SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Trimethoprim/sulfamethoxazole 80/400 mg tablets

Trimethoprim/sulfamethoxazole 160/800 mg tablets

2. Qualitative and quantitative composition

Trimethoprim/sulfamethoxazole 80/400 mg tablets
Each tablet contains 400 mg of trimethoprim/sulfamethoxazole.
Excipient with known effect.
Each gram **also** contains 0.45 mg of sodium benzoate. See section 4.4.

Trimethoprim/sulfamethoxazole 160/800 mg tablets
Each tablet contains 800 mg of trimethoprim/sulfamethoxazole.
Excipient with known effect.
Each gram **also** contains 0.90 mg of sodium benzoate. See section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Trimethoprim/sulfamethoxazole 80/400 mg tablets
White to off-white, flat, circular, bevelled-edged tablet with "MICRO" engraved on one side and the other side debossed with "COTRIM", with a break line separating the "480".

Trimethoprim/sulfamethoxazole 160/800 mg tablets
White to off-white, oval, bevelled-edged tablet, debossed with “COTRIM” on one side and scored on the other side.

The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

Trimethoprim/sulfamethoxazole is active against most strains of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic gram-positive microorganisms:
Streptococcus pneumoniae

Aerobic gram-negative microorganisms:
Escherichia coli (including susceptible enterotoxigenic strains implicated in traveler’s diarrhea)
Klebsiella species, *Enterobacter* species, *Haemophilus influenza, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Shigella flexneri, Shigella sonnei*.

Other Organisms:
Pneumocystis jiroveci.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of trimethoprim/sulfamethoxazole and other antibacterial drugs, trimethoprim/sulfamethoxazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to empiric selection of therapy.

Urinary Tract Infections
For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella species, Enterobacter species, Morganella morganii, Proteus mirabilis* and *Proteus vulgaris*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Acute Otitis Media
For the treatment of acute otitis media in paediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim offer some advantage over the use of other antimicrobial agents. To date, there is limited data on the safety of repeated use of trimethoprim/sulfamethoxazole in paediatric patients under two years of age. Trimethoprim/sulfamethoxazole is not indicated for prophylactic or prolonged administration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults
For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician trimethoprim/sulfamethoxazole offers some advantage over the use of a single antimicrobial agent.

Shigellosis
For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Pneumocystis jiroveci Pneumonia
For the treatment of documented *Pneumocystis jiroveci* pneumonia and for prophylaxis against *Pneumocystis jiroveci* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *Pneumocystis jiroveci* pneumonia.

Traveller's Diarrhoea in Adults
For the treatment of traveller’s diarrhoea due to susceptible strains of enterotoxigenic *E.coli*.

4.2 Posology and method of administration

Posology

Paediatric population
Trimethoprim/sulfamethoxazole is not recommended for use in pediatric patients less than 2 months of age.

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute Otitis Media in Children:
Adults: The usual adult dosage in the treatment of urinary tract infections is 1 trimethoprim/sulfamethoxazole 160mg /800mg (double strength) or 2 trimethoprim/sulfamethoxazole (80mg /400mg) every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Children 2 months of age or older:

Weight		Dose-every 12 hours
lb	kg	Tablets
22	10	-
44	20	1
66	30	$1^1/_2$
88	40	2 or 1 DS tablet

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15–30	½ the usual regimen
Below 15	Use not recommended

Acute Exacerbations of Chronic Bronchitis in Adults:
The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is 1 trimethoprim/sulfamethoxazole 160mg /800mg (double strength) or 2 trimethoprim/sulfamethoxazole (80mg /400mg) every 12 hours for 14 days.

Pneumocystis Jiroveci Pneumonia:
Treatment: Adults and Children:
The recommended dosage for treatment of patients with documented *Pneumocystis jiroveci* pneumonia is 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per 24 hours given in equally divided doses every 6 hours for 14 to 21 days.[1] The following table is a guideline for the upper limit of this dosage:

Weight		Dose-every 6 hours
lb	kg	Tablets
18	8	-
35	16	1
53	24	$1^1/_2$
70	32	2 or 1 DS tablet
88	40	$2^1/_2$
106	48	3 or $1^1/_2$ DS tablet
141	64	4 or 2 DS tablet
176	80	5 or $2^1/_2$ DS tablet

For the lower limit dose (75 mg/kg sulfamethoxazole and 15 mg/kg trimethoprim per 24 hours) administer 75% of the dose in the above table.

