MODULE 1.3.1.1: PROPOSED PROFESSIONAL INFORMATION FOR HUMAN MEDICINES FOR COTRIZID

SCHEDULING STATUS

1. NAME OF THE MEDICINE

COTRIZID 300 mg /25 mg /800 mg /160 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each **COTRIZID** tablet contains isoniazid 300 mg, pyridoxine hydrochloride 25 mg, sulfamethoxazole 800 mg and trimethoprim 160 mg.

3. PHARMACEUTICAL FORM

Tablet

White to off-white coloured capsule shaped, biconvex uncoated tablets scored on both the sides. The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

COTRIZID is indicated to prevent and/or reduce the risk of non-viral opportunistic and bacterial infections, including Pneumocystis jirovecii pneumonia and Toxoplasma gondii infections, Isosporiasis and/or the activation of latent tuberculosis in HIV positive adults, adolescents and children (>14kg)(WHO clinical stages 2; 3 or 4) on

appropriate antiretroviraltreatment and tuberculin test (TST) positive but without signs, symptoms and/or diagnostic interventions indicative of active tuberculosis.

4.2. Posology and method of administration

Posology

Adults and children weighing 25 kg and above:

One tablet once daily

Children weighing 14 kg to less than 24.9 kg:

Half a tablet once daily.

If aluminium containing antacids are taken, they must be taken at least one hour after isoniazid.

COTRIZID is best taken after meals with an adequate amount of fluid.

Method of administration

Tablets for oral administration.

4.3. Contraindications

- Hypersensitivity to the active substances, sulfamethoxazole, trimethoprim, isoniazid and pyridoxine or any of the excipients or sulphonamides.
- Hypersensitivity to isoniazid chemically related medication such as ethionamide, pyrazinamide and niacin.
- Patients with acute or chronic hepatic disease with moderate to severe hepatic impairment

- Active tuberculosis.
- Severe renal insufficiency
- Patients with a history of drug-induced immune thrombocytopenia and in patients with documented megaloblastic anaemia due to folate deficiency, or patients with serious haematologicaldisorders.(
- Pregnancy.
- Blood dyscrasias, hypersensitivity to sulphonylurea anti-diabetic and saluretic sulphonamide derivatives.
- Vitamin B12 and folic acid deficiency
- Porphyria.
- Concomitant use with dofetilide (see **"INTERACTIONS").**
- History of gout or acute gout.
- Infants < 6 weeks of age.
- Glucose 6 phosphate deficiency.
- Coadministration of leucovorin (follinic acid) and sulfamethoxazole/trimethoprim.
- Alcohol abuse/alcoholism.
- Concomitant use with tyramine and/or histamine containing food/beverages.
- HIV positive patients but TST (tuberculin sensitivity test) negative and in pre-ARV treatment phase.

4.4. Special warnings and precautions for use:

COTRIZID may lead to a positive test for prohibited substances in competitive sport activities.

COTRIZID may affect the performance of a child and adult learning in schools and other institutions of education, learning and training.

Frequent monitoring of side effects, haematological parameters, hepatic and renal functions, thyroid functions, eye examinations, neurological examinations, viral loads as well as appropriate clinical, laboratory and relevant imaging procedures to detect opportunistic infections, TB and other infections are mandatory. Appropriate actions should be taken regarding the above as needed.

Sulfamethoxazole/trimethoprim:

Embryofoetal toxicity:

Exposure to sulfamethoxazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot. If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the foetus.

Hypersensitivity and other fatal reactions:

Sulfonamides, including sulfonamide-containing products such as sulfamethoxazole/ trimethoprim, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. A skin rash may be followed by a more severe/fatal reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), hepatic necrosis, and serious blood disorders (agranulocytosis, aplastic anaemia and other blood dyscrasias). Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

There is an increased risk of severe adverse reactions in elderly patients or when complicating conditions exist, e.g. impaired kidney, and/or liver function, or concomitant use of other medicines (in which case the risk may be related to the dosage and duration of treatment. It should not be given in severe renal impairment (see **CONTRAINDICATIONS).**

If sulfamethoxazole/trimethoprim is given over a prolonged period, regular blood counts are required. If a significant reduction in count of any formed blood element is noted, sulfamethoxazole/trimethoprim should be discontinued. Other than in exceptional cases, sulfamethoxazole/trimethoprim should not be given to patients with serious haematological disorders. Cases of pancytopenia have been reported in patients taking the combination of trimethoprim and methotrexate.

Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole/trimethoprim.

