Professional information for BACTRIM

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BACTRIM 80 mg/400 mg per 5 mL, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BACTRIM contains as active ingredient trimethoprim (TMP) and sulfamethoxazole (SMZ)

(trimethoprim + sulfamethoxazole = cotrimoxazole).

Each 5 mL solution contains 80 mg TMP and 400 mg SMZ.

Sugar free.

Excipients with known effect:

Contains 10 % *m/v* ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear liquid not more than faintly yellow in a 5 mL glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis (primary and secondary) of *Pneumocystis*

jirovecii pneumonia in adults and children, particularly in the severely immunocompromised host.

Treatment of toxoplasmosis.

4.2 Posology and method of administration

Posology

Intravenous infusion

If oral administration is impossible, or not indicated, the ampoule for IV infusion can only be used following dilution with the appropriate infusion solutions.

Standard dosage for adults and children over 12 years of age:

2 x 5 mL ampoules twice a day (10 mL twice a day), after appropriate dilution, in the morning and in the evening.

High dosage (for particularly severe cases):

3 x 5 mL ampoules twice daily (15 mL twice a day), after appropriate dilution, in the morning and in the evening.

Duration of treatment:

As a general rule, the BACTRIM parenteral formulation should be given only during the period that oral treatment is not possible; the standard dosage for not longer than 5 consecutive days, and the high dose for not more than 3 consecutive days.

Pneumocystis jirovecii pneumonia:

The recommended dosage for patients with *Pneumocystis jirovecii* pneumonia is up to 20 mg TMP per kg and up to 100 mg SMZ per kg per 24 hours, given in equal divided doses, every 6 hours for 14 days.

Intravenous infusion

Standard dosage in children up to 12 years of age:

The average dosage is approximately 2 mL/5 kg body weight daily, divided into 2 equal doses, and given in the morning and in the evening. Thus, the recommended basis for dosage in children is 6 mg TMP plus 30 mg SMZ per kg body weight daily.

Special populations

Patients with impaired renal function

Table 1: Recommended regimen for patients with renal impairment

Creatinine clearance	Recommended dosage schedule
> 30 mL/min	Standard dosage
< 30 mL/min	Half the standard dosage
< 15 mL/min	Use of BACTRIM not recommended

Elderly/Geriatric patients

Elderly patients with normal renal function should receive the usual adult dosage.

Patients on dialysis

Patients on haemodialysis initially should receive a normal loading dose of TMP-SMZ, followed by an additional half dose after each haemodialysis session. Peritoneal dialysis results in minimal clearance of administered TMP and SMZ. Use of TMP-SMZ in patients receiving peritoneal dialysis is not recommended.

Method of administration

BACTRIM must be diluted before use. The following infusion solutions can be used for dilution: glucose 5 % and 10 %, xylitol 10 %, Ringer's solution, sodium chloride 0,9 %, sodium chloride 0,45 % + glucose 2,5 % (see section 6.6).

4.3 Contraindications

BACTRIM is contraindicated in pregnancy and lactation as safety and efficacy have not been established (see section 4.6).

Blood dyscrasias, sulfonamide or trimethoprim hypersensitivity (including allergy to sulfonylurea anti-diabetics and saluretic sulfonamide derivatives should also be considered).

Patients with marked liver parenchymal damage and severe renal insufficiency (CrCl < 15 mL/min).

BACTRIM should not be given to patients with megaloblastic anaemia, or patients with other serious haematological disorders.

It must not be given to infants during the first six weeks of life.

It should be avoided in the presence of vitamin B_{12} and folic acid deficiency states.

It should not be used in patients who suffer from porphyria.

BACTRIM must not be given in combination with dofetilide (see section 4.5).

4.4 Special warnings and precautions for use

In order to minimise the risk of undesirable reactions, the duration of treatment with BACTRIM should be as short as possible, particularly in elderly patients.

