SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)
CO-TROX TABLETS

1. Name of the medicinal product

Co-trox Tablets (Trimethoprim B.P. 80mg, Sulphamethoxazole B.P. 400mg,)

2. Qualitative and quantitative composition

Each tablet contains:

Trimethoprim B.P.	80.00mg
Sulphamethoxazole B.P.	400.00mg,

Excipients with known effect

Nipagin (Methyl Paraben)	0.36mg
Nipasol (Propyl Paraben)	0.18mg
Gum Acacia B.P.	1.50mg
Corn Starch B.P. (Paste)	26.00mg
Corn Starch B.P. (Bulk)	48.50mg
Corn Starch B.P. (Lubricant)	15.00mg
Talcum B.P.	2.00mg
Magnesium Stearate	2.00mg
Purified Water	q.s.

For the full list of excipients see section 6.1.

3. Pharmaceutical form

Tablet

White circular shaped tablet with ‘CT/480’ inscribed on one side presented in a blister strip of 10 tablets, 100 of such blisters packed in a carton with insert & HDPE plastic securi container with red press on cap containing 1000 tablets

4. Clinical particulars

4.1 Therapeutic indications

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Co-trox (sulfamethoxazole and trimethoprim) tablets and other antibacterial drugs, Co-trox (sulfamethoxazole and trimethoprim) tablets should be used only to treat or prevent infections thatare 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 ofthe 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 pediatric patients due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when in the judgment of the physician sulfamethoxazole and trimethoprim offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of Co-trox in pediatric patients under two years of age. Co-trox is not indicated for prophylactic or prolongedadministration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults*:* For the treatment of acute exacerbations ofchronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus influenzae* when a physician deems that Co-trox could offer 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 *P. jiroveci* pneumonia in individuals who are immunosuppressed and considered to be at an increased risk of developing *P. jiroveci* pneumonia.

Traveler's Diarrhea in Adults*:* For the treatment of traveler's diarrhea due to susceptible strains ofenterotoxigenic *E. coli*.

4.2 Posology and method of administration

Posology

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute OtitisMedia in Children:

Adults: The usual adult dosage in the treatment of urinary tract infections is 2 Co-trox tablets every 12 hours for 10 to 14 days. An identical dailydosage is used for 5 days in the treatment of shigellosis.

Children: The recommended dose for children with urinary tract infections or acute otitis media is40 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	1½
88	40	2 tablet

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

Creatinine Clearance (mL/min)	Recommended Dosage
Regimen Above 30 regimen	Usual standard
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 or 2 Co-trox tablets 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.[11] The following table is a guidelinefor the upper limit of this dosage:

Weight		Dose–every 6 hours
lb	kg	Tablets
18	8	–
35	16	1
53	24	1½
70	32	2 tablet
88	40	2½
106	48	3 or tablets
141	64	4 tablets
176	80	5 tablets

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 2 Co-trox 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.[13] The following table is a guideline for the attainment of this dosage in children:

Body Surface Area	**Dose–every 12**
hours(m^2)	Tablets
0.26	–
0.53	½
1.06	1

Traveler's Diarrhea in Adults:

For the treatment of traveler's diarrhea, the usual adult dosage is 2 Co-trox

tablets every 12 hours for 5 days.

4.3 Contraindications

Co-trox is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides, in patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides, and in patients with documented megaloblastic anemia due tofolate deficiency.

Co-trox is contraindicated in pediatric patients less than 2 months of age. Co-Trox is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency whenrenal function status cannot be monitored.

4.4 Special warnings and precautions for use

Warnings

Embryofetal Toxicity

Some epidemiologic studies suggest that exposure to sulfamethoxazole/trimethoprim during pregnancy may be associated with an increased risk of congenital malformations, particularly neural tube defects, cardiovascular malformations, urinary tract defects, oral clefts, and club foot.If sulfamethoxazole/trimethoprim is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazards to the fetus.

Hypersensitivity and Other Fatal Reactions

Fatalities associated with the administration of sulfonamides, although rare, have occurred due tosevere 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 (see **PRECAUTIONS**). 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 therespiratory 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 treatment of group A □-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, willnot prevent sequelae such as rheumatic fever.

Clostridium difficile associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CO-TROX, and may range in severity from mild diarrhea to fatalcolitis. 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 berefractory 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 *Pneumocystisjiroveci* pneumonia in a randomized placebo controlled trial.[6] Co-administration of trimethoprim-sulfamethoxazole and leucovorin during treatment of *Pneumocystis jiroveci* pneumonia should beavoided.

