SCHEDULING STATUS: S4

1. **NAME OF THE MEDICINE:**

   DUROBAC (TABLETS)

   DUROBAC DOUBLE STRENGTH (TABLETS)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   Each **DUROBAC** tablet contains:

   80 mg Trimethoprim and 400 mg Sulphamethoxazole.

   Each **DUROBAC DOUBLE STRENGTH** tablet contains:

   160 mg Trimethoprim and 800 mg Sulphamethoxazole.

   Sugar free

   Contains preservative: Nipastat 0.15mg

3. **PHARMACEUTICAL FORM**

   DUROBAC: Flat, white bisected tablets with bevelled edges.

   DUROBAC DOUBLE STRENGTH: White, oblong, biconvex, bisected tablets.

4. **CLINICAL PARTICULARS**

   4.1 Therapeutic indications:

   DUROBAC and **DUROBAC D/S** is effective against a wide range of Gram-positive and Gram-negative organisms.

   It is indicated for:

   - 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)).

- Renal and urinary tract infections e.g. pyelitis, pyelonephritis, urethritis, acute and chronic cystitis and cystopyelitis, including prostatitis.
- Gastrointestinal tract infections e.g. enteritis, typhoid and paratyphoid fever, typhoid carriage, bacillary dysentery and cholera. (as an adjunct to fluid and electrolyte replacement).
- Genital tract infections: both male and female including gonococcal infections.
- Skin infections e.g. pyoderma, boils, furuncles, abscesses
- 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:

Two **DUROBAC** tablets or one **DUROBAC DOUBLE STRENGTH** tablet twice daily, morning and evening after meals.

Minimum dosage and dosage for long-term treatment (more than 14 days): one **DUROBAC** tablet twice daily or half a **DUROBAC DOUBLE STRENGTH** twice daily.

Maximum dosage (for particularly severe cases): Three **DUROBAC** tablets or one and a half **DUROBAC DOUBLE STRENGTH** tablets twice daily.

In acute infections, **DUROBAC** should be given for at least 5 days or until the patient has been symptom free for 2 days.

Special populations

Renal Impairment

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

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 **DUROBA**C. If the concentration of total sulfamethoxazole exceeds 150 ug/mL then treatment should be interrupted until the value falls below 120 ug/mL.

No Information is available for children with renal failure.

Method of administration

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
- Megaloblastic anaemia due to folic acid deficiency
- Severe renal insufficiency
- Pregnancy, in women prior to delivery or by nursing mothers
- Infants during the first 6 weeks of life

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 skin adverse reactions

DUROBAC may cause the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis. Treatment should be discontinued immediately when a rash appears because the danger of severe allergic reactions.

Folate

DUROBAC should be given with caution to patients with actual or possible folate deficiency because of possible interference with human folate metabolism by trimethoprim as in DUROBAC. Administration of folinic acid could be considered

Cross-sensitivity

Cross-sensitivity has been observed between sulfamethoxazole as in DUROBAC and chemically related compounds such as some diuretics, particularly acetazolamide and thiazides, and the sulfonylurea hypoglycaemic medicines.

Prolonged treatment

All patients receiving prolonged treatment with DUROBAC should be given regular blood examinations.

Special Populations

Elderly patients

Adverse effects on the blood may be more severe in malnourished or elderly patients: there also appears to be an increased risk of thrombocytopenia in elderly patients concurrently receiving diuretics, mainly thiazides.

Renal impairment

DUROBAC 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.

DUROBAC and DUROBAC D/S contains:

DUROBAC contains Nipastat, a mixture of parahydroxybenzoate esters. It may cause allergic reactions (possibly delayed).

4.5 Interactions with other medicines and other forms of interaction

Oral anticoagulants, methotrexate and phenytoin

Sulfamethoxazole as in **DUROBAC** may potentiate the effects of some medicines such as oral anticoagulants, methotrexate, phenytoin; this may be due to displacement of the compound from plasma protein binding sites or to inhibition of metabolism.

Trimethoprim as in **DUROBAC** may potentiate the anticoagulant effect of warfarin. It also prolongs the half-life of phenytoin.

Sulfonylurea compounds

High doses of sulfamethoxazole as in **DUROBAC** may have a hypoglycaemic effect. The antidiabetic effect of the sulfonylurea compounds may be enhanced by the concomitant administration of sulfamethoxazole.

Para-aminobenzoic acid and compounds

The action of sulfamethoxazole as in **DUROBAC** 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, procainamide, and tolbutamide

Trimethoprim as in **DUROBAC** has been reported to interact with a number of other medicines by interfering with their clearance; such medicines include digoxin, procainamide, and tolbutamide.