Prophylaxis:
Adults:
The recommended dosage for prophylaxis in adults is trimethoprim/sulfamethoxazole 160mg /800mg (double strength) tablet daily.

Children:
For children, the recommended dose is 750 mg/m^2/day sulfamethoxazole with 150 mg/m^2/day trimethoprim given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 1600 mg sulfamethoxazole and 320 mg trimethoprim. The following table is a guideline for the attainment of this dosage in children:

Body Surface Area (m^2)	Dose–every 12 hours (Tablets)
0.26	-
0.53	$^1/_2$
1.06	1

Traveller's Diarrhoea in Adults:
For the treatment of traveller's diarrhoea, the usual adult dosage is 1 trimethoprim/sulfamethoxazole 160mg /800mg (double strength) or 2 trimethoprim/sulfamethoxazole (80mg /400mg) 12 hours for 5 days.

Method of administration
For oral use.

4.3 Contraindications

- Hypersensitivity to the trimethoprim or sulfonamides or any of the excipients listed in section 6.1.
- in patients with a history of drug-induced immune thrombocytopenia with the use of trimethoprim and/or sulfonamides.
- patients with documented megaloblastic anaemia due to folate deficiency.
- pregnant patients and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.
- paediatric patients less than 2 months of age.

- patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

4.4 Special warnings and precautions for use

Hypersensitivity and Other Fatal Reactions
Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Sulfonamides, including sulfonamide-containing products such as sulfamethoxazole/trimethoprim, should be discontinued at the first appearance of skin rash or any sign of adverse reaction. In rare instances, a skin rash may be followed by a more severe reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and serious blood disorders. Clinical signs, such as rash, sore throat, fever, arthralgia, pallor, purpura or jaundice may be early indications of serious reactions.

Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported in association with sulfonamide treatment.

Thrombocytopenia
Sulfamethoxazole/trimethoprim-induced thrombocytopenia may be an immune-mediated disorder. Severe cases of thrombocytopenia that are fatal or life-threatening have been reported. Thrombocytopenia usually resolves within a week upon discontinuation of sulfamethoxazole-trimethoprim.

Streptococcal Infections and Rheumatic Fever
The sulfonamides should not be used for the treatment of group A β-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever.

Clostridium difficile-associated diarrhoea
Clostridium difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including trimethoprim/sulfamethoxazole, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Adjunctive treatment with Leucovorin for Pneumocystis jiroveci pneumonia
Treatment failure and excess mortality were observed when trimethoprim-sulfamethoxazole was used concomitantly with leucovorin for the treatment of HIV-positive patients with *Pneumocystis jiroveci* pneumonia in a randomized placebo-controlled trial. Co-administration of trimethoprim/sulfamethoxazole and leucovorin during treatment of *Pneumocystis jiroveci* pneumonia should be avoided.

PRECAUTIONS
Development of drug-resistant bacteria
Prescribing trimethoprim/sulfamethoxazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Folate deficiency
Trimethoprim/sulfamethoxazole should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency or kidney failure. These effects are reversible by folinic acid therapy.

Hemolysis
In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

Hypoglycemia
Cases of hypoglycemia in non-diabetic patients treated with trimethoprim/sulfamethoxazole are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of trimethoprim/sulfamethoxazole are particularly at risk.

Phenylalanine metabolism
Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restrictions.

Porphyria and Hypothyroidism
As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

Use in the Treatment of and Prophylaxis for Pneumocystis Jiroveci Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to trimethoprim/sulfamethoxazole in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with trimethoprim/sulfamethoxazole therapy in AIDS patients who are being treated for *Pneumocystis jiroveci* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of trimethoprim/sulfamethoxazole in non-AIDS patients.

The incidence of hyperkalemia appears to be increased in AIDS patients receiving trimethoprim/sulfamethoxazole. Adverse effects are generally less severe in patients receiving trimethoprim/sulfamethoxazole for prophylaxis. A history of mild intolerance to trimethoprim/sulfamethoxazole in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis. However, if a patient develops skin rash or any sign of adverse reaction, therapy with trimethoprim/sulfamethoxazole should be reevaluated.

