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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

R-CIN PLUS coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each R-CIN PLUS tablet contains: 150 mg rifampicin and 75 mg isoniazid.

R-CIN PLUS is sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Coated tablet.

R-CIN PLUS are brick red coloured, capsule shaped, biconvex film coated tablets with a break-line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

R-CIN PLUS is indicated for the continuation phase of treatment of patients with pulmonary or extra-pulmonary tuberculosis in newly diagnosed patients and re-treatment of adult cases.

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4.2 Posology and method of administration

R-CIN PLUS tablets are recommended in the continuation phase of the treatment of pulmonary and extra-pulmonary tuberculosis.

South African National Tuberculosis Control Programme dosage recommendation:

New, smear positive patients, new smear negative patients and extra-pulmonary TB: During this phase, which lasts for 4 months, this medicine should be administered daily for 5 consecutive days per week.

WHO dosage recommendation:

During this phase, which lasts for 4 months, R-CIN PLUS should be administered on a continuous daily basis.

The total dosage requirement is as follows:

Daily:

Rifampicin 10 mg/kg maximum 600 mg per day (8-12 mg/kg)

Isoniazid 5 mg/kg maximum 300 mg/kg (4-6 mg/kg)

Patient body mass (kg)	Number of tablets (daily)
	R-CIN PLUS
30 - 37	2
38 - 54	3

Paediatric population

R-CIN PLUS tablets are not suitable for children under 12 years.

Method of administration

For oral use.

R-CIN PLUS should be taken on an empty stomach at least 30 minutes before a meal or 2 hours after a meal.

Missed dose:

Doctors should advise patients who forget to take R-CIN PLUS to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to rifamycins, isoniazid or to any of the ingredients of R-CIN PLUS (see section 6.1).
- R-CIN PLUS is contraindicated in jaundice and acute porphyria (see section 4.4).
- R-CIN PLUS can cause thrombocytopenia and purpura usually with intermittent tuberculosis regimens; further administration is contraindicated (see section 4.8).
- Concomitant use of R-CIN PLUS tablets with the combination of saquinavir/ritonavir is contraindicated (see section 4.5).
- Concomitant use of R-CIN PLUS and nevirapine are contraindicated (see section 4.5)
- R-CIN PLUS is also contraindicated in:
    - Alcoholism, active or in remission.
    - Hepatic function impairment (rifampicin is metabolised in the liver and may also

be hepatotoxic. Increased risk of hepatitis with daily consumption of alcohol or hepatic function impairment).

- Severe renal failure, an increased risk of toxicity [creatinine clearance < 10 ml/min]
- Seizure disorders (isoniazid may be neurotoxic and cause seizures).

4.4 Special warnings and precautions for use

R-CIN PLUS is not indicated for initial treatment or prophylaxis of pulmonary tuberculosis, for meningococcal infections, or in the treatment of asymptomatic meningococcal carries to eliminate *Neisseria meningitidis* from the nasopharynx.
R-CIN PLUS is a combination of rifampicin and isoniazid, each of which has been associated with liver dysfunction.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with R-CIN PLUS should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count and a platelet count (or estimate).

Patients should be seen at least monthly during therapy and should be questioned specifically about symptoms associated with adverse reactions.

All patients with abnormalities should have follow-up, including laboratory testing, if necessary. However, because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 years of age, a transaminase measurement should be obtained at baseline and at least monthly during therapy in this age group. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, intravenous drug use and being a black or Hispanic woman.

If the patient has no evidence of pre-existing liver disease and normal pre-treatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occurs.

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (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 immediately their doctor. R-CIN PLUS should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Rifampicin

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Rifampicin should be given under the supervision of a respiratory or other suitably qualified medical practitioner.

Liver

Rifampicin should be given in cases of necessity in patients with impaired liver function.
It should be given with caution and under strict medical supervision, further; liver function should be carefully monitored. Prior to therapy, serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out and then every 2 to 4 weeks during therapy. R-CIN PLUS should be withdrawn if signs of hepatocellular damage occur.
During rifampicin therapy, cases of mild to severe cholestasis have been reported. Patients should be instructed to contact their doctor immediately if they experience symptoms such as itching, weakness, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin or dark urine. R-CIN PLUS should be discontinued if cholestasis is confirmed.
Rifampicin should also be withdrawn if clinically significant changes in hepatic function occur. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily.