Cyclosporine

Reversible deterioration in renal function has been reported in patients given trimethoprim as in **DUROBAC** and cyclosporine following renal transplantation.

Pyrimethamine

Patients receiving pyrimethamine may develop megaloblastic anaemia due to the trimethoprim component as in **DUROBAC**.

Zidovudine

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

Lamivudine

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

Repaglinide

Trimethoprim as in **DUROBAC** 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 **DUROBAC** . This has been observed in Pneumocystis jirovecii pneumonia prophylaxis and treatment.

Contraceptives

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

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) may result in clinically relevant hyperkalaemia.

Diagnostic tests

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

Trimethoprim may interfere with some diagnostic tests including serum methotrexate assay where dihydrofolate reductase is used, and the Jaffe reaction for creatinine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

The components of DUROBAC (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of DUROBAC should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinemia. DUROBAC should not be given to the new-born infant during the first 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 DUROBAC may interfere with the daily activities of a patient. DUROBAC 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 DUROBAC affects them.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity reactions particularly involving the skin are among the most common adverse effects of DUROBAC and are usually due to the sulfamethoxazole component. The Stevens-Johnson and Lyell's syndromes have been reported.

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

Tabulated summary of adverse reactions

Sulfamethoxazole

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Overgrowth fungal.
	Less frequent	Pseudomembranous colitis
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, hypoprothrombinaemia, eosinophilia, methaemoglobinaemia, 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*
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, 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.
Hepato-biliary disorders	Frequent	Rash
	Less frequent	Jaundice cholestatic *, hepatic necrosis*. increased transaminases, increased blood bilirubin
Skin and subcutaneous tissue disorders	Less frequent	Photosensitivity reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell's syndrome), erythema nodosum, erythema multiforme, Steven-Johnson syndrome, systemic lupus erythematosus, fixed drug eruptions*
	Frequency unknown	Acute febrile neutrophilic dermatosis (Sweet's syndrome),

		drug reaction with eosinophilia and systemic symptoms (DRESS)*
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia
Renal and urinary disorders	Less frequent	Renal failure, lumbar pain, haematuria, oliguria, and anuria may also occur due to crystallisation in the urine, tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis

*** See below *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	Frequent	Pruritus, skin rash, fever, nausea, vomiting and sore mouth, fixed drug eruptions*

*** See below *Description of selected adverse reactions***

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 DUROBAC or to trimethoprim alone.

Pulmonary hypersensitivity reactions

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Hepatobiliary disorders

Jaundice cholestatic 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) 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 DUROBAC. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed (see section 4.4).

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to co-trimoxazole, 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.

Fixed drug eruptions (FDEs)

Dermatological manifestations of medicine reactions that often occur in the same location upon re-exposure to a medicine such as co-trimoxazole. They usually appear as erythematous-violaceous, circular patches, but several different variants have been described. They can often present without any associated symptoms, but in some cases, patients may complain of pain and pruritus.

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

4.9 Overdose

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.

If vomiting has not occurred, induction of vomiting may be desirable.

Dependent 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

Pharmacological classification: A 20.2.1 Antimicrobial (Chemotherapeutic) agents (other than antibiotics)

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

ATC code: J01EE01

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.

Paediatric population

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, MP and 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).

Special patient population

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogenated vegetable oil, magnesium stearate, nipastat, pregelatinized starch maize, purified water, sodium carboxymethyl starch, starch maize.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

DUROBAC: 36 months

DUROBAC D/S: 24 months

6.4 Special precautions for storage

Store below 25 °C.

Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container~~PRESENTATION:~~

DUROBAC: 28 or 56 tablets packed in a L.D.P.E “ziploc” plastic patient ready packs and 100, 500 or 1000 tablets packed in HDPE containers.

DUROBAC DOUBLE STRENGTH: 30 or 100 tablets packed in white securitainers and 1000 tablets packed in HDPE containers.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) LTD

100 Northern Parkway Rd,

Crownwood Office,

Block D, Ground Floor,

Ormonde, 2091

8. REGISTRATION NUMBERS

DUROBAC: J/20.2/279

DUROBAC DOUBLE STRENGTH: P/20.2/55

9. DATE OF FIRST AUTHORISATION

November 1993

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

29/01/2024

REFERENCES

1. CO-TRIMOXAZOLE DS PHARMC Y/20.2.1/144

   DUROBAC Y/20.2.1/145

   Pharmacorp (Pty) Ltd 29 Victoria Link

   Route 21 Corporate Park Irene, 0178

   RSA

   24 January 2022
2. SAHPRA SAFETY LETTER- RE: CO-TRIMOXAZOLE -RISK OF FIXED DRUG ERUPTION
3. Fixed Drug Eruption: An Underrecognized Cutaneous Manifestation of a Drug Reaction in the Primary Care Setting article

SKEDULERINGSTATUS: S4

1. **NAAM VAN DIE MEDISYNE:**

   DUROBAC (TABLETTE)

   DUROBAC DOUBLE STRENGTH (TABLETTE)

2. **KWALITATIEWE EN KWANTITATIEWE SAMESTELLING:**

   Elke **DUROBAC** tablet bevat:

   80 mg Trimetoprim en 400 mg Sulfametoksasool.