Co-administration of trimethoprim/sulfamethoxazole and leucovorin should be avoided with *Pneumocystis jiroveci* pneumonia.

A high dosage of trimethoprim, as used in patients with *Pneumocystis jiroveci* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

Information for Patients: Patients should be counseled that antibacterial drugs including trimethoprim/sulfamethoxazole should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When trimethoprim/sulfamethoxazole are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by trimethoprim/sulfamethoxazole or other antibacterial drugs in the future.

Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Diarrhoea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests: Complete blood counts should be done frequently in patients receiving Trimethoprim/sulfamethoxazole; if a significant reduction in the count of any formed blood element is noted, trimethoprim/sulfamethoxazole should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that trimethoprim/sulfamethoxazole may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when trimethoprim/sulfamethoxazole is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed. Trimethoprim/sulfamethoxazole may inhibit the hepatic metabolism of phenytoin. Trimethoprim/sulfamethoxazole, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effects.

Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

There have been reports of marked but reversible nephrotoxicity with coadministration of trimethoprim/sulfamethoxazole and cyclosporine in renal transplant recipients.

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

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if trimethoprim/sulfamethoxazole is prescribed.

The efficacy of tricyclic antidepressants can decrease when coadministered with trimethoprim/sulfamethoxazole

Like other sulfonamide-containing drugs, trimethoprim/sulfamethoxazole potentiates the effect of oral hypoglycemics.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine.

In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin-converting enzyme inhibitor.

Drug/Laboratory Test Interactions: Trimethoprim/sulfamethoxazole, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been

conducted with trimethoprim/sulfamethoxazole.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with sulfamethoxazole and trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole and trimethoprim revealed no chromosomal abnormalities.

Pediatric Use: Trimethoprim/sulfamethoxazole is contraindicated for infants younger than 2 months of age.

Geriatric Use: Clinical studies of trimethoprim/sulfamethoxazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim 160 mg were studied in 6 geriatric subjects (mean age: 78.6 years) and 6 young healthy subjects (mean age: 29.3 years) using a non-US-approved formulation. Pharmacokinetic values for sulfamethoxazole in geriatric subjects were similar to those observed in young adult subjects. The mean renal clearance of trimethoprim was significantly lower in geriatric subjects compared with young adult subjects (19 mL/h/kg vs. 55 mL/h/kg). However, after normalizing by body weight, the apparent total body clearance of trimethoprim was on average 19% lower in geriatric subjects compared with young adult subjects.

There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, possible folate deficiency, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression, a specific decrease in platelets (with or without purpura), and hyperkalemia are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Increased digoxin blood levels can occur with concomitant trimethoprim/sulfamethoxazole therapy, especially in elderly patients. Serum digoxin levels should be monitored. Hematological changes indicative of folic acid deficiency may occur in elderly patients. These effects are reversible by folinic acid therapy. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions. The trimethoprim component of trimethoprim/sulfamethoxazole may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency or when given concomitantly with drugs known to induce hyperkalemia, such as angiotensin-converting enzyme inhibitors. Close monitoring of serum potassium is warranted in these patients. Discontinuation of trimethoprim/sulfamethoxazole treatment is recommended to help lower potassium serum levels.

Pharmacokinetics parameters for sulfamethoxazole were similar for geriatric subjects and younger adult subjects. The mean maximum serum trimethoprim concentration was higher and mean renal clearance of trimethoprim was lower in geriatric subjects compared with younger subjects.

Excipients
This medicine contains sodium benzoate which may increase jaundice in newborn babies (up to 4 weeks).

4.5 Interaction with other medicinal products and other forms of interaction
Care should be exercised when giving trimethoprim/sulfamethoxazole to patients receiving:

