**Professional Information for Medicines for Human Use:**

# NUCOTRIM TABLETS

## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

**NUCOTRIM** 80 mg/400 mg, tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

| | |
|---|---|
| Trimethoprim | 80 mg |
| Sulfamethoxazole | 400 mg |
| Nipastat (as preservative) | 0,25 % *m/m* |

Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet.

White, round flat tablet bisected on one side.

The bisection line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

NUCOTRIM is effective against a wide range of Gram-positive and Gram-negative organisms and is indicated in adults and children above 12 years for the following indications (see sections 4.2, 4.3, 4.4, 4.8 and 5.1):

1. Upper and lower respiratory tract infections e.g., acute and chronic bronchitis, bronchiectasis, tonsillitis, sinusitis and pharyngitis, otitis media, pneumonia and pneumocystis carinii pneumonitis (see also section 4.8 *Pneumocystis jirovecii* Pneumonitis (PJP)).
2. Renal and urinary tract infections e.g., pyelitis, pyelonephritis, urethritis, acute and chronic cystitis and cystopyelitis, including prostatitis.
3. Gastrointestinal tract infections e.g., enteritis, typhoid and paratyphoid fever, typhoid carriage, bacillary dysentery and cholera (as an adjunct to fluid and electrolyte replacement).
4. Genital tract infections: both male and female including gonococcal infections.
5. Skin infections e.g., pyoderma, boils, furuncles, abscesses.
6. Other bacterial infections: acute brucellosis, mycetoma except those caused by true fungi, nocardiosis, acute and chronic osteomyelitis.

### 4.2 Posology and method of administration

**Posology**

***Adults and children over 12 years***

The usual dose is two NUCOTRIM tablets every 12 hours after meals.

The maximum dose (for particularly severe cases) is three NUCOTRIM tablets every 12 hours. The minimum dosage for long-term treatment is one NUCOTRIM tablet every 12 hours.

In the treatment of acute infections NUCOTRIM should be administered for at least 5 days or for at least 2 days after the symptoms have disappeared. If clinical improvement is not evident after 7 days

of therapy, the patient should be reassessed.

**Special populations**

***Renal impairment***

If NUCOTRIM is indicated for patients with renal impairment, the following dosage scheme, based on creatinine clearance is suggested:

*Adults and children over 12 years*

Above 25 mL/min: Standard dosage

15 – 25 mL/min: Standard dosage for a maximum of 3 days followed by half the standard daily dosage.

Below 15 mL/min: Not to be administered unless haemodialysis facilities are available when half the standard daily dosage may be given.

Measurements of plasma concentrations of sulfamethoxazole at intervals of 2 days are recommended in samples obtained 12 hours after administration of NUCOTRIM. If the concentration of total sulfamethoxazole exceeds 150 microgram/mL then treatment should be interrupted until the value falls below 120 microgram/mL.

*Children (6 weeks to 12 years)*

No information is available for children with renal failure.

**Method of administration**

Oral.

The tablets must be taken by mouth, after food. The tablets must be swallowed with a drink of water.

**4.3 Contraindications**

- Hypersensitivity to sulfamethoxazole, trimethoprim, sulfonamides or to any of the excipients listed in section 6.1
- Patients suffering from porphyria
- Liver parenchymal damage
- Severe renal insufficiency
- Megaloblastic anaemia and blood dyscrasia due to folic acid deficiency
- Pregnancy, in women prior to delivery or by nursing mothers (see section 4.6)
- Premature or newborn infants during the first 6 weeks of life
- Vitamin B12 and folic acid deficiency states
- Patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.

**4.4 Special warnings and precautions for use**

**Immunocompromised patients**

A high incident of side-effects occurs in immunocompromised patients such as those suffering from AIDS or patients receiving immunosuppressive therapy. The adverse effects include skin rash, recurrent fever, neutropenia, thrombocytopenia and raised liver enzyme values.

**Life-threatening adverse reactions**

Fatalities, although less frequent, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, a plastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract (see section 4.8).