Serious adverse reactions

Fatal outcome, though rare, has been reported in connection with adverse reactions such as blood dyscrasias, major exudative erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome) drug rash with eosinophilia and systemic symptoms (DRESS) and fulminant liver necrosis.

Hypersensitivity and allergic reactions

Treatment should be discontinued immediately at the first appearance of skin rash or any other serious adverse reaction. BACTRIM should be administered with caution to patients with a history of severe allergy and bronchial asthma. Pulmonary infiltrates reported in the context of eosinophilic or allergic alveolitis may manifest through symptoms such as cough or shortness of breath. Should such symptoms appear or unexpectedly worsen, the patient should be re-evaluated and discontinuation of BACTRIM therapy considered.

Renal effects

Sulfonamides, including BACTRIM, may induce diuresis, particularly in patients with oedema of cardiac origin.

Close monitoring of serum potassium and renal function is warranted in patients receiving high-dose BACTRIM, as used in patients with *Pneumocystis jirovecii* pneumonia, or in patients receiving standard-dose BACTRIM with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving medicines which induce hyperkalaemia (see section 4.5).

Special populations

There is an increased risk of severe adverse reactions in elderly patients or when complicating conditions exist, e.g. impaired kidney and/or liver function, or concomitant use of other medicines (in which case the risk may be related to the dosage and duration of treatment). In the event of renal impairment, dosage should be adjusted according to the special dosage instructions. Patients with severe renal impairment (i.e. with creatinine clearance 15 – 30 mL/min) who are receiving BACTRIM should be closely monitored for symptoms and signs of toxicity such as nausea, vomiting and hyperkalaemia. Other than in exceptional cases, BACTRIM should not be given to patients with serious haematological disorders. Cases of pancytopenia have been reported in patients taking the combination of TMP and methotrexate. In elderly patients, or in patients with pre-existing folic acid deficiency or kidney failure, haematological changes indicative of folic acid deficiency may occur. These are reversible by folinic acid therapy. Owing to the possibility of haemolysis, BACTRIM should not be given to patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency unless absolutely essential, and then only in minimal doses. As with all medicines containing sulfonamides, caution is advisable in patients with thyroid dysfunction. Patients who are slow acetylators may be more prone to idiosyncratic reactions to sulfonamides, such as BACTRIM.

Long-term treatment

If BACTRIM is given over a prolonged period, regular blood counts are required. If a significant reduction in count of any formed blood element is noted, BACTRIM should be discontinued. Urinalysis

and renal function tests should be performed regularly in patients undergoing long-term treatment with BACTRIM (particularly patients with kidney failure). During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria.

Excipients

Ethanol

BACTRIM contains 500 mg alcohol (ethanol) per ampoule (5 mL), corresponding to 100 mg/mL (10 % *w/v*). The amount is equivalent to 13 mL beer or 6 mL wine. If a dose of 3 ampoules (15 mL) of BACTRIM is administered to an adult weighing 70 kg, this leads to an exposure of 21 mg/kg ethanol. This may cause an increase in blood alcohol concentration (BAC) of approximately 3,6 mg/100 mL. If a dose of 27 mg/kg cotrimoxazole is administered to a 5-month-old child weighing 5 kg, this leads to an exposure of 28 mg/kg ethanol. This can cause an increase in blood alcohol concentration (BAC) of approximately 4,7 mg/100 mL. By comparison, if an adult drinks a glass of wine or 500 mL of beer, the BAC is likely to be 50 mg/100 mL. Concomitant use of medicines containing, for example, propylene glycol or ethanol may lead to accumulation of ethanol and cause adverse reactions, particularly in young children with low or immature metabolic capacity.

Propylene glycol

BACTRIM contains 2 050 mg propylene glycol per ampoule (5 mL), corresponding to 410 mg/mL. Co-administration with an alcohol dehydrogenase substrate, such as ethanol, may cause adverse reactions in children under 5 years of age. This should be considered when using in children under 5 years of age, especially if the patient is also receiving other medicines containing propylene glycol or alcohol. Although propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, propylene glycol may reach the fetus and pass into breast milk (see sections 4.3 and 4.6).