- ACE Inhibitors: risk of severe hyperkalaemia.
- Anaesthetics: increased risk of methaemoglobinaemia when sulphonamides are given with prilocaine.
- Antiarrhythmics: increased risk of ventricular arrhythmias with amiodarone. Plasma levels of dofetilide increased markedly by co-administration with trimethoprim/sulfamethoxazole resulting in the increase of dofetilide-induced QT prolongation and the risk of arrhythmias.
- Antibacterials: serum levels of dapsone and trimethoprim/sulfamethoxazole are possibly raised by the presence of the other. Be alert for dapsone toxicity causing methaemoglobinaemia. Increased risk of crystalluria when sulphonamides are given with methenamine. Concomitant use of trimethoprim/sulfamethoxazole and rifampicin can result in increased rifampicin serum levels and reduced plasma half-life of trimethoprim.
- Anticoagulants: effects of acenocoumarol and warfarin enhanced.
- Antidiabetics: effect of sulphonylureas enhanced.
- Antiepileptics: Trimethoprim/sulfamethoxazole prolongs the half-life of phenytoin and co-administration could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels is advisable.
- Antifolates: if considered appropriate therapy in patients receiving anti-folates, a folate supplement should be considered.
- Antimalarials: risk of megaloblastic anaemia with doses of pyrimethamine in excess of 25mg per week.
- Antivirals: plasma concentrations of lamivudine increased-avoid concomitant high dose trimethoprim/sulfamethoxazole. Concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to trimethoprim/sulfamethoxazole. Zalcitabine plasma concentrations were possibly increased by trimethoprim/sulfamethoxazole.
- Cations at physiological pH: plasma concentrations of trimethoprim and/or procainamide and/or amantadine can be increased unilaterally or bilaterally.
- Clozapine: avoid concomitant use; increased risk of fatal agranulocytosis.
- Cytotoxics: increased risk of haematological toxicity with mercaptopurine and azathioprine. Antifolate effects of methotrexate increased by trimethoprim/sulfamethoxazole (avoid concomitant use).
- Digoxin: increase in digoxin levels in a proportion of elderly patients.
- Diuretics: In elderly patients concurrently receiving diuretics, mainly thiazides, there is an increased risk of thrombocytopenia with or without purpura.
- Immunosuppressants: reversible deterioration in renal function has been observed in patients treated with trimethoprim/sulfamethoxazole and ciclosporin following renal transplantation.
- Potassium aminobenzoate: effects of sulphonamides inhibited.
- Laboratory tests- trimethoprim and sulphonamides have been reported to interfere with diagnostic tests, including serum-methotrexate and serum-plasma creatinine levels, as well as urea, urinary glucose and urobilinogen tests.

4.6 Pregnancy and lactation

Pregnancy
In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfitt and Pursell, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or sulfamethoxazole and trimethoprim. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving sulfamethoxazole and trimethoprim. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter.

Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism, trimethoprim/sulfamethoxazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Trimethoprim/sulfamethoxazole can cause neonatal haemolysis and methaemoglobinaemia when used in the third trimester, if given close to delivery kernicterus may occur due to displacement of bilirubin. Other toxicities that may be observed in the newborn include jaundice and haemolytic anaemia. The risk of kernicterus is higher in infants at increased risk of hyperbilirubinaemia, such as if the infant is ill, stressed or premature or has glucose-6-phosphate dehydrogenase deficiency.

Breastfeeding
Trimethoprim/sulfamethoxazole appears in breast milk, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus.

Fertility
No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim.

4.7 Effects on the ability to drive and use machines
As trimethoprim/sulfamethoxazole can cause dizziness, drowsiness, tinnitus, insomnia and hallucinations patients should make sure they are not affected before driving or operating machines.

4.8 Undesirable effects

The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including stevens-johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.

Very common (>1/10) Common (>1/100, <1/10) Uncommon (>1/1,000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000)

- *Infections and infestations:* monilial growths are common.
- *Blood and the lymphatic system disorders* - Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.
- *Immune system disorders* – Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.
- *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.
- *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.
- *Metabolism and nutrition disorders* – electrolyte disturbances, metabolic acidosis, hyperkalaemia and hyponatraemia especially in the elderly and with high doses.
- *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.
- *Psychiatric:* Hallucinations, depression, apathy, nervousness.
- *Endocrine:* The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.
- *Musculoskeletal disorders* - arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with trimethoprim/sulfamethoxazole, mainly in AIDS patients.
- *Respiratory, thoracic and mediastinal disorders* - cough, dyspnoea, pulmonary infiltration; indicative of hypersensitivity.
- *Hepato-biliary disorders* - jaundice, elevated hepatic transaminases, rarely hepatic necrosis and pancreatitis.
- *Skin and subcutaneous tissue disorders* - skin rashes can occur and photosensitivity, fixed drug eruptions, Henoch-Schonlein purpura, and exfoliative dermatitis have also been reported. Sulfamethoxazole: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported very rarely.
- *Renal and urinary disorders* - impaired renal function, rarely interstitial nephritis and crystalluria which can be avoided by adequate fluid intake.
- *Other* – with the higher doses used for therapy of *Pneumocystis jiroveci* (*P. carinii*) in