***Life-threatening skin adverse reactions***

- NUCOTRIM may cause life-threatening cutaneous reactions Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) also known as Lyell's syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), generalised bullous fixed drug eruptions (FDE), erythema multiforme and allergic vasculitis.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If symptoms or signs of SJS, TEN (e.g., progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g., fever, eosinophilia) or generalised bullous FDE (e.g., fever, arthralgia, numerous large blisters and ulcerated lesions) are present, NUCOTRIM treatment should be discontinued immediately because the danger of severe allergic reactions (see section 4.8).
- The best results in managing SJS, TEN, DRESS or FDE come from early diagnosis and immediate discontinuation of any suspect medicine. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS, TEN, DRESS or generalised bullous FDE with the use of NUCOTRIM, treatment must not be re-started in this patient at any time.
- At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of co-trimoxazole alone or in combination with other drugs.

Treatment should be discontinued immediately when a rash appears because the danger of severe allergic reactions.

**Haemophagocytic lymphohistiocystosis (HLH)**

Cases of HLH have been reported less frequently in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g., fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, NUCOTRIM treatment should be discontinued.

**Respiratory toxicity**

Less frequently, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, NUCOTRIM should be discontinued and appropriate treatment given.

**Elderly patients**

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g., impaired kidney and/or liver function and/or concomitant use of other medicines e.g., diuretics, mainly thiazides, which is associated with an increased risk of thrombocytopenia in elderly patients with concurrent co-trimoxazole administration (see section 4.5).

**Renal impairment**

NUCOTRIM should be used cautiously and in reduced dosage in patients with impaired renal function (see section 4.2).

Because of the risk of crystalluria, an adequate fluid intake should be maintained and the administration of alkalis may be necessary if very large doses are used.

**Urinary output**

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is less frequent, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

**Folate**

Regular monthly blood counts are advisable when NUCOTRIM is given for long periods, or to actual or possible folate deficient patients or to the malnourished or elderly patients, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate because of the possible interference with human folate metabolism by trimethoprim as in NUCOTRIM. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

**Cross-sensitivity**

Cross-sensitivity has been observed between sulfamethoxazole as in NUCOTRIM and chemically related compounds such as some diuretics, particularly acetazolamide and thiazides, and the sulfonylurea hypoglycaemic medicines (see section 4.5).

**Patients with glusose-6-phosphate dehydrogenase deficiency**

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.

**Patients with severe atopy or bronchial asthma**

NUCOTRIM should be given with caution to patients with severe atopy or bronchial asthma.

**Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci**

NUCOTRIM should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci; eradication of these organisms from the oropharynx is less effective than with penicillin.

**Phenylalanine metabolism**

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

**Patients with or at risk of porphyria**

The administration of co-trimoxazole as in NUCOTRIM to patients known or suspected to be at risk of porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria (see section 4.3).

**Patients with hyperkalaemia and hyponatraemia**

Close monitoring of serum potassium and sodium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

**Metabolic acidosis**

Co-trimoxazole as in NUCOTRIM has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

**Patients with serious haematological disorders**

Except under careful supervision co-trimoxazole as in NUCOTRIM should not be given to patients with serious haematological disorders (see section 4.8). Consideration should be given to the use of

a single effective antibacterial medicine. Co-trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

Adverse effects on the blood may be more severe in malnourished or elderly patients.

**Excipients**

***Nipastat***

NUCOTRIM contains Nipastat 0,25 % *m/m*, a mixture of parahydroxybenzoate esters. It may cause allergic reactions (possibly delayed).

**4.5 Interaction with other medicines and other forms of interaction**

**Zidovudine**

Concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to NUCOTRIM. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

**Lamivudine**

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg (co-trimoxazole) causes a 40 % increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

**Rifampicin**

Concurrent use of rifampicin and co-trimoxazole results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

**Procainamide and amantadine**

When trimethoprim as in NUCOTRIM is administered simultaneously with medicines that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g., procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the medicines.

**Diuretics (thiazides)**

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura (see section 4.4).

**Pyrimethamine**

Patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co-trimoxazole as in NUCOTRIM be prescribed concurrently, due to the trimethoprim component.

