection in adults at high risk of progression to tuberculosis disease.

Weight range	Rifapentine dose	Isoniazid dose	Number of INOZI-CO tablets once a week for 12 weeks
10 – 14 kg	300 mg	300 mg	1
14,1 – 25 kg	450 mg	450 mg	1½
25,1 – 32 kg	600 mg	600 mg	2
32,1 – 50 kg	750 mg	750 mg	2½
> 50 kg	900 mg	900 mg	3

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Special populations

Paediatric patients:

Safety and efficacy in children has not been established.

Elderly patients (65 years of age and older):

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

Hepatic impairment:

No dosage adjustment is required, however, the half-life of isoniazid may be prolonged in the presence of hepatic insufficiency. **INOZI-CO** should be used with caution in patients with mild to moderate hepatic impairment. (see sections 4.3 and 4.4).

Renal impairment:

No dosage adjustment is required when given to patients with mild renal failure. However, **INOZI-CO** is contraindicated in patients with severe renal failure (glomerular filtration rate of less than 10 mL/minute (creatinine clearance < 30 mL/min) (See Section 4.3 and 4.4).

Method of administration

For oral use.

Patients should be informed that adherence to the treatment regimen for **INOZI-CO** and other substances is essential for effective treatment, and the importance of not missing any doses must be stressed.

INOZI-CO 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).

Interactions with antacids have not been studied. However, in the clinical efficacy study, patients were advised to take **INOZI-CO** at least 1 hour before or 2 hours after the ingestion of antacids.

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4.3 Contraindications

INOZI-CO is contraindicated:

- in patients with known hypersensitivity to isoniazid and rifapentine or any of the excipients listed in section 6.1.
- Hypersensitivity to ethionamide, pyrazinamide, niacin, or other chemically related compounds or to any of the excipients (see Section 6.1).
- In patients with porphyria.
- In patients with acute or chronic liver disease.
- Severe renal failure
- Alcoholism
- Seizure disorders
- Pregnancy and lactation
- HIV-infected patients on antiretroviral therapy with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) because of potential interactions leading to loss of efficacy (See Section 4.5).

4.4 Special warnings and precautions for use

Active tuberculosis should be ruled out before initiating treatment for latent tuberculosis infection.

Hepatotoxicity

INOZI-CO may cause serious hepatic disease/injury.

Patients with abnormal liver tests and/or liver disease should only be given **INOZI-CO** if no safer alternative is available, and then with caution and under strict medical supervision (see section 4.3).

In such patients, careful monitoring of liver function parameters (especially serum transaminases and bilirubin) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If there are indications of a liver reaction or of the hepatic condition worsening, **INOZI-CO** should be discontinued.

Hypersensitivity and related reactions

Hypersensitivity reactions may occur in patients receiving **INOZI-CO.** Signs and symptoms of these

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reactions 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).

Monitor patients receiving **INOZI-CO** therapy for signs and/or symptoms of hypersensitivity reactions. If these symptoms occur, administer supportive measures and discontinue **INOZI-CO**.

Medicine interactions

Rifapentine, one of the components of **INOZI-CO** is an inducer of CYP3A4 and CYP2C8/9. Concomitant use of **INOZI-CO** with other medicines metabolised by any of these enzymes, such as protease inhibitors, non-nuclease-reverse transcriptase inhibitors (Efavirenz: CYP3A4 inducer and inhibitor), and hormonal contraceptives may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these medicines (see sections 4.5 and 5.2).

INOZI-CO 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 as contained in **INOZI-CO** (see sections 4.5 and 5.2).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in association with the use of **INOZI-CO** treatment regimen. Patients should be informed about the signs and symptoms of serious skin manifestations. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

***Clostridium difficile*-associated diarrhoea**

Pseudomembranous colitis has been reported to occur with rifamycins such as in **INOZI-CO**. Diarrhoea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following

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treatment may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, **INOZI-CO** should be stopped immediately and the patient treated appropriately without delay. Medicines inhibiting the peristalsis are contraindicated in this clinical situation.