Trimethoprim should not be given to patients with serious haematological disorders and particularly in megaloblastic anaemia secondary to folate depletion. (See **CONTRAINDICATIONS).** Care should be taken in patients with actual, or possible, folate deficiency and use of folinic acid should be considered.

In elderly patients, or in patients with pre-existing folic acid deficiency (e.g. chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states), patients with impaired hepatic function or kidney failure, haematological changes indicative of folic acid deficiency may occur. Also to those with severe allergies or bronchial asthma. These are reversible by folinic acid therapy.

Owing to the possibility of haemolysis, sulfamethoxazole/trimethoprim should not be given to patients with a glucose-6-phosphate (G6PD) deficiency (See **CONTRAINDICATIONS).**

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Caution is advised in patients with thyroid disorders/dysfunction and thyroid functions should be monitored frequently in patients on treatment with **COTRIZID.**

Thrombocytopenia:

Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole/trimethoprim.

Electrolyte abnormalities:

High dosage of trimethoprim, as used in patients with *Pneumocystis Jiroveci* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalaemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if medicines known to induce hyperkalaemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

Severe and symptomatic hyponatremia can occur in patients receiving sulfamethoxazole/ trimethoprim, particularly for the treatment of *Pneumocystis Jiroveci* pneumonia. Evaluation for hyponatremia and appropriate correction is necessary in symptomatic patients to prevent life-threatening complications.

Urinalysis and renal function test§. should be performed regularly in patients undergoing long-term treatment with **COTRIZID** (particularly patients with impairment kidney function (See **CONTRAINDICATIONS).** During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

Streptococcal Infections and Rheumatic Fever:

The sulfonamides should not be used for treatment of group A J3-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Clostridium difficile associated *diarrhoea:*

Clostridium difficile associated diarrhoea (COAD) has been reported with use of sulfamethoxazole/trimethoprim, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C/ostridium difficile.*

Clostridium difficile produces toxins A and B which contribute to the development of COAD. Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. COAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since COAD has been reported to occur over two months after the administration of antibacterial medicines.

If COAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile,* and surgical evaluation should be instituted as clinically indicated.

Adjunctive treatment with leucovorin (folinic acid) for Pneumocystis jiroveci pneumonia:

Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin (folinic acid) for the treatment of HIV positive patients with *Pneumocystis jiroveci* pneumonia in a randomized placebo controlled trial. Co-administration of trimethoprim-

sulfamethoxazole and leucovorin (folinic acid) during treatment of *Pneumocystis jiroveci* pneumonia should be avoided (See **CONTRAINDICATIONS).**

Hypoglycaemia:

Cases of hypoglycemia in non-diabetic patients treated with sulfamethoxazole/trimethoprim are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of sulfamethoxazole/trimethoprim are particularly at risk.

Use in the Treatment of and Prophylaxis for Pneumocystis Jiroveci Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS):

AIDS patients may not tolerate or respond to sulfamethoxazole/trimethoprim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with sulfamethoxazole/trimethoprim therapy in AIDS patients who are being treated for *Pneumocystis jiroveci* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of sulfamethoxazole/trimethoprim in non-AIDS patients. Adverse effects are generally less severe in patients receiving sulfamethoxazole/trimethoprim for prophylaxis. A history of mild intolerance to sulfamethoxazole/trimethoprim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with sulfamethoxazole/trimethoprim should be re-evaluated.

Co-administration of sulfamethoxazole/trimethoprim and leucovorin (folinic acid) should be avoided with *Pneumocystis Jiroveci* pneumonia (See **CONTRAINDICATIONS).**

Folate deficiency:

Sulfamethoxazole/trimethoprim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome and patients in malnutrition states) and to those with severe allergies or bronchial asthma.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with pre-existing folic acid deficiency or kidney failure. These effects are reversible by folinic acid therapy.

Haemolysis:

In glucode-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (See **CONTRAINDICATIONS).**

Phenylalanine metabolism:

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

Porphyria and Hypothyroidism:

COTRIZID contains a sulfonamides, caution is advised in patients with thyroid dysfunction.

Isoniazid:

COTRIZID, contains isoniazid, caution is advised in patients with

- Alcoholism. Daily indigestion of alcohol may be associated with a higher incidence of isoniazid hepatitis (See **CONTRAINDICATIONS).**
- Hepatic or renal function impairment (See **CONTRAINDICATIONS).**
- Convulsive disorder.
- History of psychosis.
- Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.
- Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis (See **CONTRAINDICATIONS).**

Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic or pregnant (see **"CONTRAINDICATIONS"),** should receive pyridoxine, usually at a dose of 10 mg daily, with doses of 100 - 200 mg daily for treatment if peripheral neuritis develops. **COTRIZID** contains 25 mg pyridoxine.