**Warfarin**

Co-trimoxazole as in NUCOTRIM has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with NUCOTRIM is advisable.

**Phenytoin**

Co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

**Methotrexate**

Co-trimoxazole may increase the free plasma levels of methotrexate and potentiate the effect of methotrexate. If co-trimoxazole as in NUCOTRIM is considered appropriate therapy in patients receiving other anti-folate medicines such as methotrexate, a folate supplement should be considered (see section 4.4).

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

**Sulfonylurea compounds**

Interaction with sulfonylurea hypoglycaemic agents is less frequent but potentiation has been reported. High doses of sulfamethoxazole as in NUCOTRIM may have a hypoglycaemic effect. The antidiabetic effect of the sulfonylurea compounds may be enhanced by the concomitant administration of sulfamethoxazole (see section 4,4).

Trimethoprim as in NUCOTRIM has been reported to interact with tolbutamide by interfering with its clearance.

**Para-aminobenzoic acid and compounds**

The action of sulfamethoxazole as in NUCOTRIM may be antagonised by para-aminobenzoic acid and compounds derived from it, particularly the procaine group of local anaesthetics.

Paraldehyde has been reported to increase the acetylation of sulfamethoxazole with subsequent increased risk of crystalluria.

**Digoxin**

Concomitant use of trimethoprim as in NUCOTRIM with digoxin has been shown to interfere with clearance of digoxin and increase plasma digoxin levels in a proportion of elderly patients.

**Ciclosporin**

Reversible deterioration in renal function has been reported in patients given trimethoprim as in NUCOTRIM and ciclosporin following renal transplantation.

**Hyperkalaemia**

Caution should be exercised in patients taking any other medicines that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) as in NUCOTRIM may result in clinically relevant hyperkalaemia.

**Repaglinide**

Trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

**Folinic acid**

Folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim sulfamethoxazole as in NUCOTRIM. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

**Contraceptives**

Oral contraceptive failures have been reported with antibiotics, such as NUCOTRIM. The mechanism of this effect has not been elucidated. Women on NUCOTRIM treatment should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.

**Azathioprine**

There are conflicting clinical reports of interactions between azathioprine and trimethoprim sulfamethoxazole as in NUCOTRIM, resulting in serious haematological abnormalities.

**Diagnostic tests**

Sulfamethoxazole as in NUCOTRIM may interfere with some diagnostic tests including those for urea, creatinine, and urinary glucose and urobilinogen.

Trimethoprim as in NUCOTRIM may interfere with some diagnostic tests including serum methotrexate assay where dihydrofolate reductase is used, and the Jaffe reaction (alkaline picrate reaction) for creatinine. The latter may result in an overestimation of serum/plasma creatinine of the order of 10 %. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23 % to 9 % whilst the glomerular filtration remains unchanged.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Trimethoprim and sulfamethoxazole as in NUCOTRIM cross the placenta and their safety in pregnant women has not been established. NUCOTRIM should not be used during pregnancy (see section 4.3).

**Breastfeeding**

The components of NUCOTRIM (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of NUCOTRIM should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. NUCOTRIM should not be given to the new-born infant during the first six weeks of life (see section 4.3).

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

It is not always possible to predict to what extent NUCOTRIM may interfere with the daily activities of a patient. NUCOTRIM can cause hallucinations, headache, dizziness and vertigo (see section 4.8). Patients should ensure that they do not engage in the above activities until they are aware of the measure to which NUCOTRIM affects them.

**4.8 Undesirable effects**

**a. Summary of the safety profile**

Hypersensitivity reactions particularly involving the skin are among the most frequent adverse effects of NUCOTRIM and are usually due to the sulfamethoxazole component. The Stevens-Johnson and Lyell's syndromes (the latter is also known as toxic epidermal necrolysis (TEN)) have been reported (see section 4.4).

Adverse effects on the gastro-intestinal tract may also occur fairly frequently.