In patients with impaired liver function, elderly patients, malnourished patients and possibly children under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with rifampicin.

The competition between rifampicin and bilirubin for excretory pathways of the liver at cell level, in some cases, can cause hyperbilirubinaemia in the early stage of treatment.
A single report showing an increase in bilirubin and/or transaminase level is not sufficient indication for interrupting treatment; the decision should be made after repeating the tests, and then if there are trends in the levels they must be considered in conjunction with the patient's clinical condition.

Immunological reactions/prophylaxis

Patients should be closely monitored because of the possibility of immunological reactions, including anaphylaxis, occurring with intermittent therapy (less than 2 to 3 times per week). Caution should be noted against interruption of dosage regimens as such reactions may occur.

Severe bullous reactions

Severe cutaneous adverse reactions (SCARs) including Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life- threatening or fatal, have been reported in association with R-CIN PLUS therapy – the frequency of which is not known (see section 4.8).

At the onset of therapy patients should be advised of the signs and symptoms of cutaneous adverse reactions and monitored closely for such.

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

R-CIN PLUS should be immediately withdrawn and an alternative treatment considered (as appropriate) should signs and symptoms suggestive of these reactions appear.

Depending on the conditions, the time to onset can vary, indications are that most of these reactions occurred within 2 days to 2 months after treatment initiation.

Porphyria exacerbation and metabolism of endogenous substrates

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration as a result of induction of delta amino levulinic acid synthetase (see section 4.3).

Discolouration of teeth, body fluids and contact lenses

R-CIN PLUS causes urine, faeces, saliva, sputum, sweat, and tears to turn reddish-orange to reddish brown and may also permanently discolour soft contact lenses; avoid wearing soft contact lenses. Patients should be forewarned of this (see section 4.8).

Inducing of medicine metabolising enzymes and transporters

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters and might therefore decrease concomitant drug exposure and efficacy (see section 4.5). Therefore, potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.

Vitamin K dependent coagulopathy and severe bleeding

Rifampicin, as in R-CIN PLUS, may cause vitamin K dependent coagulopathy and severe bleeding (see section 4.8). Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinaemia).

Isoniazid

Isoniazid use should be carefully monitored in patients with current severe renal dysfunction or chronic liver disease.

Liver

The development of severe and sometimes fatal hepatitis associated with isoniazid therapy may occur even after months of treatment. There is an age related risk of developing hepatitis; patients should therefore be monitored for the prodromal symptoms of hepatitis, such as fatigue, anorexia, nausea or vomiting, weakness and malaise. If these symptoms appear or if signs indicative of hepatic damage are detected R-CIN PLUS should be discontinued promptly since continued use of the medicine in these cases has been reported to cause a more severe form of liver damage.

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

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develops, the patient should be advised to consult immediately their medical practitioner. R-CIN PLUS should be permanently discontinued if an alternative etiology for the signs and symptoms cannot be established.

Pyridoxine supplementation

Diabetic, alcoholic, elderly, malnourished, uraemic or pregnant patients who are at risk of neuropathy or pyridoxine deficiency should receive pyridoxine supplementation usually in a dose of 10 mg daily.

Patients should be advised of the following precautions:

- Diabetics: False-positive reactions with copper sulphate urine glucose tests may occur.
- Regular visits to medical practitioners to check progress, as well as ophthalmologic examinations if signs of optic neuritis occur.
- Consult with medical practitioner if:
  - no improvement within 2-3 weeks
  - vascular reactions occur following concurrent ingestion of cheese or fish with isoniazid
  - signs of hepatitis or peripheral neuritis

- avoid alcoholic beverages while taking R-CIN PLUS
- use an alternative method of contraception if taking estrogen containing oral contraceptives concurrently
- R-CIN PLUS causes urine, faeces, saliva, sputum, sweat, and tears to turn reddish-orange to reddish brown and may also permanently discolour soft contact lenses; avoid wearing soft contact lenses
- use with caution when brushing teeth, using dental floss, and toothpicks; deferring dental work until blood counts have returned to normal; check with the medical practitioner or dentist concerning proper oral hygiene.