Since **COTRIZID** contains isoniazid, ophthalmologic examinations (including ophthalmoscopy) should be done before treatment is started and periodically thereafter, even without occurrence of visual symptoms.

All medicines should be stopped, and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Hepatotoxicity:

There is a possibility of severe and sometimes fatal hepatitis with isonaziad. This typically occurs within the first three months of treatment but can develop late.

Transient elevation of liver enzymes occurs in 10 % of patients, overt hepatitis occurs in less than 1 % but may be fatal. There is an increased risk of hepatitis in patients over 50 years, slow acetylators and those who consume alcohol daily.

Liver function tests should be performed every 3 months during treatment and **Isoniazid** discontinued if liver enzymes are raised more than five times the normal upper limit. Patients who develop malaise, anorexia and nausea together with raised liver enzyme levels should discontinue isoniazid promptly pending investigation.

Pyridoxine:

Patients treated with levodopa should avoid supplemental vitamins that contain more than 5 mg pyridoxine in the daily dose. However, when levodopa is co-administered along with **COTRIZID** as a prophylactic treatment in HIV patients, the recommended dose of pyridoxine is not known.

Pyridoxine reduces the activity of altretamine. It has also been reported to decrease serum concentrations of phenobarbitone and phenytoin.

Women taking oral contraceptives and patients taking hydralazine, isoniazid and penicillamine may exhibit increased pyridoxine requirements.

4.5. Interaction with other medicines and other forms of interaction:

Sulfamethoxazole/trimethoprim:

An increased incidence of thrombocytopenia with purpura has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides.

Increased digoxin blood levels can occur with concomitant **COTRIZID** therapy, especially in elderly patients. Serum digoxin levels should be monitored.

It has been reported that **COTRIZID** may significantly increase the hypoprothombotic effect of the anticoagulant warfarin. This interaction should be borne in mind when **COTRIZID** is given to patients already on anticoagulant therapy. In such cases the coagulation time should be frequently monitored

COTRIZID may inhibit the hepatic metabolism of phenytoin. A 39 % increase in phenytoin half-life and a 27 % decrease in the metabolic clearance rate of phenytoin have been observed following administration of **COTRIZID** at normal clinical dosages. If the two medicines are given concurrently, it is important to watch for signs of phenytoin toxicity. Given the increased risk of phenytoin toxicity with isoniazid, it is critical to monitor phenytoin levels and adjust the **COTRIZID** dose as needed.

Reversible deterioration of renal function (nephrotoxicity), manifested by increased serum creatinine, has been observed in patients treated with **COTRIZID** and cyclosporine following renal transplantation. This combined effect is presumably due to the trimethoprim component. (A reversible decrease in creatinine clearance has been observed in patients with normal renal function. This is probably due to a reversible inhibition of the tubular secretion of creatinine).

The efficacy of tricyclic antidepressants can decrease when co-administered with **COTRIZID.** Sulfonamides, including sulfamethoxazole can compete with protein binding and also with the renal transport of methotrexate, thus increasing the free methotrexate fraction and the systemic exposure to methotrexate.

Cases of pancytopenia have been reported in patients taking the combination of trimethoprim and methotrexate. Trimethoprim has a low affinity for human dehydrofolate reductase but may increase toxicity of methotrexate and may lead to the possibility of haematological adverse medicine interactions with methotrexate, especially in the presence of other risk factors such as old age, hypoalbuminaemia, impaired renal function, decreased bone marrow reserve. Such adverse medicine reactions may occur especially with methotrexate given in high dose regimen. It is recommended that those patients be treated with folic acid or calcium folinate to counteract the effects of haematopoiesis.

Patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly, may develop megaloblastic anaemia if **COTRIZID** is prescribed concurrently.

Sulfamethoxazole/trimethoprim as contained in **COTRIZID** potentiates the effect of oral hypoglycaemics that are metabolized by CYP2C8 (e.g., pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 {e.g., glipizide and glyburide) or eliminated renally via OCT2 (e.g., metformin). Additional monitoring of blood glucose may be warranted. Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Toxic delirium after concomitant intake of **COTRIZID** and amantadine may occur.

There is evidence that trimethoprim, by inhibiting it renal transport system, can interact with dofetilide. Trimethoprim 160 mg in combination with sulfamethoxazole 800 mg (as contained in **COTRIZID)** co-administered twice daily with dofetilide 500 µg twice daily for four days may result in an increase in the maximum concentration (Cmax). Dofetilide may cause serious ventricular dysrhythmias associated with QT interval prolongation, including torsades de pointes which are directly related to the dofetilide plasma concentration. The concurrent administration of dofetilide and **COTRIZID** is contraindicated.