Sodium

BACTRIM contains 34 mg of sodium per ampoule (5 mL), which is equivalent to 1,7 % of the World

Health Organization (WHO) recommended maximum daily intake of 2 g for an adult.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

Trimethoprim is an inhibitor of the organic cation transporter 2 (OCT2), and a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9.

Systemic exposure to medicines transported by OCT2 may increase when co-administered with BACTRIM. Examples include dofetilide, amantadine, memantine and lamivudine.

BACTRIM must not be given in combination with dofetilide (see section 4.3). There is evidence that TMP inhibits renal excretion of dofetilide. Trimethoprim 160 mg in combination with sulfamethoxazole 800 mg co-administered twice daily with dofetilide 500 µg twice daily for four days resulted in a 103 % increase in the dofetilide area under the concentration-time curve (AUC), and a 93 % increase in the maximum concentration (C_{max}). Dofetilide can cause serious ventricular arrhythmias associated with QT interval prolongation, including torsades de pointes, which are directly related to the dofetilide plasma concentration.

Patients receiving amantadine or memantine may be at increased risk of neurological adverse events such as delirium and myoclonus.

Systemic exposure to medicines metabolised primarily by CYP2C8 may increase when co-administered with BACTRIM. Examples include paclitaxel, amiodarone, dapsone, repaglinide, rosiglitazone and pioglitazone.

Paclitaxel and amiodarone have a narrow therapeutic index. Therefore, concomitant administration with BACTRIM is not recommended.

Both dapsone and BACTRIM can cause methaemoglobinaemia, and there is therefore potential for both pharmacokinetic and pharmacodynamic interactions. Patients receiving both dapsone and BACTRIM should be monitored for methaemoglobinaemia. Alternative therapies should be considered if possible.

Patients receiving repaglinide, rosiglitazone or pioglitazone should be monitored regularly for hypoglycaemia.

Increased digoxin blood levels can occur with concomitant BACTRIM therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Systemic exposure to medicines metabolised primarily by CYP2C9 may increase when co-administered with BACTRIM. Examples include coumarins (warfarin, acenocoumarol, phenprocoumon), phenytoin, and sulfonylurea derivatives (glibenclamide, gliclazide, glipizide, chlorpropamide, and tolbutamide). In such cases the prothrombin time/international normalised ration (PT/INR) coagulation time should be regularly monitored. A 39 % increase in half-life and a 27 % decrease in clearance rate of phenytoin have been observed following administration of standard doses of BACTRIM. Patients receiving phenytoin should be monitored for signs of phenytoin toxicity. Patients receiving sulfonylurea derivatives (including glibenclamide, gliclazide, glipizide, chlorpropamide and tolbutamide), should be monitored regularly for hypoglycaemia.

Pharmacodynamic interactions and interactions of undefined mechanism

Incidence rate and severity of myelotoxic and nephrotoxic adverse reactions may be increased when BACTRIM is administered concomitantly with other medicines known to be myelosuppressive or associated with renal impairment, such as nucleoside analogues, tacrolimus, azathioprine or mercaptopurine. Patients receiving BACTRIM concomitantly with such medicines should be monitored for haematological and/or renal toxicity.

Co-administration with clozapine, a medicine known to have a substantial potential for causing agranulocytosis, should be avoided.

An increased incidence of thrombocytopenia has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides. Platelets should be monitored regularly in patients receiving diuretics.

Reversible deterioration of renal function has been observed in patients treated with BACTRIM and ciclosporin following renal transplantation.

Sulfonamides, including SMZ, can compete with protein binding and also with the renal transport of methotrexate, thus increasing the free methotrexate fraction and the systemic exposure to methotrexate.