Precautions

Development of drug resistant bacteria

Prescribing Co-trox (sulfamethoxazole and trimethoprim) tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit tothe patient and increases the risk of the development of drug-resistant bacteria.

Folate deficiency

Co-Trox 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 byfolinic acid therapy.

Hemolysis

In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction isfrequently dose-related (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Hypoglycemia

Cases of hypoglycemia in non-diabetic patients treated with Co-trox are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition orthose receiving high doses of Co-trox are particularly at risk.

Phenylalanine metabolism

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance inphenylketonuric patients on appropriate dietary restriction.

Porphyria and Hypothyroidism

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria orthyroid dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for CO-TROX to Affect Other Drugs

Trimethoprim is an inhibitor of CYP2C8 as well as OCT2 transporter. Sulfamethoxazole is an inhibitor of CYP2C9. Caution is recommended when Co-trox is co-administered with drugs thatare substrates of CYP2C8 and 2C9 or OCT2.

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increasedincidence of thrombocytopenia with purpura has been reported.

It has been reported that Co-trox may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin (a CYP2C9 substrate). This interaction should be kept in mindwhen Co-trox is given to patients already on anticoagulant therapy, and the

coagulation time should be reassessed.

Co-trox may inhibit the hepatic metabolism of phenytoin (a CYP2C9 substrate). Co-trox,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 effect.

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

There have been reports of marked but reversible nephrotoxicity with coadministration of Co-trox and cyclosporine in renal transplant recipients.

Increased digoxin blood levels can occur with concomitant Co-trox therapy, especially inelderly patients. Serum digoxin levels should be monitored.

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

Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in dosesexceeding 25 mg weekly may develop megaloblastic anemia if Co-trox is prescribed.

The efficacy of tricyclic antidepressants can decrease when coadministered with Co-trox.

Co-trox potentiates the effect of oral hypoglycemics that are metabolized by CYP2C8 (e.g.,pioglitazone, repaglinide, and rosiglitazone) or CYP2C9 (e.g., glipizide and glyburide) or eliminated renally *via* OCT2 (e.g., metformin). Additional monitoring of blood glucose may bewarranted.

In the literature, a single case of toxic delirium has been reported after concomitant intake of sulfamethoxazole/trimethoprim and amantadine (an OCT2 substrate). Cases of interactions withother OCT2 substrates, memantine and metformin, have also been reported.

In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant intake of sulfamethoxazole/trimethoprim and an angiotensin converting enzymeinhibitor.[8,9]

Drug/Laboratory Test Interactions: Co-trox, specifically the trimethoprim component, caninterfere 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 ofnormal values.
importance in pregnancy).

4.6 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Sulfamethoxazole was not carcinogenic when assessed in a 26-week tumorigenic mouse (Tg-rasH2) study at doses up to 400 mg/kg/day sulfamethoxazole; equivalent to 2.4-fold thehuman systemic exposure (at a daily dose of 800 mg sulfamethoxazole *b.i.d.*).

Mutagenesis*: In vitro* reverse mutation bacterial tests according to the standard protocol have not been performed with sulfamethoxazole and trimethoprim in combination. An *in vitro* chromosomalaberration test in human lymphocytes with sulfamethoxazole/trimethoprim was negative. In *in vitro* and *in vivo* tests in animal species, sulfamethoxazole/trimethoprim did not damage chromosomes. *In vivo* micronucleus assays were positive following oral administration of sulfamethoxazole/trimethoprim. Observations of leukocytes obtained from patients treated withsulfamethoxazole and trimethoprim revealed no chromosomal abnormalities.

Sulfamethoxazole alone was positive in an *in vitro* reverse mutation bacterial assay and in *in vitro* micronucleus assays using cultured human lymphocytes.

Trimethoprim alone was negative in *in vitro* reverse mutation bacterial assays and in *in vitro* chromosomal aberration assays with Chinese Hamster ovary or lung cells with or without S9 activation. In *in vitro* Comet, micronucleus and chromosomal damage assays using cultured humanlymphocytes, trimethoprim was positive. In mice following oral administration of trimethoprim, noDNA damage in Comet assays of liver, kidney, lung, spleen, or bone marrow was recorded.