Influence on diagnostic methods: **COTRIZID,** specifically the trimethoprim component, may interfere with a serum methotrexate assay using the competitive protein-binding technique when bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by radio-immune-assay.

The presence of trimethoprim and sulfamethoxazole (as contained in **COTRIZID)** may also interfere with the Jaffe alkaline picate reaction assay for creatinine, causing values in the normal range to be increased by about 10 %.

Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when sulfamethoxazole/trimethoprim is co-administered with medicines that are substrates of CYP2C8 and CYP2C9 or OCT2.

In some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to sulfamethoxazole/trimethoprim as contained in **COTRIZID.** If concomitant treatment is necessary, monitoring of haematological parameters is needed.

Administration of trimethoprim/sulfamethoxazole 160mg/800mg as contained in **COTRIZID** causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Cases of hyperkalaemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim, as contained in **COTRIZID,** and an angiotensin converting enzyme inhibitor.

Isoniazid:

Chronic use of isoniazid may decrease the plasma clearance and/or prolong the duration of action of alfenatil, (warfarin), benzodiazepines (diazepam), anticonvulsants (carbamazepine, phenytoin, primidone, valproic acid), haloperidol, ketoconazole and theophylline due isoniazid being an inducer of cytochrome P450. Concurrent use of paracetamol, alcohol, rifampicin and other hepatotoxic medication, may increase the potential for isoniazid-induced hepatotoxicity. Aluminium containing antacids may delay and decrease absorption and serum concentrations of isoniazid and isoniazid should be administered 1 hour before aluminium hydroxide.

Because isoniazid might have some MAO inhibiting activity, when it is used with selective serotonin reuptake inhibitors patients should be monitored for serotonin

syndrome. **As a** result of probable alterations in dopamine metabolism, patients receiving isoniazid and disulfiram have experienced coordination difficulties and psychotic episodes.

Isoniazid is an inducer of cytochrome P450 (CYP) 2E1. It inhibits CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Since carbamazepine is a CYP3A4 substrate its concentrations may increase with isoniazid administration, resulting in atazia, headache, vomiting, blurred vision, drowsiness, and confusion. These symptoms will subside after discontinuation of isoniazid or dose reduction of carbamazepine. Since phenytoin is a CYP2C19 substrate, its concentrations may increase with isoniazid administration, resulting in phenytoin toxicity. Phenytoin toxicity may also arise in slow isoniazid inactivators.

Food Interactions:

Because isoniazid has some monoamine oxidase inhibiting activity, an interaction with tyramine-containing foods (cheese, red wine) may occur (itching of skin, rapid or pounding heart, chills or headache). Diamine oxidase may also be inhibited, causing exaggerated response (eg, headache, sweating, palpitations, flushing and hypotension) to foods containing histamine (eg, skipjack, tuna, other tropical fish). Tyramine- and histamine-containing foods should be avoided by patients receiving isoniazid, as contained in **COTRIZID.**

Glucocorticosteroids may increase hepatic metabolism and/or excretion of isoniazid. Concurrent use of cycloserine, disulfiram and other neurotoxic medicines may increase the potential for central nervous system toxicity. The central nervous system

effects of meperidine (drowsiness), cycloserine (dizziness, drowsiness), and disulfiram (acute behavioural and coordination changes) may be exaggerated with isoniazid as contained in **COTRIZID.**

Concurrent **COTRIZID,** because it contains isoniazid, and levodopa administration may produce symptoms of excess catecholamine stimulation (agitation, flushing, palpitations) or lack of levodopa effect.

Fast acetylation of isoniazid may produce high concentrations of hydrazine that facilitate deflorination of enflurane. Isoniazid may increase the formation of potentially nephrotoxic inorganic fluoride metabolites when used concurrently with enflurane.

False positive reactions with copper sulphate urine glucose tests may occur.

Corticosteroids(e.g. prednisolone) may decrease the serum concentration of isoniazid by increasing acetylation rate and/or renal clearance. Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid by competition of acetylating enzymes.

Isoniazid may produce hyperglycaemia and lead to loss of glucose control in patients on oral hypoglycaemics.

Pyridoxine:

Pyridoxine supplements should not be given to patients receiving levodopa, because the action of the latter drug is antagonized by pyridoxine. However, pyridoxine

(Vitamin 85) may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa.