### b. Tabulated list of adverse reactions

**Sulfamethoxazole**

| System Organ Class | Frequency | Adverse reactions |
|---|---|---|
| Infections and infestations | Frequent | fungal overgrowth |
| | Less frequent | pseudomembranous colitis |
| Blood and lymphatic system disorders | Less frequent | agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, hypoprothrombinaemia, eosinophilia (including pulmonary eosinophilia), methaemoglobinaemia, sulphaemoglobinaemia, acute haemolytic anaemia often associated with glucose-6-phosphate dehydrogenase deficiency, neutropenia |
| Immune system disorders | Less frequent | anaphylaxis, serum sickness, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus, severe hypersensitivity reactions associated with PJP, rhabdomyolysis, pyrexia |
| Endocrine disorders | Frequency unknown | hypothyroidism |
| Metabolism and nutrition disorders | Frequent | hyperkalaemia |
| | Less frequent | hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis |
| Psychiatric disorders | Less frequent | depression, hallucination |
| | Frequency unknown | psychotic disorder |

| | | |
|---|---|---|
| Nervous system disorders | Frequent | headache |
| | Less frequent | ataxia, dizziness, fatigue, insomnia, peripheral neuritis, seizure |
| Eye disorders | Less frequent | optic neuropathy, transient myopia, uveitis |
| Ear and labyrinth disorders | Less frequent | vertigo,<br>tinnitus |
| Respiratory, thoracic and mediastinal disorders | Less frequent | cough*, dyspnoea*, lung infiltration* |
| | Frequency unknown | cyanosis due to methaemoglobinaemia or sulphaemoglobinaemia |
| Gastrointestinal disorders | Frequent | nausea, diarrhoea |
| | Less frequent | vomiting, glossitis, stomatitis, pancreatitis. |
| Hepatobiliary disorders | Less frequent | cholestatic jaundice*, hepatic necrosis*;<br>increased transaminases, increased blood bilirubin |
| Skin and subcutaneous tissue disorders* | Frequent | rash |
| | Less frequent | photosensitivity reactions, exfoliative dermatitis, angioedema, fixed drug eruption (FDE), toxic epidermal necrolysis (TEN or Lyell's syndrome), erythema nodosum, erythema multiforme, Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP). |
| | Frequency unknown | acute febrile neutrophilic dermatosis (Sweet's syndrome), drug reaction with eosinophilia and systemic symptoms (DRESS)* |
| Musculoskeletal and connective tissue disorders | Less frequent | arthralgia, myalgia |

| | | |
|---|---|---|
| Renal and urinary disorders | Less frequent | renal impairment (sometimes reported as renal failure), lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine, tubulointerstitial nephritis and uveitis (TINU) syndrome, renal tubular acidosis. |

*See below section c for description of selected adverse reactions.

**Trimethoprim**

| **System Organ Class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Nervous system disorders | Frequent | headache |
| | Less frequent | aseptic meningitis* |
| Skin and subcutaneous tissue disorders* | Less frequent | pruritus, skin rash, pyrexia, nausea, vomiting, sore mouth |

*See below section c for description of selected adverse reactions.

**c. Description of selected adverse reactions**

***Aseptic meningitis***

Aseptic meningitis was rapidly reversible on withdrawal of the medicine, but recurred in a number of cases on re-exposure to either co-trimoxazole as in NUCOTRIM or to trimethoprim alone.

***Pulmonary hypersensitivity reactions***

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while occurring less frequently, has been fatal.

***Hepatobiliary disorders***

Cholestatic jaundice and hepatic necrosis may be fatal.

***Severe cutaneous adverse reactions (SCARs)***

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and medicine reaction with eosinophilia and systemic symptoms (DRESS) and generalised bullous fixed drug eruption (FDE) have been reported to be life-threatening (see section 4.4)

Allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of NUCOTRIM. Cases of acute generalised exanthematous pustulosis (AGEP) have been observed less frequently (see section 4.4).

***Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management***

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, increased hepatic enzymes, hyperkalaemia, hyponatraemia and rhabdomyolysis have been reported at the high dosages used for PJP management, with severe hypersensitivity reactions necessitating cessation of therapy.

Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to co-trimoxazole as in NUCOTRIM, sometimes after a dosage interval of a few days. Rhabdomyolysis has been reported in HIV positive patients receiving co-trimoxazole for prophylaxis or treatment of PJP.

**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 "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

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

Alternately you can contact Gulf Drug Company (Pty) Ltd at +27 31 538 8700 or per info@gulfdrug.co.za.

**4.9 Overdose**

**Symptoms and signs**

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage (see also section 4.8). Bone marrow depression has been reported in acute trimethoprim overdosage.

**Treatment**

If vomiting has not occurred, induction of vomiting may be desirable. Dependant on the status of renal function administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and Class: A 20.2.1 Antimicrobial (Chemotherapeutic) agents (other than antibiotics)

Pharmacotherapeutic group: Antibacterials for systemic use – Sulfonamides and trimethoprim, incl. derivatives

ATC code: J01EE01

**Mechanism of action**

Co-trimoxazole exerts its bacterial action by the sequential blockade of two enzymes intervening in the biosynthesis of folinic acid in the micro-organism. Co-trimoxazole is bactericidal at concentrations at which the active ingredients trimethoprim and sulfamethoxazole are usually bacteriostatic. It is therefore often active against organisms resistant to one of the active ingredients thereby minimising the risk of bacterial resistance.

### 5.2 Pharmacokinetic properties

**Absorption**

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2 to 3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other**.**

**Distribution**

Approximately 50 % of trimethoprim in the plasma is protein bound. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high

concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humour, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 66 % of sulfamethoxazole in the plasma is protein bound.

The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 – 50 % of the plasma concentration.

**Biotransformation**

Renal excretion of intact sulfamethoxazole accounts for 15 – 30 % of the dose. This medicine is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72-hour period, approximately 85 % of the dose can be accounted for in the urine as unchanged medicine plus the major (N4-acetylated) metabolite.

**Elimination**

The half-life of trimethoprim in man is in the range 8,6 – 17 hours in the presence of normal renal function. It is increased by a factor of 1,5 to 3,0 when the creatinine clearance is less than 10 mL/minute. There appears to be no significant difference in older patients compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50 % of the dose is excreted in the urine within 24 hours as unchanged medicine. Several metabolites have been

identified in the urine. Urinary concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function. There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 mL/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15 % and 30 % of the dose recovered in the urine is in the active form. In older patients there is a reduced renal clearance of sulfamethoxazole.

**Special patient populations**

***Renal impairment***

The elimination half-life of trimethoprim is increased by a factor of 1,5 – 3,0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of co-trimoxazole should be reduced (see section 4.2).

***Elderly patients***

In elderly patients, a slight reduction in renal clearance of sulfamethoxazole but not trimethoprim has been observed.

**Paediatric population**

The pharmacokinetics in the paediatric population with normal renal function of both components of co-trimoxazole, trimethoprim (TMP) and sulfamethoxazole (SMZ) are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The

differences are most prominent in young infants (> 1,7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3,6 years), children (7,5 years and < 10 years) and adults (see section 4.2).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Magnesium stearate

Maize starch

Microcrystalline cellulose

Nipastat (as preservative)

Pregelatinised starch

Purified water.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months.

### 6.4 Special precautions for storage

Store at or below 25 ºC in a cool, dry place. Protect from light and moisture.

Keep HDPE containers tightly closed.

Do not remove tablets from blister until required for use.

**6.5 Nature and contents of container**

LDPE Patient Ready Packs (PRPs) of 20, 28, 40 and 56 tablets.

White, round HDPE containers with white screw cap of 100, 500 and 1000 tablets.

10 or 14 tablets in clear PVC/Al blisters packed in pre-printed unit cartons of 20, 28, 40 and 56 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Gulf Drug Company (Pty) Ltd

22 Burnside Drive

Old Mill Industrial Park

Mount Edgecombe

4300

**8. REGISTRATION NUMBER**

Z/20.2/0026

**9. DATE OF FIRST AUTHORISATION**

03 February 1998.

**10. DATE OF REVISION OF THE TEXT**

02 July 2025.