Discolouration of body fluids

INOZI-CO 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.

The administration of 10 mg pyridoxine daily is recommended to prevent or minimise symptoms of peripheral neuritis, as well as for those who are diabetic, alcoholic, malnourished or uraemic, infected with HIV (currently not on antiretroviral therapy).
INOZI-CO should be given with caution in patients suffering from convulsive disorders and diabetes mellitus and patients with a history of psychosis.
INOZI-CO 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.
If symptoms of hepatitis deteriorate in these patients, **INOZI-CO** should be discontinued immediately.

Periodic eye examination during treatment is recommended.

4.5 Interaction with other medicines and other forms of interaction

Effect of INOZI-CO on other medicines

- ***Effect on medicines metabolised by CYP3A4 and CYP2C8/9***

Rifapentine as contained in **INOZI-CO** is an inducer of CYP3A4 and CYP2C8/9. Therefore, **INOZI-CO** 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

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CYP3A4 or CYP2C8/9 are co-administered with **INOZI-CO**.

Induction of enzyme activities by **INOZI-CO** occurred after the first dose of **INOZI-CO**. Enzyme activities returned to baseline levels, in general, 14 days after discontinuing **INOZI-CO**.

Examples of such substances include:

- Antiretroviral medicines:
  - Protease inhibitors: indinavir, darunavir, lopinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, atazanavir, tipranavir.
  - Non-nucleoside reverse transcriptase inhibitors: rilpivirine, efavirenz
  - 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.

Inhibition of CYP450 Isoniazid, as in **INOZI-CO** 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 (diazepam/carbamazepine) and isoniazid, as in **INOZI-CO** therapy, has been reported to result in benzodiazepine toxicity (sedation, respiratory depression, etc.).

Concurrent administration of **INOZI-CO** and rifampicin may lead to a higher risk of hepatotoxicity, while

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increased central nervous system adverse effects have occurred when **INOZI-CO** is given with potentially neurotoxic medicines such as cycloserine or disulfiram. Hepatotoxic reactions have been reported when paracetamol is given concurrently with **INOZI-CO**, while chronic alcoholism increases the risk of isoniazid induced hepatitis.

When isoniazid, as in **INOZI-CO** is given to patients receiving paraminosalicyclic 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 **INOZI-CO**.

Aluminium-containing antacids may delay and decrease absorption and serum concentrations of isoniazid. It is therefore recommended that **INOZI-CO** be administered at least 1 hour before taking antacids (see section 4.2).

Isoniazid, as in **INOZI-CO** may reduce the therapeutic effects of levodopa. Concomitant administration of isoniazid, as in **INOZI-CO** 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, as in **INOZI-CO** 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.

- ***Effect of INOZI-CO on transporter substrates***

In vitro, **INOZI-CO** has been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (P-gp substrate) (see section 5.2).

Because of the narrow therapeutic index of digoxin, appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with **INOZI-CO**.

- ***Effect of INOZI-CO on antiretroviral medicines***

- *Protease inhibitors and non-nucleoside reverse transcriptase inhibitors*

Concomitant use of rifapentine with protease inhibitors and non-nucleoside 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. Concomitant use of **INOZI-CO** with protease inhibitors and non-nucleoside reverse transcriptase inhibitors is contraindicated.

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- ***Hormonal contraceptives***

INOZI-CO may reduce the effectiveness of hormonal contraceptives.

Women taking oral contraception, using a transdermal patch, or other systemic hormonal contraceptives who need **INOZI-CO** 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 INOZI-CO

Potential interaction with CYP450 inducer/inhibitor medicines, as well as with transporters inhibitor/inducer medicines are not expected (see section 5.2).

Since **INOZI-CO** is highly bound to albumin, medicine displacement interactions with non-steroidal anti-inflammatory drugs (NSAIDs), sulfonylureas and oral anticoagulants may also occur.