4.6. Fertility, pregnancy and lactation:

COTRIZID is contraindicated in pregnancy and lactation (See **CONTRAINDICATIONS).**

Pregnancy:

Sulfamethoxazoleltrimethoprim:

COTRIZID use in late pregnancy increases the risk of jaundice and kernicterus in the newborn and should not be used.

Teratogenic Effects:

In rats, oral doses of approximately 5 and 6 times the recommended human daily dose based on a body surface area produced teratologic effects manifested mainly as cleft palates. In rabbit studies, an overall increase in fgetal loss (dead and resorbed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose based on body surface area.

Jsoniazid:

Teratogenic Effects:

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy.

Pyridoxine:

The requirement for pyridoxine appears to be increased during pregnancy.

Breastfeeding:

COTRIZID should not be administered to mothers breastfeeding their babies. a

Sulfamethoxazo/e/trimethoprim:

Both trimethoprim and sulfamethoxazole, as contained in COTRIZID, pass into the breast milk and increase the risk of jaundice and kernicterus in the baby.

Isoniazid:

COTRIZID contains isoniazid. Isoniazid is known to pass into maternal breast milk. Mothers on treatment with **COTRIZID** or isoniazid should not breastfeed their babies (See **CONTRAINDICATIONS).**

Pyridoxine:

The need for pyridoxine is increased during lactation but the despite the increased need of pyridoxine, mothers breastfeeding theirs babies should not be treated with **COTRIZID.** It is not known whether pyridoxine, as contained in **COTRIZID,** is excreted in human milk.

4.7. Effects on ability to drive and use machines:

Treatment with **COTRIZID** may affect the ability of patients to drive and use machines as reflected by the adverse event profile of the medicines contained in **COTRIZID.** Patients should not drive and use machines unless they do not experience adverse events that negatively affect their mental and/or physical abilities

to perform or execute tasks or activities requiring mental alertness, judgement and/or sound coordination and vision.

4.8. Undesirable effects:

Sulfamethoxazole and Trimethoprim:

The most frequent side effects are skin reactions (such as rash and urticaria) and gastrointestinal disturbances (nausea, vomiting, anorexia).

Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Infectious and infestations:

Less frequent:	Fungal infections such as candidiasis.

Blood and the lymphatic system disorders:

Frequent:	Leukopenia, granulocytopenia, and thrombocytopenia.
Less frequent:	Agranylocytosis, anaemia (megaloblastic, haemolytic/autoimmune, aplastic), pancytopenia, methemoglobinaemia, purpura, neutropenia hypoprothrombinemia, methemoglobinemia, eosinophilia.

Immune system disorders:	Hypersensitivity reactions (fever, chills,
Frequent:	angiooedema, anaphylactic reactions and serum sickness, skin eruptions, lymphadenopathy, vasculitis), Pulmonary infiltrates such as occur in eosinophilic or allergic alveolitis {cough, shortness of breath).
Less frequent:	Allergic myocarditis, conjunctiva! and scleral injection, lupus erythematosus.
Metabolism and nutrition disorders:	
Frequent:	Hyperkalaemia, hypernatraemia, hypoglycaemia.
Psychiatric disorders:	
Less frequent:	Hallucinations, depression, apathy, nervousness.
Nervous system disorders:	
Frequent:	Neuropathy {including peripheral neuropathy and paresthesia), uveitis, aseptic meningitis or meningitis-like symptoms, ataxia, convulsions, tinnitus, vertigo, headache.
Frequency unknown:	Insomnia, dizziness, drowsiness, fatigue, mental depression.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Pulmonary eosinophilia, fibrosing alveolitis.
Frequency unknown:	Cough, shortness of breath, and pulmonary infiltrates.

Gastrointestinal disorders:

Frequent:	Nausea (with or without vomiting), stomatitis, glossitis,diarrhoea, pseudomembranous enterocolitis, acute pancreatitis, pellagra.

Hepato-biliary disorders:

Frequent:	Elevated transaminases and bilirubin, hepatitis, cholestasis liver necrosis.
Less frequent:	Vanishing bile duct syndrome, cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Frequent:	Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), purpura, Henoch-Schoenlein purpura, exfoliative dermatitis, pruritus, urticaria!, rash.
Frequency unknown:	Anaphylaxis, allergic myocarditis, angioedema, drug fever, chills, serum sickness, generaliii!ed allergic reactions,

generalized skin eruptions, conjunctiva! and scleral injection, periarteritis nodosa and systemic lupus erythematosus.

Musculoskeletal, connective tissues and bone disorders:

Frequent:	Athralgia, myalgia.
Less frequent:	Rhabdomyolysis.

