DOCTRIM SUSPENSION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOCTRIM SUSPENSION 40 mg/200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of suspension contains:

Trimethoprim	40 mg
Sulfamethoxazole	200 mg
Contains sugar as sucrose	2 500 mg
Contains sweetener as sodium saccharin	20 mg
Nipastat (as preservative)	0,5 % *w/v*
Ethanol	0,5 % *v/v*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension.

A white, opaque viscous suspension with a faintly characteristic aniseed odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOCTRIM SUSPENSION is effective against a wide range of Gram-positive and Gram-negative organisms and is indicated in adults, adolescents, children and infants from the age of 6 weeks 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 with difficulties swallowing tablets

DOCTRIM SUSPENSION is recommended in adults and children above 12 years only if there are difficulties in swallowing tablets.

20 mL (four medicine measures) DOCTRIM SUSPENSION every 12 hours (i.e. morning and evening).

Infants and children

6 weeks to 5 months: Half a medicine measure (2,5 mL) every 12 hours.

6 months to 5 years: One medicine measure (5 mL) every 12 hours.

6 to 12 years: Two medicine measures (10 mL) every 12 hours.

In the treatment of acute infections DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION is indicated for patients with renal impairment, the following dosage scheme, based on creatinine clearance is suggested:

Adults and children over 12 years with difficulties swallowing tablets

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 DOCTRIM SUSPENSION. 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.
Bottle to be shaken before use.
The suspension must be taken by mouth, after food or drink to minimise the possibility of gastrointestinal disturbance.

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

- DOCTRIM SUSPENSION 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, DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION, 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, DOCTRIM SUSPENSION 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, DOCTRIM SUSPENSION 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

DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION. 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 DOCTRIM SUSPENSION 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

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

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

DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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).

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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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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

DOCTRIM SUSPENSION contains Nipastat 0,5 % *w/v*, a mixture of parahydroxybenzoate esters. It may cause allergic reactions (possibly delayed).

Alcohol

DOCTRIM SUSPENSION contains alcohol 0,025 mg of alcohol (ethanol) in each 5 mL which is equivalent to 0,5 % *v/v* alcohol (ethanol). The amount in 5 mL of this medicine is equivalent to 0,5 mL of beer and less than 0,5 mL of wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Sucrose

DOCTRIM SUSPENSION contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take DOCTRIM SUSPENSION. The sucrose content of 2 500 mg per 5 mL dose should be taken into account in patients with diabetes mellitus.

Sodium

DOCTRIM SUSPENSION contains less than 1 mmol sodium (23 mg) per 5 mL, and therefore is essentially 'sodium free'.

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 DOCTRIM SUSPENSION. 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION be prescribed concurrently, due to the trimethoprim component.

Warfarin

Co-trimoxazole as in DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION has been reported to interact with tolbutamide by interfering with its clearance.

Para-aminobenzoic acid and compounds

The action of sulfamethoxazole as in DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives

Oral contraceptive failures have been reported with antibiotics, such as DOCTRIM SUSPENSION. The mechanism of this effect has not been elucidated. Women on DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION, resulting in serious haematological abnormalities.

Diagnostic tests

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

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

Breastfeeding

The components of DOCTRIM SUSPENSION (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of DOCTRIM SUSPENSION should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION may interfere with the daily activities of a patient. DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION 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
	Less frequent	depression, hallucination

Psychiatric disorders	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, 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*; 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 DOCTRIM SUSPENSION 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 DOCTRIM SUSPENSION. 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 DOCTRIM SUSPENSION, 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

Aluminium magnesium silicate
Aniseed oil
Ethanol
Nipastat (as preservative)
Polysorbate 80
Purified water
Sodium carboxymethylcellulose

Sodium citrate
Sodium saccharin
Sucrose.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store at or below 25 ºC in a cool, dry place. Protect from light and moisture.

6.5 Nature and contents of container
Round amber HDPE bottles of 50 mL or 100 mL with a white LDPE snap-on cap.

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
28/20.2/0378

9. DATE OF FIRST AUTHORISATION
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06 November 2024.