Cases of pancytopenia have been reported in patients taking the combination of TMP and methotrexate. TMP has a low affinity for human dihydrofolate reductase but may increase toxicity of methotrexate, especially in the presence of risk factors such as old age, hypoalbuminaemia, impaired renal function, and decreased bone marrow reserve, and in patients receiving high doses of methotrexate. At-risk patients should be treated with folic acid or calcium folinate to counteract the effects of methotrexate on haematopoiesis.

Reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly, may develop megaloblastic anaemia if BACTRIM is prescribed concurrently.

Due to the potassium-sparing effects of BACTRIM, caution should be used when BACTRIM is co-administered with other medicines that increase serum potassium, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, potassium-sparing diuretics and prednisolone.

Influence on diagnostic methods

BACTRIM, specifically the TMP component, can interfere with a serum methotrexate assay using the competitive protein-binding technique when bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by radioimmunoassay. The presence of TMP and SMZ may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, causing values in the normal range to be increased by about 10 %.

4.6 Fertility, pregnancy and lactation

Pregnancy

BACTRIM is contraindicated in pregnancy and lactation as safety has not been demonstrated. The risk of birth malformations has not been consistently demonstrated with cotrimoxazole therapy in women during early pregnancy. Two large observational studies have suggested a 2 to 3,5-fold increased risk of spontaneous abortion in women treated with TMP alone and in combination with SMZ during the first trimester compared to either no exposure to antibiotics or to exposure to penicillins. Animal studies have shown that very high doses of cotrimoxazole produced fetal malformations typical of folic acid antagonism. Both TMP and SMZ cross the placental barrier and may interfere with folic acid metabolism.

Lactation

Both TMP and SMZ pass into the breast milk. Due to the known risks to the infant (kernicterus, hypersensitivity) mothers receiving BACTRIM should not breastfeed their infants (see section 5.2 – Distribution).

4.7 Effects on ability to drive and use machines

It is not always possible to predict to what extent BACTRIM may interfere with the daily activities of a patient. BACTRIM can cause hallucinations (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 BACTRIM affects them.

4.8 Undesirable effects

At the recommended dosages, BACTRIM is usually well tolerated. The most common side effects are skin rashes and gastrointestinal disturbances. The following standard categories for frequency are used below: Very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100; rare ≥ 1/10 000 and < 1/1 000 and very rare < 1/10 000. Not known (cannot be estimated from the available data).

Adverse events reported in the general patient population treated with TMP-SMZ

System organ class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Fungal infections, such as candidiasis			
Blood and lymphatic system disorders			Leucopenia, Granulocytopenia, Thrombocytopenia, Anaemia (megaloblastic, haemolytic/ autoimmune, aplastic)	Methemoglobinaemia, Agranulocytosis, Pancytopenia	
Immune system disorders				Hypersensitivity/Allergic reactions (fever, angioedema,	

System organ class	Common	Uncommon	Rare	Very rare	Not known
				anaphylactoid reactions, serum sickness)	
Metabolism and nutrition disorders			Hypoglycaemia		
Psychiatric disorders			Hallucinations		
Nervous system disorders		Convulsions	Neuropathy (including peripheral neuritis and paraesthesia)	Ataxia, Aseptic meningitis/ meningitis-like symptoms	Cerebral vasculitis
Eye disorders				Uveitis	Retinal vasculitis
Ear and labyrinth disorders				Tinnitus, Vertigo	
Cardiac disorders				Allergic myocarditis	
Vascular disorders				Purpura, Henoch-Schönlein purpura	Vasculitis, Necrotising vasculitis, Granulomatosis with polyangiitis,