Adverse reactions have occurred when **INOZI-CO** has been given with anti-epileptics such as phenytoin, primidone, carbamazepine, and ethosuximide, with benzodiazepines, such as diazepam or triazolam, and with warfarin.

Interferences with laboratory and diagnostic tests

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Similar interferences should be considered for **INOZI-CO**. Therefore, alternative assay methods should be considered.

Food interactions:

Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea, sweating and itching on the skin have been reported following ingestion of cheese, red wine, and some fish.

4.6 Fertility, pregnancy and lactation

Pregnancy

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Safety during pregnancy has not been established. **INOZI-CO** is not recommended during pregnancy.

Human data:

Rifampicin is known to cause postnatal haemorrhages in the mother and infant when taken during the last few weeks of pregnancy. Since **INOZI-CO** might have a similar effect, appropriate coagulation testing should be performed when pregnant women are inadvertently exposed to **INOZI-CO** during late pregnancy. Treatment with vitamin K may be indicated.

Breastfeeding

Mothers on treatment with **INOZI-CO** should not breastfeed their babies.

It is not known whether **INOZI-CO** is excreted in human milk.

INOZI-CO may produce a red-orange discolouration of body fluids, including breast milk.

Fertility

No data on the effect of **INOZI-CO** on fertility is available.

4.7 Effects on ability to drive and use machines

INOZI-CO may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Rifapentine:

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations	-	Influenza	pneumonia

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Immune system disorders	Hypersensitivity	-	-

Nervous system disorders	-	Headache	-

Gastrointestinal disorders	-	Nausea, Upper abdominal pain	Pancreatitis, oesophageal irritation

Hepatobiliary disorders	-	Hepatitis	-

Skin and subcutaneous tissue disorders	-	Skin reaction	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 and connective tissue disorders	-	Myalgia	-

General disorders and administration site conditions	-	Influenza-like illness, fatigue, chills, pyrexia, asthenia	-

Isoniazid:

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Blood and lymphatic system disorders:	-	Haematological effects (various anaemias, agranulocytosis, thrombocytopenia and eosinophilia).	-
Immune system disorders:	-	Hypersensitivity reactions (fever, skin rashes, joint pain).	-
Metabolism and nutrition disorders:	-	Hyperglycaemia, metabolic acidosis.	-
Psychiatric disorders:	-	Neurotoxicity (psychotic reactions)	-
Nervous system disorders:	Peripheral neuritis.	Convulsions, hyperreflexia	-
Eye disorders:	-	Optic neuritis	-
Ear and labyrinth disorders:	-	Vertigo	-

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Gastrointestinal disorders:	Nausea, vomiting, constipation, dry mouth, gastrointestinal irritation.	-	-
Hepato-biliary disorders:	Hepatitis, hepatitis prodromal symptoms (loss of appetite, nausea or vomiting, unusual tiredness or weakness), transient increases in liver enzymes.	-	-

Skin and subcutaneous tissue disorders:		Skin reactions such as purpura, acneform syndrome, lupus erythematosus-like syndrome, exfoliative dermatitis, pellagra, alopecia, urticaria.	

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Musculoskeletal and connective tissue disorders:	-	-	Rheumatoid syndrome

Renal and urinary disorders:	**-**	Urinary retention.	-

Reproductive system and breast disorders:	**-**	Gynaecomastia.	-

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

Treatment consists of gastric lavage following intubation (if the patient is in a coma and seen within one hour after overdose) symptomatic and supportive therapy. This includes use of large doses of pyridoxine (1:1) and anti-convulsants given intravenously – to prevent and/or control convulsions, and sodium bicarbonate for metabolic acidosis.