   Elke **DUROBAC DOUBLE STRENGTH** tablet bevat:

   160 mg Trimetoprim en 800 mg Sulfametoksasool.

   Suiker-vry

   Bevat preserveermiddel: Nipastat 0,15 mg

3. **FARMASEUTIESE VORM**

   DUROBAC: Plat, wit, gedeelde tablette met afgeskuinste kante.

   DUROBAC DOUBLE STRENGTH: Wit, langwerpige, bikonvekse, gedeelde tablette.

4. **KLINIESE BESONDERHEDE**

   4.1 Terapeutiese indikasies:

   DUROBAC en **DUROBAC D/S** is effektief teen ‘n wye reeks van Gram-positiewe en Gram-negatiewe organismes.

   Dit word aangedui vir:

   - Boonste en onderste lugweginfeksies bv. akute en chroniese brongitis, brongiëkstase, tonsillitis, sinusitis en faringitis, otitis media, pneumonie en

pneumocystis carinii pneumonitis (sien ook afdeling 4.8 Pneumocystis jirovecii Pneumonitis (PJP)).

- Niere en urienweg-infeksies bv. piëlitis, piëlonefritis, uretritis, akute en chroniese sistitis en sistopiëlitis, insluitend prostatitis.
- Gastroïntestinale weg-infeksies bv. enteritis, tifoïed- en paratifoïed-koors, tifoïed-vrag, basilêre disenterie en cholera (as ‘n adjunk tot vloeistof en elektroliet-vervanging).
- Genitale weg-infeksies: beide manlike en vroulike, insluitend gonokokkale infeksies.
- Vel-infeksies bv. pioderma, bloedvinte, furunkel, absesse.
- Ander bakteriële infeksies: akute brusellose, misetoom wat veroorsaak word deur suiwer fungi, nokardiase, akute en chroniese osteomiëlitis.

4.2 Posologie en metode van toediening

Posologie

Volwassenes en kinders oor 12 jaar oud:

Twee **DUROBAC** tablette of een **DUROBAC DOUBLE STRENGTH** tablet twee keer per dag, soggens en saans na ete.

Minimum dosering en dosering vir langtermyn behandeling (meer as 14 dae): een **DUROBAC** tablet twee keer per dag of ‘n halwe **DUROBAC DOUBLE STRENGTH** twee keer per dag.

Maksimum dosering (veral by ernstige gevalle): Drie **DUROBAC** tablette of een en ‘n half **DUROBAC DOUBLE STRENGTH** tablet twee keer per dag.

By akute infeksies moet **DUROBAC** toegedien word vir ten minste 5 dae of totdat die pasiënt simptoom-vry is vir 2 dae.

Spesiale bevolkings

Renale Inkortings

Indien **DUROBAC** aangedui word by pasiënte met renale inkorting, word die volgende dosering, gebaseer op kreatinienopruiming voorgestel:

Meer as 25 mL/min: Standaard dosering

15 – 25 mL/min: Standaard dosering vir ‘n maksimum van 3 dae gevolg deur ‘n helfte van die standaard daaglikse dosering.

Benede 15 mL/min: Moet nie toegedien word nie tensy hemodialise fasiliteite beskikbaar is waar die helfte van die standaard daaglikse dosering toegedien kan word.

Metings van plasma-konsentrasies van sulfametoksasool met intervalle van 2 dae word aanbeveel in monsters verkry 12 uur na toediening van **DUROBA**C. Indien die konsentrasie van totale sulfametoksasool 150 ug/mL oorskry moet die behandeling onderbreek word totdat die waarde afneem tot minder as 120 ug/mL.

Geen inligting is beskikbaar vir kinders met nierversaking nie.

Metode van toediening

Die tablette moet per mond geneem word, na voedsel. Die tablette moet ingesluk word met ‘n bietjie water.

4.3 Kontra-indikasies:

- Hipersensitiwiteit vir sulfametoksasool, trimetoprim, sulfonamiede of vir enige van die eksipiënte gemeld in afdeling 6.1.
- Pasiënte met porfirie
- Lewer parengimale skade
- Megaloblastiese anemie weens foliensuur-tekort
- Ernstige renale ontoereikendheid
- Swangerskap, by vrouens voor baring of deur moeders wat borsvoed
- Kleuters gedurende die eerste 6 weke van lewe

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Immuun-gekompromitteerde pasiënte

‘n Hoë insidensie van newe-effekte kom voor in immuun-gekompromitteerde pasiënte soos dié met VIGS of pasiënte wat immuunonderdrukkende terapie ontvang. Die ongunstige effekte sluit in veluitslag, herhalende koors, neutropenie, trombositopenie en verhoogde lewerensiemwaardes.