System organ class	Common	Uncommon	Rare	Very rare	Not known
					Polyarteritis nodosa
Respiratory, thoracic and mediastinal disorders				Pulmonary infiltrates	Pulmonary vasculitis
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea	Glossitis, Stomatitis		Acute pancreatitis
Hepato-biliary disorders	Elevated transaminases	Elevated bilirubin, Hepatitis	Cholestasis	Liver necrosis	Vanishing bile duct syndrome
Skin and subcutaneous tissue disorders	Fixed drug eruption, Exfoliative dermatitis, Rash, Maculopapular rash, Morbilliform rash, Erythema, Pruritus	Urticaria		Erythema multiforme, Photosensitivity, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug rash with eosinophilia and systemic symptoms	Skin and subcutaneous tissue disorders
Musculoskeletal and connective tissue				Rhabdomyolysis	Arthralgia, Myalgia

System organ class	Common	Uncommon	Rare	Very rare	Not known
disorders					
Renal and urinary disorders	Elevated blood urea nitrogen, Elevated serum creatinine	Impaired renal function	Crystalluria	Interstitial nephritis, Increased diuresis	Renal and urinary disorders
Pregnancy, puerperium and perinatal conditions					Spontaneous abortion
General disorders and administration site conditions			Venous pain and phlebitis		
Investigations					Hyperkalaemia, Hyponatraemia

Description of selected adverse events

Most of the haematological changes observed have been mild, asymptomatic and reversible on withdrawal of therapy.

As with any other medicine, allergic reactions may occur in patients who are hypersensitive to the medicine ingredients. The most common skin reactions observed with BACTRIM have been

generally mild and quickly reversible after withdrawal of the medicine. Pulmonary infiltrates reported in the context of eosinophilic or allergic alveolitis may manifest through symptoms such as cough of shortness of breath (see section 4.4).

High-dose TMP, as used in patients with *Pneumocystis jirovecii* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even at recommended doses TMP may cause hyperkalaemia when administered to patients with underlying disorders of potassium metabolism or renal insufficiency, or who are receiving medicine which induce hyperkalaemia (see section 4.4).

Cases of hypoglycaemia have been reported in non-diabetic patients treated with TMP-SMZ, usually after a few days of therapy (see section 4.5). Patients with impaired renal function, liver disease or malnutrition or receiving high doses of TMP-SMZ are particularly at risk. Several of the patients with acute pancreatitis had serious illnesses, including acquired immunodeficiency syndrome (AIDS).

Safety of BACTRIM in human immunodeficiency virus (HIV)-infected patients

The HIV patient population is similar to the general patient population in terms of the spectrum of adverse events that may occur. However, some adverse events may occur with a higher frequency and a difference in the clinical picture. These differences concern the following system organ classes:

System organ class	**Very common**	**Uncommon**
Blood and lymphatic system disorders	Leucopenia, Granulocytopenia, Thrombocytopenia	
Metabolism and nutrition disorders		Hypoglycaemia
Gastrointestinal disorders	Anorexia, nausea, vomiting, diarrhoea	
Hepatobiliary disorders	Elevated transaminases	

System organ class	Very common	Uncommon
Skin and subcutaneous tissue disorders	Maculopapular rash, Pruritus	
General disorders and administration site conditions	Fever (usually in conjunction with maculopapular rash)	
Investigations	Hyperkalaemia	Hyponatraemia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BACTRIM is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the 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

Symptoms of acute overdosage may include: nausea, vomiting, diarrhoea, headache, vertigo, dizziness, mental and visual disturbances; crystalluria, haematuria and anuria may occur in severe cases. In chronic overdosage, bone marrow depression, manifested as thrombocytopenia or leukopenia, and other blood dyscrasias due to folinic acid deficiency may occur.

The following treatment measures may be considered depending on the symptoms: promotion of renal excretion by forced diuresis (alkalinisation of urine increases sulfamethoxazole elimination), haemodialysis (note: peritoneal dialysis is not effective), monitoring of blood count and electrolytes. If significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Calcium folinate, 3 to 6 mg intramuscularly, for 5 to 7 days, may be given to counteract the effects of trimethoprim on haematopoiesis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2 Anti-microbial (chemotherapeutic) agents: other than antibiotics

Pharmacotherapeutic groups: Antibacterials for systemic use – Sulfonamides and trimethoprim

ATC code: J01EE01

BACTRIM contains two active ingredients acting synergistically by the sequential blockade of two bacterial enzymes that catalyse successive stages in the biosynthesis of folinic acid in the micro-organism.

