Applicant: Oethmaan Biosims (Pty) Ltd	**SAHPRA approval date:** 22 April 2024
Product: XEROPRIM	**Dosage form and strength:** Each tablet contains 400 mg Sulphamethoxazole and 80 mg Trimethoprim

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

XEROPRIM, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each tablet contains:

Trimethoprim	80 mg
Sulphamethoxazole	400 mg

Preservative:

Nipastat 0,025 % *m/m*

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White, round flat tablet bisected on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

The treatment of infections of the upper and lower respiratory tract, the urinary tract and the alimentary and genital tract in both sexes, and skin infections caused by sensitive organisms.

Xeroprim is indicated for:

Initial: 22/04/2024

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 older than 12 years:

Two tablets every 12 hours for a period of 10 to 14 days.

Special populations

Renal Impairment

If XEROPRIM 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 XEROPRIM. If the concentration of total sulfamethoxazole exceeds 150 µg/ml then treatment should be interrupted until the value falls below 120 µg/ml.

No Information is available for children with renal failure.

Paediatric population

Cotrimoxazole paediatric formulations to be used in children under 12 years.

Method of administration

For oral use.

Tablets must be swallowed with a sufficient quantity of liquid.

4.3 Contraindications

- XEROPRIM is contraindicated in patients with known hypersensitivity to sulphonamide, sulphamethoxazole, trimethoprim or to any of the excipients listed in section 6.1.
- Patients who are suffering from porphyria.
- It should not be used in patients suffering from liver parenchyma damage.
- Severe renal insufficiency.
- Co-trimoxazole should not be used during pregnancy and lactation.
- Use of the substance in premature or new-born infants during the first two months of life, is contraindicated.
- Should not be given to patients with megaloblastic anaemia or blood dyscrasias.

- Contraindicated in the presence of vitamin b_{12} and folic acid deficiency state.

4.4 Special warnings and precautions for use

Life threatening skin adverse reactions

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

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.

Folate

XEROPRIM is contraindicated in patients with actual or possible folate deficiency because of possible interference with human folate metabolism by trimethoprim as in XEROPRIM (see Section 4.3).

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.

Prolonged treatment

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

Renal impairment

XEROPRIM 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.

Cross-sensitivity

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

Direct exposure to sunlight should be avoided as it facilitates development of sensitisation dermatitis.

XEROPRIM should be used with caution in patients with allergic conditions or bronchial asthma.

High doses of XEROPRIM may have a hypoglycaemic effect.

Thyroid tests must be carried out in patients with thyroid disorders.

Excipients with known effect

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

Paediatric population

Not recommended for children under 12 years (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Diuretics

Previous or simultaneous administration of diuretics with co-trimoxazole may cause an increased risk of thrombocytopenia, especially in elderly patients with heart failure; death may occur.

Paraldehyde

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

p-aminobenzoic acid

XEROPRIM may be antagonized by *p*-aminobenzoic acid and compounds derived from it.

Protein binding, anticoagulants and methotrexate

Sulphamethoxazole is strongly bound to proteins. Patients receiving anticoagulants of the coumarin group or methotrexate concomitantly should therefore be carefully monitored.

Sulphonylureas

Sulphamethoxazole increases the hypoglycaemic action of sulphonylureas in diabetic patients.

Pyrimethamine or immunosuppressive therapy

XEROPRIM should be used with caution in patients receiving pyrimethamine or immunosuppressive therapy. Patients receiving pyrimethamine may develop megaloblastic anaemia due to the trimethoprim component in XEROPRIM.

Phenytoin

Trimethoprim prolongs the half-life of phenytoin.

Digoxin, procainamide and tolbutamide

XEROPRIM may interact with the following medicines by interfering with their clearance: digoxin, procainamide and tolbutamide.

Diagnostic tests

Sulphamethoxazole has been reported to interfere with some diagnostic tests including those for urea, creatinine, urinary glucose and urobilinogen.

Trimethoprim may interfere with some diagnostic tests including serum methotrexate assay and the jaffé reaction for creatinine.

Ciclosporin

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

Zidovudine

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

Lamivudine

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

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.

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 XEROPRIM. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

It is not always possible to predict to what extent XEROPRIM may interfere with the daily activities of a patient. XEROPRIM 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 XEROPRIM affects them.

4.8 Undesirable effects

a. *Summary of the safety profile*

Hypersensitivity reactions particularly involving the skin are among the most common adverse effects of XEROPRIM 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.

b. *Tabulated list of adverse reactions*

Sulphamethoxazole and Trimethoprim

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Pseudomembranous colitis	Less frequent
Blood and lymphatic system disorders	Haematological changes such as anaemia (including aplastic, haemolytic and macrocytic), coagulation disorders, granulocytopenia, agranulocytosis, purpura, henoch—schönlein purpura; and sulphaemoglobinaemia, megaloblastosis, leucopenia or thrombocytopenia, polyarteritis nodosa	Less frequent
Immune system disorders	Anaphylaxis	Less frequent
Endocrine disorders	Goitre, hypothyroidism	Less frequent
Metabolism and nutrition disorders	Acidosis, anorexia, high doses of XEROPRIM may have a hypoglycaemic effect	Less frequent