Lewensgevaarlike vel ongunstige reaksies

DUROBAC kan die voorkoms van erythema multiforme veroorsaak, toksiese dermale nekrolise en allergiese vaskulitis. Behandeling moet onmiddellik gestaak word indien ‘n uitslag voorkom weens die gevaar van ernstige allergiese reaksies.

Folaat

DUROBAC moet versigtig toegedien word aan pasiënte met werklike of moontlike folaat-tekort weens die moontlike inmenging met menslike folaat metabolisme deur trimetoprim, soos in **DUROBAC**. Toediening van foliniensuur moet oorweeg word.

Kruis-sensitiwiteit

Kruis-sensitiwiteit is waargeneem tussen sulfametoksasool, soos in **DUROBAC**, en chemies verwante samestellings, soos sommige diuretiese middels, veral asetasolamied en tiasiede en die sulfonielureum hipoglisemiese medisynes.

Verlengde behandeling

Alle pasiënte wat verlengde handeling met **DUROBAC** ontvang moet gereëlde bloed-ondersoeke ondergaan.

Spesiale Bevolkings

Bejaarde pasiënte

Ongunstige effekte op die bloed kan meer ernstig wees by wanvoeding of bejaarde pasiënte: daar blyk ook ‘n toenemende risiko te wees van trombositopenie by bejaarde pasiënte, wat ook diuretika ontvang, hoofsaaklik tiasiede.

Renale inkorting

DUROBAC moet versigtig gebruik word en in verminderde doserings by pasiënte met ingekorte renale funksie (sien afdeling 4.2).

Weens die risiko van kristallurie, moet ‘n voldoende vloeistof inname gehandhaaf word en die toediening van alkalië kan nodig wees, indien baie groot doserings gebruik word.

DUROBAC en DUROBAC D/S bevat:

DUROBAC bevat nipastat, ‘n mengsel van parahidroksibensoaat esters. Dit kan allergiese reaksies veroorsaak (moontlik vertraagde).

4.5 Interaksies met ander medisynes en ander vorms van interaksie

Orale antikoagulante, metotreksaat en fentoïen

Sulfametoksasool, soos in **DUROBAC,** kan die effekte van sommige medisynes potensieer, soos orale antikoagulante, metotreksaat, fenitoïen, en dit kan wees weens die verplasing van die samestelling van plasmaproteienbinding situs of die inhibisie van metabolisme.

Trimetoprim, soos in **DUROBAC,** kan die antikoagulante effek potensieer van warfarien. Dit verleng ook die halfleeftyd van fenitoïen.

Sulfonielureum samestestellings

Hoë doserings van sulfametoksasool, soos in **DUROBAC,** kan ‘n hipoglisemiese effek hê. Die antidiabetiese effek van die sulfonielureum samestellings kan toeneem deur die meegaande toediening van sulfametoksasool.

Para-aminobensoësuur en samestellings

Die werking van sulfametoksasool, soos in **DUROBAC,** kan ge-antagoniseer word deur para-aminobensoësuur en samestelling afkomstig daarvan, veral die prokaïen groep van plaaslike narkosemiddels.

Paraldehied is gerapporteer om die asetilering van sulfametoksasool te verhoog met gevolglike risiko van kristallurie.

Digoksien, prokaïenamied en tolbutamied

Trimetoprim, soos in **DUROBAC,** was gerapporteer om in te meng met die hoeveelheid van ander medisynes deur in te meng met hulle opruiming, soos medisynes wat digoksien, prokaïenamied en tolbutamied bevat.

Siklosporien

Omkeerbare agteruitgang in renale funksie was gerapporteer by pasiënte wat trimetoprim ontvang het, soos in **DUROBAC,** en siklosporien na renale oorplanting.

Pirimetamien

Pasiënte wat pirimetamien ontvang kan megaloblastiese anemie ontwikkel weens die trimetoprim komponent, soos in **DUROBAC**.

Sidovudien

Meegaande behandeling met sidovudien kan die risiko laat toeneem van hematologiese ongunstige reaksies tot **DUROBAC.** Indien meegaande behandeling nodig is, moet oorweging gegee word aan monitering van hematologiese parameters.