4.5 Interaction with other medicines and other forms of interaction

R-CIN PLUS:

Interactions with other medicines

When R-CIN PLUS is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of R-CIN PLUS with saquinavir/ritonavir is contraindicated (see section 4.3).

Cytochrome P-450 enzyme interaction

Rifampicin is known to induce, and isoniazid is known to inhibit certain cytochrome P-450 enzymes. In general, the impact of the competing effects of rifampicin and isoniazid on the metabolism of medicines that undergo biotransformation through the affected pathways is unknown. Therefore, caution should be used when prescribing R-CIN PLUS with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of

medicines metabolised by these enzymes may require adjustment when starting or stopping R-CIN PLUS.

Interactions with Rifampicin

Pharmacodynamic interactions

Chronic use of hepatic enzyme inducing agents prior to anaesthesia
except isoflurane, may increase anaesthetic metabolism, leading to increased risk of hepatotoxicity.
Halogenated inhalation anaesthetics have been reported to increase hepatotoxicity of both compounds.
The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid, as in R-CIN PLUS, should be monitored closely for hepatotoxicity.

The concomitant use of rifampicin with other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (specially with high doses).

Effect of rifampicin on other medicines

Induction of Drug Metabolising Enzymes and Transporters

Rifampicin accelerates the metabolism of many medicines by inducing microsomal liver enzymes (in particular cytochrome P450 isoenzyme (CYP) 1A2, 2B6, 2C8, 2C9, 2C19 and 3A4, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, or medicine

transporter proteins (such as p-glycoprotein)) and multidrug resistance-associated protein 2 (MRP2). Most medicines are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by R-CIN PLUS simultaneously. Therefore, R-CIN PLUS may accelerate the metabolism and reduce the activity of certain co-administered medicines and has the potential to perpetuate clinically important interactions against many medicines and across many medicine classes (refer below).

Medicines so affected may require an increase in dosage to maintain efficacy and patients should be monitored closely when starting or stopping concurrent rifampicin treatment such as R-CIN PLUS.

Examples of medicine or medicine classes affected by R-CIN PLUS

Alcohol: concurrent daily consumption of alcohol may increase the risk of rifampicin-induced hepatotoxicity and increased metabolism of rifampicin; dosage adjustments of rifampicin and therefore R-CIN PLUS may be necessary, and patients should be monitored closely for signs of hepatotoxicity. (see sections 4.3 and 4.4).

Antibacterials: Use of clofazimine may decrease the rate of absorption of rifampicin thus delaying its time to peak concentration, and increasing its half-life.

Antifungals: Rifampicin may increase the metabolism of azole antifungals (e.g. fluconazole, itraconazole, ketoconazole), lowering the plasma concentrations; the dose of an azole antifungal may need to be increased. Rifampicin serum concentrations are reduced when given with ketoconazole. Separation of doses 30 mins to 12 hours may result in similar rifampicin concentrations to those attained when rifampicin is given alone. Rifampicin may

increase metabolism of aminophylline, oxtriphylline and theophylline by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance.

Antiretrovirals (ARVs): Rifampicin accelerates the metabolism of zidovudine, protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir and saquinavir, atazanavir, lopinavir), NNRTIs (delavirdine, efavirenz and nevirapine) through induction of hepatic P450 cytochrome oxidases, resulting in sub-therapeutic levels of the these ARVs; in addition, these protease inhibitors and NNRTIs retard the metabolism of rifampicin, resulting in increased serum levels of rifampicin and the likelihood of increased toxicity. Rifampicin also decreases the serum concentration of the CCR-5 receptor antagonist maraviroc.

Antidysrhythmics such as disopyramide, lorcainide, mexiletine, propafenone, quinidine, tocainide as well as digoxin may have enhanced metabolism resulting in significantly lower serum antidysrhythmic concentrations; serum antidysrhythmic concentrations should be monitored and dosage adjustment may be necessary.

Anticoagulants: Rifampicin may enhance the metabolism of anticoagulants (e.g. warfarin), resulting in a considerable decrease in the activity and efficacy of the anticoagulants; prothrombin time determinations may be required as frequently as once a day; dosage adjustments of anticoagulants may be required before and after R-CIN PLUS therapy.

Antidiabetic agents (Oral): Rifampicin may enhance the metabolism of tolbutamide, chlorpropamide and glyburide by induction of hepatic microsomal enzymes, resulting in lower serum sulfonylurea concentrations; other oral antidiabetic agents may also interact with rifampicin; dosage adjustments may be required.