Renal and urinary disorders:

Frequent:	Impaired renal function, and tubular necrosis, interstitial nephritis, elevated blood urea, elevated serum creatinine, crystalluria, sulphonamides induce increased diuresis, toxic nephrosis with oliguria and anuria, nephrotoxicity in association with cyclosporine, haematuria, lumbar pain.

Safety of su/famethoxazoleltrimethoprim in HIV-infected patients:

The HIV patient population is similar to the general patient population in terms of the spectrum adverse events that may occur. However, some adverse events may occur with a higher frequency and a difference in the clinical picture. These differences concern the following system organ classes:

Blood and the lymphatic system disorders:

Less frequent:	Agranulocytosis, aplastic anaemia, hypoprothrombinaemia, eosinophilia.
Frequency unknown:	Neutropenia, hemolytic anaemia, megaloblastic anaemia, methemoglobinaemia

Metabolism and nutrition disorders:

Frequent:	Hyperkalaemia.
Less frequent:	Hyponatraemia, hypoglycaemia.

Gastrointestinal disorders:

Frequent:	Anorexia, nausea with or without vomiting, diarrhoea, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, emesis, abdominal pain.

Hepatowbiliary disorders:

Frequent:	Elevated transaminases and bilirubin, hepatitis (including cholestatic jaundice and hepatic necrosis), hepatomegaly.

Skin and subcutaneous tissue disorders:

Frequent:	Maculopapular rash, usually with pruritus.

General disorders and administration site conditions:

Frequent:	Fever, usually in conjunction with maculopapular eruption.
Frequency unknown:	Weakness, fatigue. insomia

Post-marketing experience (sulfamethox azoleltrimethoprim):

The following adverse reactions have been identified during post-approval use of sulfamethoxazole/trimethoprim. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenia purpura.
- Idiopathic thrombocytopenic purpura.
- QT prolongation resulting in ventricular tachycardia and torsade de pointes.

Isoniazid:

The most frequent reactions are those affecting the nervous system and the liver.

Blood and the lymphatic system disorders:

Frequent:	Sideroblastic, aplastic, or haematolytic anaemia.
Less frequent:	Agranylocytosis, thrombocytopenia, eosinophilia.
Frequency unknown:	Hemolytic

Endocrine disorders:

Frequent:	Gynecomastia.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics {acetazolamide and the thiazides) and oral hypoglycaemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulfonamides.

Immune **system disorders:**

Frequent:	Hypersensitivity reactions {skin eruptions, fever, lymphadenopathy, vasculitis associated with positive antinuclear antibodies, anaphylactic reactions, Stevens Johnson syndrome).
Frequency unknown:	Lupus-like syndrome, rheumatoid syndrome.

Metabolism and nutrition disorders:

Frequency unknown:	Hyperglycaemia, metabolic acidosis, pyridoxine deficiency, pellagra.

Frequency unknown:	Gynecomastia

Psychiatric disorders:

Less frequent:	Toxic psychosis.

Nervous system disorders:

Frequent:	Psychotic reactions, convulsions, peripheral neuropathy.
Less frequent:	Memory impairment, toxic encephalopathy, optic neuritis and atrophy
Frequency unknown:	Vertigo.

Eye disorders:

Less frequent:	Optic neuritis.

Gastrointestinal disorders:

Frequent:	**Nausea,** vomiting, pellagra, pancreatitis, epigastric distress.
Frequency unknown:	Dry mouth, constipation.

Hepato-biliary disorders:

Frequent:	Elevated serum transaminases (ALT. AST) bilirubinemia, bilirubinuria, jaundice, severe and sometimes fatal hepatitis.

Skin and subcutaneous tissue disorders:

Less frequent:	Skin rashes including a pellagra-like dermatitis in malnourished patients.
Frequency unknown:	Purpura.

Musculoskeletal, connective tissues and bone disorders:

Frequency unknown: Hyperreflexia.

Renal and urinary disorders:

Frequency unknown: Urinary retention.

Reproductive system and breast disorders:

Frequency unknown: Gynecomastia.

Peripheral neuropathy is the most common toxic effect. It is dose related, occurs most often in the malnourished and in those predisposed to neuritis (e.g. alcoholics and diabetics), and is usually preceded by paraesthesia of the feet and hands. The incidence is higher in "slow inactivators".

Frequent prodromal symptoms related to hepatic effects are anorexia, nausea, vomiting, fatigue, malaise and weakness. Mild and transient elevation of serum transaminase levels occurs in 10 to 20 % of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, **COTRIZID,** which contains isoniazid should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2,3 % of those over 50 years of age.