Lamivudien

Toediening van trimetoprim/sulfametoksasool 160 mg/800 mg, soos in **DUROBAC,** veroorsaak ‘n 40 % toename in lamivudien blootstelling weens die trimetoprim komponent. Lamivudien het geen effek op die farmakokinetika van trimetoprim of sulfametoksasool nie.

Repaglinied

Trimetoprim, soos in **DUROBAC,** kan die blootstelling van repaglinied laat toeneem, wat tot gevolg kan hê in hipoglisemie.

Foliniese suur

Foliniese suur aanvulling het gewys om in te meng met die antimikrobiale effektiwiteit van trimetoporim sulfametoksasool, soos in **DUROBAC**. Dit was waargeneem in *Pneumocystis jirovecii* pneumonie profilakse en behandeling.

Kontraseptiewe middels

Orale kontraseptiewe middels mislukking was gerapporteer met antibiotika, soos in **DUROBAC**. Die meganisme van hierdie effek was nie opgeklaar nie. Vrouens op **DUROBAC**-behandeling behoort tydelik ‘n versperringsmetode, addisioneel tot die orale kontraseptiewe middel te gebruik, of ‘n ander metode van kontrasepsie te gebruik.

Asatioprien

Daar is teenstrydige kliniese verslae van interaksies tussen asatioprien en trimetoprim sulfametoksasool, soos in **DUROBAC**, met gevolglike ernstige hematologiese abnormaliteite.

Hiperkalemie

Omsigtigheid is nodig by pasiënte wat enige ander medisynes neem wat hiperkalemie veroorsaak, by voorbeeld AOE-inhibeerders, angiotensien reseptor blokkers en kalium-sparende diuretika soos spironolaktoon. Meegaande gebruik van trimetoprim-sulfametoksasool (ko-trimoksasool) kan tot gevolg hê in klinies relevante hiperkalemie.

Diagnostiese toetse

Sulfametoksasool kan inmeng met sommige diagnostiese toetse, insluitend die vir ureum, kreatinien en urinêre glukose en urobilinogeen.

Trimetoprim kan inmeng met sommige diagnostiese toetse, insluitend serum-metotreksaat toetse waar dihidrofolaat reduktase gebruik word en die Jaffe reaksie vir kreatinien.

4.6 Fertiliteit, swangerskap en laktasie

Swangerskap

Trimetoprim en sulfametoksasool, soos in **DUROBAC**, kruis die plasenta en hulle veiligheid in swanger vrouens is nog nie vasgestel nie. **DUROBAC** moet nie gebruik word gedurende swangerskap nie (sien afdeling 4.3).

Borsvoeding

Die bestanddele van **DUROBAC** (trimetoprim en sulfametoksasool) word uitgeskei in borsmelk. Toediening van **DUROBAC** moet vermy word in laat swangerskap en by lakterende moeders waar die moeder of kleuter ‘n besondere risiko het vir ontwikkeling van hiperbilirubinemie. **DUROBAC** moet nie toegedien word aan pasgebore kleuters gedurende die eerste weke van lewe nie (sien afdeling 4.3)

4.7 Effekte op vermoë om te bestuur en gebruik van masjinerie

Dit is nie altyd moontlik om te voorspel tot watter mate **DUROBAC** kan inmeng met die daaglikse aktiwiteite van ‘n pasiënt nie. **DUROBAC** kan hallusinasies, hoofpyn, duiseligheid en vertigo veroorsaak (sien afdeling 4.8). Pasiënte moet seker maak dat hulle nie deelneem aan die bogemelde aktiwiteite nie totdat hulle seker is tot watter mate **DUROBAC** hulle beïnvloed.

4.8 Ongewenste effekte

Opsomming van die veiligheidsprofiel

Hipersensitiwiteitsreaksies, veral van die vel is van die mees algemene ongunstige effekte van **DUROBAC** en is gewoonlik weens die sulfametoksasool komponent. Die Stevens-Johnson en Lyell se sindrome is gerapporteer.

Ongunstige effekte op die gastroïntestinale kanaal kan ook dikwels voorkom.

Getabuleerde opsomming van ongunstige reaksies

Sulfametoksasool

Stelsel Orgaan Klas	**Frekwensie**	**Ongunstige reaksies**
Infeksies en infestasies	Dikwels	Oorgroei van fungus.
	Minder dikwels	Pseudomembraneuse kolitis
Bloed- en limfatiese stelsel-afwykings	Minder dikwels	Agranulositose, aplastiese anemie, trombositopenie, leukopenie, hipoprotrombinemie, esinofilie, methemoglobinemie, akute hemolitiese anemie dikwels geassosieer met glukose-6-fosfaat dehidrogenase tekort, neutropenie