Contraceptives: Rifampicin may decrease the efficacy of oestrogen containing oral contraceptives because of stimulation of oestrogen metabolism or reduction in enterohepatic

circulation of oestrogens, resulting in menstrual irregularities, intermenstrual bleeding, and unplanned pregnancies; patients should be advised to use an additional method of contraception throughout the whole cycle while taking rifampicin (see section 4.4). Diabetes may become more difficult to control.

Corticosteroids, glucocorticoid and mineralocorticoids: Rifampicin may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; rifampicin has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison's disease.

Isoniazid: An increased risk of hepatotoxicity, especially in patients with pre-existing hepatic function impairment and/or in fast acetylators of isoniazid; patients should be monitored closely for signs of hepatotoxicity during the first 3 months.

Methadone: R-CIN PLUS may decrease the effects of methadone resulting in symptoms of withdrawal if the patient is dependent on methadone; dosage adjustments may be necessary during and after R-CIN PLUS therapy.

Phenytoin: The elimination of phenytoin is increased and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after R-CIN PLUS therapy.

Hepatitis-C antiviral medicines: (e.g. daclatasvir, simeprevir, sofosbuvir, telaprevir). Rifampicin 600 mg daily reduced the exposure (AUC) of daclatasvir by 79 %, simeprevir by 48 %, sofosbuvir by 77 % and telaprevir by 92 % compared to control subjects. Concurrent use of treatment of hepatitis-C antiviral medicines and rifampicin should be avoided.

Narcotic analgesics: Plasma concentrations of oxycodone and morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Clopidogrel: Increases active metabolite exposure. R-CIN PLUS strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.

Other examples of medicines metabolised by cytochrome P-450 enzyme are:
Barbiturates, systemic beta-adrenergic blocking agents (e.g. metoprolol or propranolol, bisoprolol), bone marrow depressants, clofibrate, immunosuppressive medicines (e.g. ciclosporin, sirolimus, tacrolimus, azathioprine), dapsone*, diazepam and benzodiazepine-related medicines (e.g. zopiclone, zolpidem), trimethoprim, probenecid, estrogens, anti-estrogens (e.g. tamoxifen, toremifen, gestrinone), antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine), systemic hormonal contraceptives including estrogens and progestogens, chloramphenicol, clarithromycin, doxycycline, fluoroquinolones (moxifloxacin, ciprofloxacin, levofloxacin), gestrinone, narcotic analgesics, praziquantel, progestins, quinine, riluzole, selective 5-HT3 receptor antagonists (e.g. ondansetron), statins metabolised by CYP 3A4, telithromycin, thiazolidinediones (e.g. rosiglitazone) tricyclic antidepressants (e.g. amitriptyline, nortriptyline), antipsychotics (e.g. haloperidol, aripiprazole), irinotecan, thyroid hormone (e.g. levothyroxine), losartan, quinine, riluzole, theophylline,

cytotoxics (e.g. imatinib), diuretics (e.g. eplerenone), enalapril and trimethoprim. Dosage adjustments may be necessary for these medicines.
**Dapsone (dosage adjustments are not required during concurrent therapy with rifampicin for leprosy).*

The concentration of enalaprilat, the active metabolite of enalapril, may be decreased. Dosage adjustment may be required.

If p-aminosalicylic acid and rifampicin are both included in the treatment regime, they should be given not less than eight hours apart to ensure satisfactory blood levels.

Effect of other medicines on rifampicin
Concomitant antacids, medicines that reduce gastric motility (anticholinergics and opioids), ketoconazole, or preparations containing bentonite (e.g. some aminosalicylic acid preparations) administration may reduce the absorption of rifampicin.
Daily doses of R-CIN PLUS should be given at least 1 hour before the ingestion of antacids.

Other medicine interactions with rifampicin
When the two medicines were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Interference with laboratory and diagnostic tests

Therapeutic levels of R-CIN PLUS have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Alternative assay methods should be used.

Transient elevation of serum bilirubin has also been observed.

Biliary excretion of contrast media used for visualisation of the gallbladder may be impaired by R-CIN PLUS due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

Interactions with Isoniazid

Isoniazid can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity.