BACTRIM is bactericidal *in vitro* for some organisms at concentrations at which the components, TMP and SMZ alone, are usually bacteriostatic. BACTRIM is effective *in vitro* against a range of gram-positive and gram-negative organisms. *In vitro* sensitivity does not necessarily imply clinical efficacy.

Antibacterial spectrum (in vitro): The antibacterial effect of BACTRIM *in vitro* covers a wide range of Gram-positive and Gram-negative pathogenic organisms. The sensitivity of BACTRIM is dependent upon the prevalence of resistance in the geographical area.

*Resistant organisms (MIC > 160 mg/L) [1]**

- *Mycoplasma* spp., *Mycobacterium tuberculosis*, *Treponema pallidum*.

* SMZ equivalents

The local prevalence of resistance to BACTRIM among bacteria relevant to the infection treated should be known when BACTRIM is prescribed on an empirical basis. To exclude resistance, especially in infections likely to be caused by a partially sensitive pathogen, the isolate should be tested for sensitivity.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, TMP and SMZ are almost completely absorbed from the upper portion

of the gastrointestinal tract. Following a single dose of 160 mg TMP and 800 mg SMZ, peak plasma concentrations of 1,5 – 3 µg/mL for TMP and 40 – 80 µg/mL for SMZ are reached after 1 to 4 hours. Following repeated administration of the above dosage at 12-hour intervals, minimum plasma concentrations at steady state, achieved in 2 – 3 days, range between 1,3 and 2,8 µg/mL for TMP and between 32 and 63 µg/mL for SMZ.

Bioavailability

The absorption of TMP and SMZ is complete as reflected by the absolute oral bioavailability reaching 100 % for both medicines.

Distribution

The volume of distribution is approximately 1,6 L/kg for TMP and approximately 0,2 L/kg for SMZ, while the plasma protein binding reaches 37 % for TMP and 62 % for SMZ. In humans, TMP and SMZ were detected in the fetal tissues (placenta, liver, lung), umbilical cord blood and amniotic fluid, indicating placental transfer of both medicines. In general, fetal concentrations of TMP are similar, and those of SMZ lower, than maternal concentrations (see section 4.6).
Both medicines are excreted in breast milk. Concentrations in breast milk are similar to (TMP), or lower than (SMZ) those in maternal plasma (see section 4.6).

Metabolism

Around 30 % of a TMP dose is metabolised. Based on results from an *in vitro* study with human liver microsomes, the involvement of CYP3A4, CYP1A2 and CYP2C9 in the oxidative metabolism of TMP cannot be excluded. The principal TMP metabolites are 1- and 3-oxides and the 3- and 4-hydroxy derivatives; some metabolites are microbiologically active. Around 80 % of a SMZ dose is metabolised in the liver, predominantly to the N_4 acetyl-derivative (≈ 40 % of the dose) and to a lesser extent, by glucuronide conjugation; the metabolites are inactive. SMZ also undergoes oxidative metabolism. The first step of the oxidative pathway, which leads to the formation of the hydroxylamine derivative, is catalysed by CYP2C9.

Elimination

The elimination half-lives of the two components are similar (a mean of ten hours for TMP and eleven hours for SMZ). Both substances, as well as their metabolites, are eliminated almost entirely by the kidneys through both glomerular filtration and tubular secretion, giving urine concentrations of both active substances considerably higher than the concentration in the blood. Around two thirds of the TMP dose and one fifth of the SMZ dose are excreted unchanged into the urine. The total plasma clearance of TMP equals 1,9 mL/min/kg. The total plasma clearance of SMZ equals 0,32 mL/min/kg. A small part of each substance is eliminated via the faeces.