Immuunstelselafwykings	Minder dikwels	Anafilakse, serum-siekte, allergiese miokarditis, hipersensitiwiteit vaskulitis ooreenstemmend met Henoch-Schoenlein purpura, peri-arteritis nodosa, sistemiese lupus erythematosus, ernstige hipersensitiwiteitsreaksies geassosieer met PJP*
Endokrienafwykings	Frekwensie onbekend	Hipotiroïedisme
Metabolisme en voedingsafwykings	Dikwels	Hiperkalemie
	Minder dikwels	Hipoglisemie, hiponatremie, afname in aptyt, metaboliese asidose
Psigiatriese afwykings	Minder dikwels	Depressie, hallusinasie
	Frekwensie onbekend	Psigotiese afwyking
Senuweestelselafwykings	Dikwels	Hoofpyn
	Minder dikwels	Ataksie, duiseligheid, uitputting, insomnie, perifere neuritis, siekte-aanval
Oogafwykings	Minder dikwels	Optiese neuropatie, kortstondige miopie, uveitis
Oor- en labirintafwykings	Minder dikwels	Vertigo, tinnitus

Respiratoriese, torakale en mediastinale afwykings	Minder dikwels	Hoes*, dispnee*, long-infiltrasie*,
	Frekwensie onbekend	Sianose weens methemoglobinemie of sulfamoglobinemie
Gastroïntestinale afwykings	Dikwels	Naarheid, diarree
	Minder dikwels	Braking, glossitis, stomatitis, pankreatitis.
Hepato-bilière afwykings	Dikwels	Uitslag
	Minder dikwels	Geelsug cholestatiese*, hepatiese nekrose*, verhoogde transaminase, verhoogde bloed-bilirubien
Vel- en subkutaneuse weefselafwykings	Minder dikwels	Fotosensitiwiteitsreaksies, eksfoliatiewe dermatitis, toksiese epidermale nekrolise (Lyell se sindroom), erythema nodosum, erythema multiforme, Steven-Johnson se sindroom, sistemiese lupus erythematosus, vaste-middel erupsies*
	Frekwensie onbekend	Akute febriele neutrofiliese dermatose (Sweet se sindroom),

		middel-reaksie met esinofilie en sistemiese simptome (DRESS)*
Muskuloskeletale, bindweefsel en beenafwykings	Minder dikwels	Artralgie, mialgie
Renale en urinêre afwykings	Minder dikwels	Renale versaking, lumbale pyn, hematurie, oligurie en anurie kan ook voorkom weens kristallisering in die uriene, tubuloïnterstisiële nefritis en uveïtis sindroom, renale tubulêre asidose

*** Sien hieronder *Beskrywing van geselekteerde ongunstige reaksies***

Trimetoprim

Stelsel Orgaan Klas	**Frekwensie**	**Ongunstige reaksies**
Senuweestelselafwykings	Dikwels	Hoofpyn
	Minder dikwels dikwelsess	Aseptiese meningitis *
Vel- en subkutaneuse weefselafwykings	Dikwels	Pruritus, veluitslag, koors, naarheid, braking en seer mond, vaste-middel erupsies*

*** Sien hieronder *Beskrywing van geselekteerde ongunstige reaksies***

Beskrywing van geselekteerde ongunstige reaksies

Aseptiese meningitis

Aseptiese meningitis was vinnig omkeerbaar by onttrekking van die medisyne, maar het weer voorgekom in ‘n paar gevalle deur her-blootstelling aan òf **DUROBAC** òf aan trimetoprim alleen.

Pulmonêre hipersensitiwiteitsreaksies

Hoes, dispnee en longinfiltrasie kan vroeë aanduidings wees van respiratoriese hipersensitiwiteit wat, alhoewel raar, noodlottig kan wees.

Hepatobiliêre afwykings

Geelsug cholestaties en hepatiese nekrose kan noodlottig wees.

Ernstige kutaneuse ongunstige reaksies (EKORs)

Stevens-Johnson se sindroom (SJS), toksiese epidermale nekrolise (TEN) en medisyne reaksie met esinofilie en sistemiese simptome (DRESS) is gerapporteer om lewensgevaarlik te wees (sien afdeling 4.4).

Allergiese reaksies soos ‘n jeukerige uitslag en netelroos kan voorkom by pasiënte met hipersensitiwiteit vir die bestanddele van **DUROBAC**. Baie rare gevalle van akute algemene eksantemateuse pustulose (AGEP) was waargeneem (sien afdeling 4.4).

Effekte geassosieer met Pneumocystis jirovecii Pneumonitis (PJP) beheer

Ernstige hipersensitiwiteitsreaksies, uitslag, pireksie, neutropenie, trombositopenie, hepatiese ensiem toename, hiperkalemie, hiponatremie, rabdomiolise.