The following medicines may interact with isoniazid:

Antiepileptics: Isoniazid inhibits the hepatic metabolism of such medicines as carbamazepine, ethosuximide, primidone and phenytoin causing increased concentrations and potentially leading to increased toxicity.

Stavudine: There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine.

Acetaminophen: Increased potential for hepatotoxicity and possibly nephrotoxicity.

Aluminium-containing antacids: Delayed and decreased absorption of isoniazid; it should be avoided or advised to take oral isoniazid at least 1 hour before aluminium containing antacids

Alfentanil: Isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil.

Anticoagulants such as warfarin display decreased hepatic metabolism thus resulting in increased concentrations or toxicity.

Benzodiazepines such as diazepam, triazolam, chlordiazepoxide, flurazepam and prazepam may have decreased metabolism and thus increased plasma concentrations of benzodiazepines.

Clofazimine: Isoniazid has been associated with increased concentrations and enhanced effects or toxicity of clofazimine.

Corticosteroids, glucocorticoids such as prednisolone, and other related corticosteroids with INH may increase hepatic metabolism and/or excretion of INH, resulting in decreased plasma concentrations and efficacy of INH, especially in patients who are rapid acetylators; INH dosage adjustments may be required.

Disulfiram: concurrent use in alcoholics may result in increased incidence of CNS effects such as dizziness, incoordination, irritability or insomnia; reduced dosage or discontinuation of disulfiram may be necessary.

Enflurane: Increased formation of the potentially nephrotoxic inorganic fluoride metabolite.

Hepatotoxic medicines increase the potential for hepatotoxicity and should be avoided (see section 4.4).

Neurotoxic medicines may produce additive neurotoxicity.

Pyridoxine: Isoniazid may cause peripheral neuritis by acting as a pyridoxine antagonist or increasing renal excretion of pyridoxine; requirements for pyridoxine may be increased in patients receiving isoniazid.

Rifampicin used concurrently with isoniazid may increase the risk of hepatotoxicity, especially in patients with pre-existing hepatic impairment and/or in fast acetylators of isoniazid. Patients should be monitored closely for signs for hepatotoxicity during the first 3 months of therapy.

Zalcitabine: Concomitant use of zalcitabine with isoniazid has been shown to approximately double the renal clearance if isoniazid in HIV infected patients. Appropriate adjustments of these medicines should be made.

Alcohol: Concomitant daily use of alcohol may result in increased incidence of isoniazid-induced hepatotoxicity and increased metabolism of isoniazid; dosage adjustments of isoniazid may be necessary; patients should be monitored closely for signs of hepatotoxicity and should be advised to restrict intake of alcoholic beverages (see section 4.4).

Other interactions

Para-aminosalicylic acid: May increase the plasma concentration and elimination half- life of isoniazid.

General anaesthetics may increase the hepatotoxicity of isoniazid.

Antacids: The absorption of isoniazid is reduced by antacids.

Cycloserine: Increased incidence of CNS effects such as dizziness or drowsiness. Dosage adjustments may be necessary.

Ketoconazole given with isoniazid has been reported to decrease serum concentrations of ketoconazole; use R-CIN PLUS with caution.

Theophylline: Reduced metabolism of theophylline thus increasing theophylline plasma concentrations.

Interactions with food

Concurrent ingestion of cheese (e.g. mature cheeses), red wine, beer or fish such as tuna, skipjack, mackerel, salmon or sardinella with isoniazid may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache or light headedness; this is thought to be due to the inhibition of plasma monoamine oxidase and diamine oxidase by isoniazid, interfering with the metabolism of histamine and tyramine found in fish and cheese.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of R-CIN PLUS has not been established in pregnancy and lactating women.

Rifampicin

Blood coagulation monitoring and treatment with Vitamin K to mothers and neonates is recommended when the mother has received rifampicin during the last few weeks of pregnancy as rifampicin can cause post-natal haemorrhages in the mother and infant. Neonates should be carefully observed for evidence of adverse effects.

Isoniazid

Isoniazid crosses the placenta, resulting in foetal serum concentrations that may exceed maternal serum concentrations. Pyridoxine supplementation is recommended for all pregnant women receiving isoniazid.

Breastfeeding

Rifampicin and isoniazid are excreted into breast milk. Infants should not be breast fed by a patient receiving R-CIN PLUS.