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Instillation of activated charcoal slurry via naso-gastric tube into the stomach, may help adsorb any remaining medicine from the gastrointestinal tract. Forced diuresis and haemodialysis or peritoneal dialysis has been used in case isoniazid (as contained) in **INOZI-CO** have been used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.3 Tuberculostatics

ATC Code for isoniazid: J04AC01

ATC code for rifapentine: J04AB05

Isoniazid

Isoniazid is a synthetic, bactericidal antitubercular medicine, which is active against many mycobacteria, primarily those that are actively dividing.

The mechanism of action is by entering the bacilli through passive diffusion. Isoniazid then inhibits the biosynthesis of mycolic acids which are essential components of the cell wall of Mycobacterium tuberculosis, leading to bacterial cell death.

Rifapentine

Rifapentine, a cyclopentylrifamycin, is an antimycobacterial medicine.

Rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* but does not affect mammalian cells at concentrations that are active against these bacteria. At therapeutic levels, rifapentine inhibits RNA transcription by preventing the initiation of RNA chain formation. 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 *M. tuberculosis bacilli.*

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5.2 Pharmacokinetic properties

Isoniazid:

Absorption

Isoniazid is readily absorbed from the gastrointestinal tract following oral administration, but may however undergo significant first pass metabolism.

Absorption and bioavailability are reduced when administered with food.

Distribution

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

The ratio of isoniazid in the epithelial lining fluid to that in plasma is 1 / 2 and for CSF is 0,9.

Biotransformation

The primary metabolic route is acetylation.

Isoniazid is metabolised by hepatic arylamine *N*-acetyltransferase type 2 (NAT2). Isoniazid is N-acetylated to N-acetylisoniazid in reactions that uses acetyl-coA.

Acetylisoniazid is excreted by the kidney; acetylisoniazid can also be converted to acetylhydrazine and then to hepatoxic metabolites by CYP2E1. Alternatively, acetylhydrazine may be further acetylated by NAT2 to diacetylhydrazine, which is non-toxic.

Isoniazid clearance in patients is classified as one of two phenotypic groups: “slow” acetylators and “fast” acetylators. Rapid acetylators will remove acetylhydrazine while slower acetylators or induction of CYP2E1 will lead to more toxic metabolites.

Elimination:

The plasma half-life for isoniazid ranges from about 1 to 4 hours. The half-life of isoniazid is 1,1 ± 0,1 hours for rapid acetylators and 3,1 ± 1,1 for slow acetylators. 75 – 95 % of a dose of isoniazid is excreted in the urine within 24 hours, mostly as acetylisoniazid and isonicotinic acid.

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Small amounts are excreted in the faeces.

Rifapentine

Absorption:

Rifapentine bioavailability is affected by food.

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.

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

Distribution:

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 hepatically impaired subjects.

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.

Biotransformation:

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.

Elimination:

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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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core contains:

Calcium stearate, croscarmellose sodium, disodium EDTA, low-substituted hydroxypropyl cellulose, hypromellose, hydroxypropyl cellulose, iron oxide red, microcrystalline cellulose, povidone, pregelatinised starch, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate.

The tablet film-coating material contains

Hypromellose, macrogol, red iron oxide, titanium dioxide,talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 25 °C in a dry place protected from light.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

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6.5 Nature and contents of container

Blister pack:

Tablets are packed in a blister containing aluminium foil as lidding material and cold form laminate OPA/ aluminium foil / PVC as the forming material.

Blister pack in plain laminated pouch

Tablets are packed in a blister containing aluminium foil as lidding material and cold form laminate OPA/ aluminium foil / PVC as the forming material. Blister is packed in plain laminated pouch.

Strip pack

Tablets are packed in a strip pack containing aluminium foil (soft tempered) laminated with 150 gauge polyethylene film as forming and lidding material.

Pack sizes include 12, 28, 36, 56, 84, 112 or 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

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8. REGISTRATION NUMBERS

INOZI-CO: 54/20.2.3/0161.160

9. DATE OF FIRST AUTHORISATION

INOZI-CO: 08 March 2022

10. DATE OF REVISION OF THE TEXT

29 August 2023

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