Psychiatric disorders	Depression, hallucinatory manifestations, psychosis, fatigue, insomnia, nightmares, confusion	Less frequent
Nervous system disorders	Headache	Frequent
	Dizziness, drug fever, drowsiness, ataxia, peripheral neuritis	Less frequent
Ear and labyrinth disorders	Vertigo, tinnitus	Less frequent
Gastro-intestinal disorders:	Nausea, vomiting, glossitis, stomatitis	Frequent
	Diarrhoea	Less frequent
Hepato-biliary disorders	Jaundice has been noted and appears to have the histological features of allergic cholestatic hepatitis.	Less frequent
Skin and subcutaneous tissue disorder	Reddening exanthema and itch. Exfoliative dermatitis, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (Lyell's Syndrome). Fixed drug eruption.	Less frequent

	When a rash appears, this medicine must be discontinued.	
Musculoskeletal and connective tissue disorders	Arthralgia	Less frequent
Renal and urinary disorders	Toxic nephrosis	Less frequent

Sulphamethoxazole

System Organ Class	**Adverse reaction**	**Frequency**
Infections and infestations	Overgrowth fungal	Frequent
	Pseudomembranous colitis	Less frequent
Blood and lymphatic system disorders	Agranulocytosis, aplastic anaemia, thrombocytopenia, leukopenia, hypoprothrombinaemia, eosinophilia, methaemoglobinaemia, acute haemolytic anaemia often associated with glucose-6-phosphate dehydrogenase deficiency, neutropenia	Less frequent
Immune system disorders	Anaphylaxis, serum sickness, allergic	Less frequent

	myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus, severe hypersensitivity reactions associated with PJP*	
Endocrine disorders	Hypothyroidism	Frequency unknown
Metabolism and nutrition disorders	Hyperkalaemia	Frequent
	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis	Less frequent
Psychiatric disorders	Depression, hallucination	Less frequent
	Psychotic disorder	Frequency unknown
Nervous system disorders	Headache	Frequent
	Ataxia, dizziness, fatigue, insomnia, peripheral neuritis, seizure	Less frequent

Eye disorders	Optic neuropathy, transient myopia, uveitis	Less frequent
Ear and labyrinth disorders	Vertigo, tinnitus	Less frequent
Respiratory, thoracic and mediastinal disorders	Cough*, dyspnoea*, lung infiltration*	Less frequent
	Cyanosis due to methaemoglobinaemia or sulphaemoglobinaemia	Frequency unknown
Gastro-intestinal disorders:	Nausea, diarrhoea	Frequent
	Vomiting, glossitis, stomatitis, pancreatitis.	Less frequent
Hepato-biliary disorders	Jaundice cholestatic *, hepatic necrosis*. increased transaminases, increased blood bilirubin	Less frequent
Skin and subcutaneous tissue disorder	Rash	Frequent
	Photosensitivity reactions, exfoliative dermatitis, toxic epidermal necrolysis (Lyell's syndrome), erythema nodosum, erythema	Less frequent

	multiforme, Steven-Johnson syndrome, systemic lupus erythematosus	
	Acute febrile neutrophilic dermatosis (Sweet's syndrome), drug reaction with eosinophilia and systemic symptoms (DRESS)*, fixed drug eruptions (FDE)	Frequency unknown
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia	Less frequent
Renal and urinary disorders	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	Less frequent

*See below section c

Trimethoprim

System Organ Class	Adverse reaction	Frequency

Nervous system disorders	Headache	Frequent
	Meningitis aseptic *	Less frequent
Gastro-intestinal disorders	Nausea, vomiting and sore mouth	Frequent
Skin and subcutaneous tissue disorder	Pruritus, skin rash	Frequent
General disorders and administrative site conditions	Fever	Frequent

* See below section c

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 XEROPRIM 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 XEROPRIM. 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 cotrimoxazole 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 providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms and signs

Nausea, vomiting, cyanosis, heamaturia, oliguria, or anuria and allergic skin reactions (skin rashes, anaphylaxis, etc.) (see also section 4.8). Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

Treatment is supportive and symptomatic.

If vomiting has not occurred, induction of vomiting may be desirable. Absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. 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

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

Pharmacotherapeutic group: Antibacterials for systemic use - Sulphonamides and trimethoprim, incl. derivatives

ATC code: J01EE01

Xeroprim is a combination of trimethoprim and sulphamethoxazole and results in synergistic effects causing a batericidal action (*in vitro*). The action of co-trimoxazole is achieved by the sequential blocking of two enzymes essential in folinic acid synthesis in the organism.

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).

Elderly patients

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

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

Microcrystalline cellulose

Pregelatinised starch

Maize starch

Nipastat

Sodium carboxy methyl cellulose

Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a cool dry place, below 25 ºC. Protect from light and heat. Keep out of reach of children.

6.5 Nature and contents of container

Packed into patient ready packs of 28, 56 and 100 tablets and bottles of 20, 100 and 500 tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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Initial: 22/04/2024

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8 REGISTRATION NUMBER(S):

27/20.2/0077

9 DATE OF FIRST AUTHORISATION

18 January 2006

10 DATE OF REVISION OF THE TEXT

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