4.7 Effects on ability to drive and use machines

R-CIN PLUS may influence the ability to drive as dizziness, drowsiness and visual disorders are side effects (see section 4.8). Patients should be informed of these, and advised that if affected, they should not drive or operate machinery until they know how R-CIN PLUS affects them.

4.8 Undesirable effects

Summary of the safety profile

RIFAMPICIN:

Reactions to rifampicin occurring with either daily or intermittent dosage regimens include:

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequency unknown	Pseudomembranous colitis, Influenza
Blood and lymphatic system disorders	Frequent Less frequent Frequency unknown	Thrombocytopenia with or without purpura may occur, usually when given as intermittent therapy, but may be reversible if the medicine is discontinued as soon as purpura occurs. Leukopenia Disseminated intravascular coagulation, eosinophilia, haemolytic anaemia, oedema, muscle weakness and myopathy, agranulocytosis, Vitamin K dependent coagulation disorders
Immune system disorders	Frequency unknown	Anaphylactic reaction

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Endocrine disorders	Frequency unknown	Chronic pancreatic insufficiency, adrenal insufficiency in patients with compromised adrenal function
Metabolism and nutrition disorders	Frequency unknown	Decreased appetite
Psychiatric disorders	Frequency unknown	Psychotic disorder
Nervous system disorders	Frequent Less frequent	Headache, drowsiness, ataxia, dizziness, and numbness Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	Less frequent Frequency unknown	Eye irritation, visual disturbances Tear discolouration
Vascular disorders	Frequency unknown	Shock, flushing, vasculitis, bleeding
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Pulmonary fibrosis and pneumonitis, dyspnoea, wheezing, sputum and saliva discoloured
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting, anorexia, epigastric distress Diarrhoea Gastrointestinal bleeding, erosive gastritis, ulcerative colitis and eosinophilic colitis, tooth discolouration which may be permanent
Hepatobiliary disorders	Frequency unknown	Hepatitis, hyperbilirubinaemia, cholestasis (see section 4.4)

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Skin and subcutaneous tissue disorders	Frequency unknown	Erythema multiforme, Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) (see section 4.4), skin reaction, pruritus, rash pruritic urticaria, allergic dermatitis pemphigoid, sweat discolouration
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle weakness, myopathy, bone pain
Renal and urinary disorders	Frequency unknown	Alterations in kidney function and renal failure, acute kidney injury usually due to acute tubular necrosis or to acute interstitial nephritis, chromaturia
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Post-partum haemorrhage, foetal-maternal haemorrhage
Reproductive system and breast disorders	Frequency unknown	Disturbances of the menstrual cycle
Congenital and familial/genetic disorders	Frequency unknown	Porphyria exacerbation
General disorders and administrative site conditions	Frequent Less frequent Frequency unknown	Soft contact lenses may become permanently stained. Adverse effects during intermittent therapy or after restarting interrupted treatment. “Flu Syndrome” consisting of episodes of fever, chills, headache, dizziness, and bone pain, shortness of breath and malaise Oedema

Investigations	Frequent Frequency unknown	Increased blood bilirubin aspartate aminotransferase alanine aminotransferase Decreased blood pressure, increased blood creatinine and hepatic enzyme

ISONIAZID:

Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Eosinophilia, agranulocytosis, thrombocytopenia, anaemia, bleeding associated with acquired inhibition of fibrin stabilisation or factor XIII and red cell aplasia
Immune system disorders	Less frequent Frequency unknown	Fever, skin reactions (including erythema multiforme) and vasculitis Anaphylactic reactions
Endocrine disorders	Less frequent	Isoniazid induced pancreatitis
Metabolism and nutrition disorders	Frequency unknown	Hyperglycaemia, pellagra
Psychiatric disorders	Frequency unknown	Psychotic reactions
Nervous system disorders	Less frequent Frequency unknown	Peripheral neuropathy, ataxia, cerebellar toxicity, psychotic reactions (characterised by delusions, hallucinations and confusion, seizures, memory impairment, toxic psychosis), convulsions toxic encephalopathy, optic neuritis and atrophy Polyneuritis presenting as paraesthesia, muscle weakness, loss of tendon reflexes
Ear and labyrinth disorders	Frequency unknown	Vertigo

Gastrointestinal disorders	Frequent Less frequent	Nausea, vomiting, epigastric distress, constipation, dry mouth Pancreatitis
Hepatobiliary disorders	Less frequent	Severe and sometimes fatal hepatitis
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Rash, acne, exfoliative dermatitis Alopecia, urticaria, purpura, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4), rash, acne, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome, pemphigus
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Systemic lupus erythematous-like syndrome
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia
General disorders and administrative site conditions	Less frequent	Fever
Investigations	Frequency unknown	Anti-nuclear bodies

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Information pertaining to overdose involving combination of rifampicin and isoniazid is limited.