By die hoë doserings gebruik vir PJP beheer was ernstige hipersensitiwiteitsreaksies gerapporteer waar dit nodig was vir onderbreking van terapie. Ernstige hipersensitiwiteitsreaksies is gerapporteer by PJP pasiënte op herblootstelling aan ko-

trimaksosool, soms na ‘n doseringsinterval van ‘n paar dae. Rabdomiolise is gerapporter by MIV-positiewe pasiënte wat ko-trimoksasool ontvang het vir profilakse of behandeling van PJP.

Vaste middel-erupsies (VMEs)

Dermatologiese manifestasies van medisyne reaksies wat dikwels voorkom in dieselfde plek met herblootstelling aan ‘n medisyne, soos ko-trimoksasool. Dit kom gewoonlik voor as erythematous-violaceous, sirkulêre kolle, maar etlike verskillende variante was beskryf. Dit kan dikwels voorkom sonder enige geassosieerde simptome. maar in sommige gevalle, kan pasiënte kla van pyn en pruritus.

Rapporteer van vermoedelike ongunstige reaksies

Rapporteer van vermoedelike ongunstige reaksies na goedkeuring van die medisyne is belangrik. Dit laat toe vir volgehoue monitering van die voordeel/risiko balans van die medisyne. Gesondheidsorgpersoneel word gevra om enige vermoedelike ongunstige reaksies te rapporteer aan SAHPRA via die “6.04 Adverse Drug Reaction Reporting Form”, wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8

4.9 Oordosering

Naarheid, braking, duiseligheid en verwarring is moontlike tekens/simptome van oordosering (sien ook afdeling 4.8). Beenmurg-onderdrukking is gerapporteer by akute trimetoprim-oordosering.

Indien braking nie voorgekom het nie, kan induksie van braking wenslik wees.

Afhanklik van die status van renale funksie, word toediening van vloeistowwe aanbeveel indien urien-uitvloei laag is.

Beide trimetoprim en aktiewe sulfametoksasool is matig dialiseerbaar deur hemodialise, Peritoneale dialise is nie effektief nie.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Farmakologiese klassifikasie: A 20.2.1 Antimikrobiese (Chemoterapeutiese) middels (ander as antibiotika) Farmakoterapeutiese groep: Antibakteriële vir sistemiese gebruik – Sulfonamiede en trimetoprim, insl. derivatief

ATC kode: J01EE01

Ko-trimoksasool oefen sy bakteriese werking uit deur die opvolgingsblokkade van twee ensieme steurend in die biosintese van foliniese suur in die mikro-organisme. Ko-trimoksasool is bakterisideel by konsentrasies waar die aktiewe bestanddele trimetoprim en sulfametoksasool gewoonlik bakteriostaties is. Dit is dus dikwels aktief teen organismes weerstandig tot een van die aktiewe bestanddele wat daardeur die risiko van bakteriële weerstand verminder.

5.2 Farmakokinetiese eienskappe

Absorpsie

Na orale toediening word trimetoprim en sulfametoksasool vinnig en amper volledig geabsorbeer. Die teenwoordigheid van voedsel blyk nie om die absorpsie te vertraag nie. Piek vlakke in die bloed kom voor tussen een en vier ure na inname en die vlak wat

bereik word is dosis-verwant. Effektiewe vlakke duur voort in die bloed vir tot 24 uur na ‘n terapeutiese dosis. Vaste vlakke by volwassenes word bereik na dosering van 2 tot 3 dae. Geen komponent het ‘n beduidende effek op die konsentrasies wat bereik word in die bloed deur die ander nie.

Distribusie

Ongeveer 50 % van trimetoprim in die plasma is proteïen-gebonde. Weefselvlakke van trimetoprim is gewoonlik hoër as ooreenstemmende plasma-vlakke, die longe en niere, wat veral hoë konsentrasies wys. Trimetoprim-konsentrasies is meer as in plasma in die geval van gal, prostatiese vloeistof en weefsel, saliva, sputum en vaginale sekresies. Vlakke in die waterige vloeistof, borsmelk, serebrospinale vloeistof, middeloor vloeistof, sinoviale vloeistof en weefsel (intestinale) vloeistof is voldoende vir antibakteriële aktiwiteit. Trimetoprim gaan deur in die amniotiese vloeistof en fetale weefsels bereik konsentrasies van ongeveer die van maternale serum. Ongeveer 66 % van sulfametoksasool in die plasma is proteïen-gebonde.

Die konsentrasie van aktiewe sulfametoksasool in amniotiese vloeistof, waterige vloeistof, gal, serebrospinale vloeistof, middeloor vloeistof, sputum, sinoviale vloeistof en weefsel (interstisiële) vloeistof is in die omvang van 20 – 50 % van die plasma-konsentrasie.

