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