Rifampicin

Acute and chronic effects: Mental obtundation; periorbital or facial oedema; pruritus, generalised; Redman syndrome, headache and increasing lethargy, pruritus and gastrointestinal intolerance (nausea, vomiting, abdominal pain) occurred in most patients and will probably occur within a short time after acute ingestion, unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has occurred in most patients.

Hypotension, sinus tachycardia, ventricular dysrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatalities in adults occurred with doses over 14 g. Fatalities are more likely to occur if there is underlying

hepatic disease, frequent use or abuse of alcohol, or concurrent intake of other hepatotoxic medicines.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Isoniazid

Isoniazid doses of 6 g or more are associated with severe toxicity and doses above 15 g may be fatal without appropriate treatment. Symptoms may not occur until 2 hours after ingestion.

Acute and chronic effects: Gastrointestinal disturbances (severe nausea and vomiting); neurotoxicity (dizziness, slurred speech, lethargy, disorientation, hyperflexia, seizures; coma).

Patients may be asymptomatic for 30 minutes to 2 hours after an acute overdose.

Early symptoms include nausea and vomiting, dizziness, slurred speech, lethargy, disorientation, blurring of vision, visual hallucinations (including bright colours and strange designs) and hyperflexia. Seizures usually occur within 1 to 3 hours after ingestion, and are often repetitive and refractory to treatment with usual anticonvulsants. Lactic acid accumulation produces an anion-gap metabolic acidosis within a few hours, which is often severe and refractory to treatment with sodium bicarbonate. Severe metabolic acidosis, acetonuria, hyperglycaemia, glycosuria and ketonuria have also been reported.

Management of overdose:

Because seizures may occur soon after ingestion, induction of emesis with ipecac is not recommended. Gastric lavage may be performed within 2 to 3 hours of ingestion, and activated

charcoal and a cathartic may be administered if the patient's seizures are controlled and the airway protected.

Supportive measures such as establishing intravenous lines, hydration, correction of electrolyte imbalance, oxygenation, and support of ventilatory function are essential for maintaining the vital functions of the patient. Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

If acute isoniazid overdose is suspected, even in asymptomatic patients, the administration of intravenous pyridoxine (vitamin B6) should be considered. In patients with seizures not controlled with pyridoxine, anticonvulsant therapy should be administered. Sodium bicarbonate should be given to control metabolic acidosis. Haemodialysis is advised for refractory cases; if this is not available, peritoneal dialysis can be used along with forced diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, Combinations of drugs for treatment of tuberculosis.

ATC code: J04AM02

Pharmacological classification: A.20.2.3 Tuberculostatics

Mechanism of action

Rifampicin and isoniazid are bactericidal antituberculosis medicines. They specifically act against rapidly dividing extracellular organisms and have intracellular bactericidal activity. Rifampicin inhibits DNA-dependant RNA polymerase action in susceptible cells.

It particularly interacts with bacterial RNA polymerase; however, it does not inhibit the mammalian enzyme. Rifampicin has shown cross-resistance with other rifamycins. Isoniazid is active against actively dividing tubercle bacilli. Its exact mechanism of action is not known, but it may relate to inhibition of mycolic acid synthesis and disruption of the cell wall in susceptible organisms.

5.2 Pharmacokinetic properties

Pharmacokinetic studies in normal subjects show that rifampicin and isoniazid show comparable bioavailability when given together either as separate dosage forms or in combination.

Rifampicin

Absorption:

Rifampicin is well absorbed from the gastrointestinal tract. Peak blood levels in normal adults and children differ widely for each individual. After a dose of 600 mg, peak serum concentrations of the order of 10 µg/ml occurred at about 2 to 4 hours. Absorption of rifampicin is reduced when ingested with food.