Biotransformasie

Renale ekskresie van intakte sulfametoksasool is verantwoordelik vir 15 – 30 % van die dosis. Hierdie medisyne word meer ekstensief gemetaboliseer as trimetoprim, via asetilasie, oksidasie of glukuronidasie. Oor ‘n 72 uur periode, word ongeveer 85 % van

die dosering gevind in die uriene as onveranderde medisyne plus die hoof (N4-asetiel) metaboliet.

Eliminasie

Die halfleeftyd van trimetoprim in die mens is in die omvang van 8,6 – 17 uur in die teenwoordigheid van normale renale funksie. Dit word verhoog deur ‘n faktor van 1,5 tot 3,0 wanneer die kreatinien-opruiming minder is as 10 mL/minuut. Daar blyk geen beduidende verskil te wees by ouer pasiënte in vergelyking met jong pasiënte nie.

Die hoof roete van ekskresie van trimetoprim is renaal en ongeveer 50 % van die dosis word uitgeskei in die uriene binne 24 uur as onveranderde medisyne. Etlike metaboliete was geïdentifiseer in die uriene. Urinêre konsentrasies van trimetoprim is baie veranderlik.

Die halfleeftyd van sulfametoksasool in die mens is ongeveer 9 tot 11 uur in die teenwoordigheid van normale renale funksie. Daar is geen verandering in die halfleeftyd van aktiewe sulfametoksasool nie met ‘n afname in renale funksie maar daar is verlenging van die halfleeftyd van die major, asetileerde metaboliet wanneer die kreatinienopruiming minder is as 25 mL/minuut.

Die hoof roete van ekskresie van sulfametoksasool is renaal; tussen 15 % en 30 % van die dosis herwin in die uriene in die aktiewe vorm. By ouer pasiënte is daar ‘n verminderde renale opruiming van sulfametoksasool.

Pediatriese bevolking

Die farmakokinetika in die pediatriese bevolking met normale renale funksie van beide komponente van ko-trimoksasool, MP en SMZ is ouderdom-afhanklik. Eliminasie van TMP-SMZ is verminder in neonate, gedurende die eerste twee maande van lewe, daarna wys beide TMP en SMZ ‘n hoër eliminasie met ‘n groter liggaamsopruiming en ‘n korter eliminasie halfleeftyd. Die verskille is meestal prominent by jong kleuters (> 1,7 maande tot 24 maande) en verminder moet toenemende ouderdom, wanneer vergelyk met jong kinders (1 jaar tot 3,6 jaar), kinders (7,5 jaar en < 10 jaar) en volwassenes (sien afdeling 4.2).

Spesiale pasiënt bevolking

Renale inkorting

Die eliminasie halfleeftyd van trimetoprim word verhoog deur ‘n faktor van 1,5 – 3,0 wanneer die kreatinien-opruiming minder is as 10 mL/minute. Wanneer die kreatinien-opruiming afkom benede 30 mL/min moet die dosering van ko-trimoksasool verminder te word (sien afdeling 4.2).

Bejaarde pasiënte

By bejaarde pasiente was daar ‘n effense afname waargeneem in renale opruiming van sulfametoksasool, maar nie van trimetoprim nie.

6. FARMASEUTIESE BESONDERHEDE

6.1 Lys van eksipiënte

Gehidrogeneerde groente olie, magnesiumstearaat, nipastat, gepregelatiniseerde mieliestysel, gesuiwerde water, natrium karboksimetiel stysel, mieliestysel.

6.2 Onverenigbaarhede

Nie van toepassing nie.

6.3 Rakleeftyd

DUROBAC: 36 maande

DUROBAC D/S: 24 maande

6.4 Spesiale voorsorgmaatreëls vir berging

Berg benede 25 °C.

Beskerm teen lig en vog.

HOU BUITE DIE BEREIK VAN KINDERS.

6.5 Aard en inhoud van die houer

DUROBAC: 28 of 56 tablette verpak in ‘n L.D.P.E “ziploc” plastiese pasiënt-gereed pakkies en 100, 500 of 1000 tablette verpak in HDPE houers.

DUROBAC DOUBLE STRENGTH: 30 of 100 tablette verpak in wit securitainers en 1000 tablette verpak in HDPE houers.

6.6 Spesiale voorsorgmaatreëls vir weggooi

Geen spesiale voorsorgmaatreëls vir weggooi.

7. HOUER VAN SERTIFIKAAT VAN REGISTRASIE

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8. REGISTRASIENOMMERS

DUROBAC: J/20.2/279

DUROBAC DOUBLE STRENGTH: P/20.2/55

9. DATUM VAN EERSTE GOEDKEURING

November 1993

10. DATUM VAN REVISIE VAN DIE TEKS

29/01/2024