patients with AIDS if effects such as rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia and hyponatraemia occur stopping therapy may be necessary. If signs of bone marrow depression occur 5 to 10mg/day of calcium folinate should be given. Re-exposure of trimethoprim-sulfamethoxazole to HIV-infected patients has caused severe hypersensitivity reactions, even after a dosage interval of a few days. Also shows signs of weakness, fatigue and insomnia.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of trimethoprim-sulfamethoxazole. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- Thrombotic thrombocytopenic purpura
- Idiopathic thrombocytopenic purpura

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Adverse Drug Reaction (ADR)/ Serious Adverse Event (SAE) electronic form linked to the MCAZ database using the following link: https://primaryreporting.who-umc.org/ZW.

4.9 Overdose

Acute
The amount of a single dose of trimethoprim/sulfamethoxazole that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating sulfamethoxazole and trimethoprim.

Chronic
Use of trimethoprim/sulfamethoxazole at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 7.2.3. Sulphonamides (*including combinations with trimethoprim*).

Trimethoprim is an antibacterial. Sulfamethoxazole is a sulphonamide.

Mechanism of action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacterio stasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity in vitro between the two agents.

Trimethoprim binds to plasmodial DHFR but less tightly than to the bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times that of the corresponding bacterial enzyme.

Many common pathogenic bacteria are sensitive in vitro to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after administration of recommended doses. In common with other antibiotics, however, in vitro activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory sensitivity testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

5.2 Pharmacokinetic properties

Trimethoprim is readily absorbed from the gastrointestinal tract and peak concentrations in the circulation occur between 1 and 4 hours after a dose is taken. Trimethoprim is a weak base with a pKa of 7.4, it is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, with the lungs and kidneys showing especially high concentrations. About 50% is bound to plasma proteins. The elimination half-life is in the range of 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 10ml/min. There appears no significant difference in the elderly compared with the young patients. About 40 - 60% of a dose is excreted unchanged in the urine within 24 hours, together with metabolites. Trimethoprim is removed by haemodialysis to some extent.

Sulfamethoxazole is readily absorbed from the gastrointestinal tract and peak plasma concentrations are reached between 1 and 4 hours. Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in a variety of body fluids is of the order of 20 to 50% of the plasma concentration. About 66% is bound to plasma albumin and the plasma half-life is in the range of 9 - 11 hours. It is prolonged in patients with severe renal impairment. About 15% of sulfamethoxazole in the blood is present as the acetyl derivative. Elimination in the urine is dependent on pH. In the region 25% of a single 2g dose of sulfamethoxazole has been reported to be excreted in the urine within eight hours, around 60% being in the form of the acetyl derivative.

When trimethoprim/sulfamethoxazole is administered, plasma concentrations of trimethoprim and sulfamethoxazole are generally in the ratio of 1:20; in urine this ratio may vary from 1:1 to 1:5. About 50% of each drug is excreted in the urine within 24 hours, but a larger proportion of sulfamethoxazole appears as inactive metabolite.

5.3 Preclinical safety data
Non-clinical data with sevelamer reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Reproductive toxicology
At doses in excess of the recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium starch glycolate
Docusate sodium with sodium benzoate
Pregelatinized starch
Magnesium Stearate
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
60 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
Blister packs: The tablets are packed in PVC/PVDC-Alu blister packs.
Pack size: 10 x 10, 50 x 10, 100 x 10 tablets.

HDPE bottles: The tablets are packed in HDPE bottles closed with HDPE caps.
Pack size: 100 and 500 tablets.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
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8. MANUFACTURERS

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9. REGISTRATION DETAILS

Trimethoprim/sulfamethoxazole 80/400 mg tablets
Zimbabwe registration number: 2024/7.2.3/6545
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Trimethoprim/sulfamethoxazole 160/800 mg tablets
Zimbabwe registration number: 2024/7.2.3/6546
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF TEXT

April 2024