Distribution:

Rifampicin is approximately 80 % protein bound and is well distributed throughout the body. It is detectable in many organs and body fluids, including cerebrospinal fluid. It diffuses well to most body tissues and fluids, including the cerebrospinal fluid (CSF), where concentrations are increased if the meninges are inflamed; concentrations in the liver, gallbladder, bile, and urine are higher than those found in the blood; therapeutic concentrations are achieved in the saliva, reaching 20 % of serum concentrations; crosses the placenta, with foetal serum concentrations

at birth found to be approximately 33 % of the maternal serum concentration; penetrates into aqueous humor; and is distributed into breast milk.

Biotransformation:

Rifampicin is extensively eliminated in the bile and undergoes enterohepatic circulation. Rifampicin is metabolised by deacetylation to its active metabolite. It takes approximately 6 hours for almost all of the rifampicin in the bile to be in the form of this metabolite. Essentially complete antibacterial activity is retained by this metabolite. Deacetylation reduces reabsorption in the intestine and facilitates elimination. Rifampicin is rapidly deacetylated by auto-induced microsomal oxidative enzymes to active metabolite (25-O-desacetylrifampin). Other identified metabolites include rifampin quinone, desacetyl rifampin quinone, and 3-formylrifampin.

Elimination:

Elimination half-life of rifampicin is initially 2 – 5 hours, the longer elimination time occurs with the higher doses. With repeated administration and auto induced metabolism, elimination time may decrease by up to 40 % during the first two weeks, the half-life decreases to 1 to 3 hours. In patients with liver disease the half-life is prolonged. At a dose of up to 600 mg/day, the half-life is not affected by renal failure; therefore, dosage adjustment is not required. Up to 30 % of the given dose of rifampicin is excreted in the urine. Approximately 50 % of this excretion is unchanged medicine. Rifampicin is not removed from the blood by either haemodialysis or peritoneal dialysis.

Isoniazid

Absorption:

Isoniazid is absorbed readily from the gastrointestinal tract. Peak plasma concentrations are reached within 1 – 2 hours after ingestion. Peak concentrations of about 3 to 8 µg/ml appear in blood after a fasting dose of 300 mg. Absorption of isoniazid is reduced when ingested with food.

Distribution:

Isoniazid is distributed into body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs, saliva, sputum and faeces. Isoniazid crosses the placental barrier and into milk. The concentrations in milk are about equal to those in plasma.

Biotransformation:

Isoniazid is metabolised by hepatic acetylation and dehydrasination. It is acetylated by *N*-acetylisoniazid; it is then biotransformed to isonicotinic acid and monoacetylhydrazine. Monoacetylhydrazine is associated with hepatotoxicity via formation of a reactive intermediate metabolite when *N*-hydroxylated by the cytochrome P450 mixed oxidase system. The rate of acetylation is genetically determined; slow acetylators are characterised by a relative lack of hepatic *N*-acetyltransferase.

Elimination:

In adults with normal renal function, over 75 % of the oral dose is excreted in the urine within 24 hours, mainly as metabolites. Small amounts are also excreted in the faeces. Isoniazid is removed from the blood by haemodialysis. A single 5 hour haemodialysis period has removed up to 73 % of the isoniazid in the blood. Peritoneal dialysis is of limited benefit.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Antioxidant: Ascorbic acid

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

Coating materials

Hypromellose

Iron oxide red

Polyethylene glycol 4000

Simethicone emulsion

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ºC in a cool, dry place. Do not take tablets from the blisters until time for administration. Keep blisters in the carton until required for use.

6.5 Nature and contents of container

R-CIN PLUS tablets are packed in:

PVC/PVDC/Aluminium foil blister strips (15) of 6 tablets and (24) of 28 tablets packed into an outer cardboard carton.

Cold form Aluminium-aluminium foil blister strips of 14 tablets for pack sizes of 56 and 84 packed into an outer carton.

White HDPE container with inner LDPE bag and closed with a white screw cap containing 1 000 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

APPROVED PROFESSIONAL INFORMATION

A54/20.2.3/0315

9. DATE OF FIRST AUTHORISATION

Date of registration: 26 May 2020

10. DATE OF REVISION OF THE TEXT

14 March 2023