Pyridoxine:

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies;

Doses of more than 2 grams daily for 2 - 40 months have been associated with sensory neuropathy. However, since this is nearly 100 times the dose of 25 mg daily provided in **COTRIZID,** this toxicity is not expected.

Paraesthesia, somnolence, and low serum folic acid levels have been reported.

4.9. Overdose

A **COTRIZID** overdose may precipitate side effects and/or the severity thereof.

Sulfamethoxazoleltrimethoprim:

The amount of a single dose of sulfamethoxazole/trimethoprim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported.

Symptoms of acute overdose may include nausea, vomiting, diarrhoea, headache, vertigo, dizziness, mental and visual disturbances, crystalluria, haematuria and anuria, anorexia, colic, drowsiness, unconsciousness, pyrexia may occur in severe cases.

In chronic overdose, bone marrow depression, manifested as thrombocytopenia or leukopenia, and other blood dyscrasias due to folinic acid deficiency may occur. If signs of bone marrow depression occur, the patient should be given leucovorin/folinic acid 5 mg to 15 mg daily until normal haematopoiesis is restored.

Jaundice is a potential late manifestation of overdosage.

on the symptoms:

Gastric lavage or emesis, promotion of renal excretion by forced diuresis (alkalinisation of urine increases sulfamethoxazole elimination), haemodialysis (note peritoneal dialysis is not effective), monitoring of blood count and electrolytes. If significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Calcium folinate, 3 to 6 mg intramuscularly, for 5 to 7 days, may be given to counteract the effects of trimethoprim on haematopoiesis.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethoxazole and trimethoprim.

Isoniazid:

Symptoms of isoniazid overdose includes slurred speech, metabolic acidosis, hyperglycaemia, hallucinations, respiratory and CNS depression, convulsions and coma. Fatalities can occur. Treatment consists of gastric lavage, symptomatic and supportive therapy.

Untreated or inadequately treated cases of gross isoniazid overdosage can be fatal, but good response has been reported in most patients treated within the first few hours after ingestion.

Ingested acutely, as little as 1,5 g isoniazid may cause toxicity in adults. Doses of 35 to 40 mg/kg have resulted in seizures. Ingestion of 80 to 150 mg/kg isoniazid has been associated with severe toxicity and, if untreated, significant mortality.

Pyridoxine:

In patients, oral doses up to 1000 mg daily have not caused adverse reactions.

Pyridoxine given to animals in amounts of 3 to 4 g/kg of body weight produces convulsions and death. In man, a dose of 25 mg/kg of body weight is well tolerated.

5. PHARMACOLOGICAL PROPERTIES:

Sulfamethoxazole and Trimethoprim acts synergistically by the sequential blockade of two bacterial enzymes that catalyse successive stages in the biosynthesis of folinic acid in the micro-organism.

The combination of sulfamethoxazole and trimethoprim is bactericidal *in vitro* for some organisms at concentrations at which the components, trimethoprim and sulfamethoxazole alone, are usually bacteriostatic and is effective *in vitro* against a range of gram-positive and gram-negative organisms.

In vitro sensitivity does not necessarily imply clinical efficacy.

Isoniazid is rapidly active against actively dividing *Mycobacterium tuberculosis,* and bacteriostatic against semi-dormant organisms.

Pyridoxine is a vitamin supplement and oral therapy is of proven benefit in correcting sideroblastic anemias associated with the antituberculosis drugs isoniazid and pyrazinamide, which act as vitamin Bs antagonists.

5.1. Pharmacodynamics properties:

Antibacterial Spectrum (In vitro}:

The antibacterial effect of sulfamethoxazole and trimethoprim *in vitro* covers a wide range of gram-positive and gram-negative pathogenic organisms. The sensitivity of sulfamethoxazole and trimethoprim is heavily dependent upon the prevalence of resistance of the geographical area.

In vitro sensitivity does not necessarily imply *in vivo* activity / efficacy.

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with paraaminobenzoic acid (PABA). Trimethoprim blocks the production oftetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole or trimethoprim alone.

Isoniazid inhibits the biosynthesis of mycolic acids which are major components of the cell wall of *Mycobacterium tuberculosis.*

Isoniazid depletes pyridoxine supplies by binding to pyridoxine. Pyridoxine is required by GABA transaminase and glutamic acid decarboxylase, which both synthesize GABA.

Pyridoxine is converted to active forms of Vitamin 86, pyridoxal phosphate and pyridoxamine phosphate. These forms act as coenzymes in reactions of intermediary metabolism.