Special populations

Children

The results of different clinical pharmacokinetic studies in the paediatric population with normal renal function have confirmed that the pharmacokinetics of both components of BACTRIM, TMP and SMZ, are age dependent in this population. While 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 3,6 years), to children (7,5 years and < 10 years) and adults (see section 4.2).

Elderly

Based on the importance of renal clearance in the TMP elimination process and taking into account that creatinine clearance decreases physiologically with increasing age, a decrease of renal clearance and total body clearance of TMP with age can be anticipated. The pharmacokinetics of SMZ should be less affected by age increase as renal clearance of SMZ corresponds only to 20 % of total SMZ clearance.

Renal impairment

In patients with severely impaired renal function (creatinine clearance 15 – 30 mL/min), the elimination half-lives of both components are increased, requiring dosage regimen adjustment. Intermittent or continuous ambulatory peritoneal dialysis does not significantly contribute to TMP-SMZ elimination. TMP and SMZ are removed to a significant degree during haemodialysis and haemofiltration. It was suggested to increase by 50 % the dose of TMP-SMZ after each haemodialysis session. In children with renal insufficiency (CrCl < 30 mL/min) the clearance of TMP is reduced and its elimination half-life prolonged. The TMP-SMZ dose in paediatric patients with renal impairment should be based on renal function (see section 4.2).

Hepatic impairment

The pharmacokinetics of TMP and SMZ in patients with moderate or severe hepatic impairment are not significantly different from those observed in healthy subjects.

Patients with cystic fibrosis

The renal clearance of TMP and the metabolic clearance of SMZ are increased in patients with cystic fibrosis. Consequently, the total plasma clearance is increased, and the elimination half-life is decreased for both medicines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Ethanolamine

Propylene glycol

Sodium hydroxide

Water for injection.

6.2 Incompatibilities

Do not add any products to BACTRIM infusions, in particular products lowering the pH below 8 as precipitation may occur.

Levulose 5 %, Hartmann solution and sodium bicarbonate 1,4 % solution must not be used for diluting BACTRIM.

6.3 Shelf life

60 months.

Store at or below 30 °C.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

Type 1 flint glass ampoules packed in trays containing 5 ampoules.

6.6 Special precautions for disposal and other handling

It is important to adhere to the following minimum dilution scheme, which is based on a proportion of 1 mL BACTRIM ampoule (solution) to approximately 25 – 30 mL infusion solution.

1 ampoule BACTRIM (5 mL) to 125 mL infusion solution.

2 ampoules BACTRIM (10 mL) to 250 mL infusion solution.

3 ampoules BACTRIM (15 mL) to 500 mL infusion solution.

These mixtures with BACTRIM should be prepared immediately before use. After addition of BACTRIM to the infusion solution the mixture should be swirled or shaken in order to ensure thorough mixing. Should visible turbidity or crystallisation appear in the solution prior to, or during the infusion, it should be replaced by a freshly prepared solution. Infusion solutions containing BACTRIM should be used within 6 hours of preparation.

Dilution ratio for patients on fluid restriction

In those instances where fluid restriction is desirable, each 5 mL BACTRIM for infusion may be added to 75 mL glucose 5 %, sodium chloride 0,9 % or Ringer's solution. The solutions should be prepared just prior to use and must be administered within 2 hours at room temperature and diffuse daylight.

To achieve effective blood levels, the duration of the infusion, which will depend on the quantity of fluid, should not exceed one and a half hours. The normal duration is 30 – 60 minutes.

Special note: BACTRIM should be injected intravenously only in the form of the infusion solutions described above, and may not be injected undiluted, either intravenously or directly into the infusion tube. BACTRIM should not be administered intramuscularly or subcutaneously. The prepared BACTRIM infusion solution should not be mixed with other medicines or solutions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBER

F/20.2/191

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 March 1974

10. DATE OF REVISION OF THE TEXT

20 February 2024