5.2. Pharmacokinetic properties:

Sulfamethoxazo/eltrimethoprim:

Following oral administration, trimethoprim and sulfamethoxazole are almost completely absorbed from the upper portion of the gastrointestinal tract. Following a single dose of 160 mg trimethoprim and 800 mg sulfamethoxazole peak plasma concentrations of 1,5 - 3 µg/mt for trimethoprim and 40 - 80 µg/ml for sulfamethoxazole are reached after 1 to 4 hours.

Following repeated administration of the above dosage at 12 hour intervals, minimum plasma concentrations at steady state, achieved in 2-3 days, range between 1,3 and 2,8 µg/mt for trimethoprim and between 32 and 63 µg/ml for sulfamethoxazole.

The volume of distribution of trimethoprim is about 130 liters and that of sulfamethoxazole, about 20 litres. At the above concentrations, 45 % of trimethoprim

and 66 % of sulfamethoxazole is bound to plasma proteins. In humans, trimethoprim and sulfamethoxazole were detected in the foetal tissues (placenta, liver, lung), umbilical cord blood and amniotic fluid, indicating placental transfer of both drugs. In general, foetal concentrations of trimethoprim are similar, and those of sulfamethoxazolelower, than maternal concentrations.

Both sulfamethoxazole and trimethoprim are excreted in breast milk. Concentrations in breast milk are similar to (trimethoprim), or lower than (sulfamethoxazole) those in maternal plasma.

The volume of distribution for trimethoprim is 100 - 120 L while that of sulfamethoxazole is 12 - 18 L.

Approximately 50 - 70 % of the trimethoprim dose and 10 - 30 % of the sulfamethoxazole dose are excreted unchanged in the urine. The principal trimethoprim metabolites are 1- and 3-oxides and the 3 - and 4-hydroxy derivatives; some metabolites are microbiologically active. Sulfamethoxazole is metabolized in the liver, predominantly by N4-acetylation, and to a lesser extent, by glucuronide conjugation; the metabolites are inactive.

The elimination half-lives of sulfamethoxazole and trimethoprim are similar (a mean of 11 hours for trimethoprim and 10 hours for sulfamethoxazole).

Both sulfamethoxazole and trimethoprim, as well as their metabolites, are eliminated almost entirely by the kidneys through both glomerular filtration and tubular secretion,

giving urine concentrations of both active substances considerably higher than the concentration in the blood. A small part of each substance is eliminated via the faeces.

Jsoniazid:

For isoniazid, plasma concentrations of the drug in rapid isoniazid inactivators are 20 - 50 % of those in slow isoniazid inactivators.

Approximately 10 % of isoniazid is bound to protein.

Isoniazid is metabolized by hepatic arylamine N-acetyltransferase type 2 (NAT2), encoded by a variety of NAT alleles. The medicine is N-acetylated to N-acetylisoniazid in a reaction that uses acetyl-coA.

Half-lives of 30 - 100 minutes (isoniazid, fast acetylators) and 2 - 5 hours (isoniazid, slow acetylators).

75 - 95 % of isoniazid are excreted in urine within 24 hours, mostly as acetylisoniazid and isonicotinic acid. The metabolite (4-pyridoxic acid) of pyridoxine are excreted in urine.

Pyridoxine:

Pyridoxine is absorbed from the GI tract with normal serum concentrations of 30 - 80 ng/mt.

The forms of pyridoxine in the blood, pyridoxal and pyridoxal phosphate are highly protein bound.

The half-life of pyridoxine is 15 - 20 days.

The metabolite (4-pyridoxic acid) of pyroxidine is excreted in urine.

Pharmacokinetics in special clinical situations:

The elimination half-lives of trimethoprim and sulfamethoxazole are not significantly changes in elderly patients. In patients with severely impaired renal function (creatinine clearance 15 - 30 ml/min), the elimination half-lives of both components are increased, requiring dosage regimen adjustment.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium starch glycolate,

Povidone,

Docusate sodium benzoate,

Magnesium stearate.

Maize starch

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 30 °C.

Keep the container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and content of container

COTRIZID is packed in 65cc white high density polyethylene (HOPE) bottle with 45mm non child resistant white cap with induction sealing containing 30 tablets and rayon in the bottle.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Sulfamethoxazole/Trimethoprim/Isoniazid/Pyridoxine Hydrochloride 800 mg/160 mg/300 mg/25 mg tablets should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

7. MARKETING AUTHORISATION HOLDER:

CIPLA MEDPRO (PTY) LTD

Building 9

Pare du Cap

Mispel Street

Bellville

7530

RSA

8. MARKETING AUTHORISATION NUMBER(S):

52/20.2/0208

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION:

18 February 2020

10. DATE OF REVISION OF THE TEXT