Impairment of 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/daytrimethoprim, doses roughly two times the recommended human daily dose on a body surface areabasis.

Pregnancy:
While there are no large, well-controlled studies on the use of sulfamethoxazole and trimethoprim in pregnant women, Brumfitt and Pursell,[10] 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 receivedplacebo and 3.3% (4 of 120) in those receiving sulfamethoxazole and trimethoprim. There were noabnormalities 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, Co-Trox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Pregnancy

Category D.Human Data:

While there are no large prospective, well controlled studies in pregnant women and their babies, some retrospective epidemiologic studies suggest an association between first trimester exposure to sulfamethoxazole/trimethoprim with an increased risk of congenital malformations, particularlyneural tube defects, cardiovascular abnormalities, urinary tract defects, oral clefts, and club foot. These studies, however, were limited by the small number of exposed cases and the lack of adjustment for multiple statistical comparisons and confounders. These studies are further limited by recall, selection, and information biases, and by limited generalizability of their findings.

Lastly, outcome measures varied between studies, limiting cross-study comparisons. Alternatively,other epidemiologic studies did not detect statistically significant associations between sulfamethoxazole/trimethoprim exposure and specific malformations.

Animal Data:
In rats, oral doses of either 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palates. These doses are approximately 5 and 6 timesthe recommended human total daily dose on a body surface area basis. 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 some rabbit studies, an overall increase in fetal loss (dead and resorbed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose basedon body surface area.

Nonteratogenic Effects: See **CONTRAINDICATIONS** section.

Nursing Mothers: Levels of trimethoprim/sulfamethoxazole in breast milk are approximately 2–5% of the recommended daily dose for infants over 2 months of age. Caution should be exercisedwhen CO-TROX is administered to a nursing woman, especially when breastfeeding, jaundiced, ill, stressed, or premature infants because of the potential risk of bilirubin displacement and kernicterus.

4.7 Effects on ability to drive and use machines

None known

4.8 ADVERSE REACTIONS

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 (SEE WARNINGS SECTION).

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia,hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.

Allergic Reactions: 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 skineruptions, 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 ofserum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxicnephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.

Metabolic and Nutritional: Hyperkalemia, hyponatremia (see **PRECAUTIONS: *ElectrolyteAbnormalities*).**

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 withthese agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reportedwith CO-TROX, mainly in AIDS patients.

Respiratory: Cough, shortness of breath and pulmonary infiltrates (see **WARNINGS**).

Miscellaneous: Weakness, fatigue, insomnia.

4.9 Overdose

Acute: The amount of a single dose of Co-trox 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 a 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 ineliminating sulfamethoxazole and trimethoprim.

Chronic: Use of Co-trox at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. Ifsigns 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

Clinical Pharmacology

Co-trox is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. Sulfamethoxazole is metabolized in humansto at least 5 metabolites: the N_4-acetyl-, N_4-hydroxy-, 5-methylhydroxy-, N_4-acetyl-

5-methylhydroxy- sulfamethoxazole metabolites, and an N-glucuronide conjugate. The formulation of N_4-hydroxy metabolite is mediated *via* CYP2C9.

Trimethoprim is metabolized *in vitro* to 11 different metabolites, of which, five are glutathione adducts and six are oxidative metabolites, including the major metabolites, 1- and 3-oxides and the3- and 4-hydroxy derivatives.

The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeuticallyactive forms.

In vitro studies suggest that trimethoprim is a substrate of P-glycoprotein, OCT1 and OCT2, andthat sulfamethoxazole is not a substrate of P-glycoprotein.

Approximately 70% of sulfamethoxazole and 44% of trimethoprim are bound to plasma proteins.The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see **DOSAGE AND ADMINISTRATION** section). Detectable amounts of sulfamethoxazole and trimethoprim are present in the blood 24 hours after drug administration. During administration of 800 mg sulfamethoxazole and 160 mg trimethoprim b.i.d., the mean steady-state plasma concentration of trimethoprim was 1.72 µg/mL. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 µg/mL and 68.0 µg/mL, respectively. These steady-state levels were achieved after three days of drug administration.[1] Excretion of sulfamethoxazole and trimethoprimis primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of sulfamethoxazole and trimethoprim is 84.5% for total sulfonamideand 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free

sulfamethoxazole, with the remaining as N_4-acetylated metabolite.[2] When administered together assulfamethoxazole and trimethoprim, neither sulfamethoxazole nor trimethoprim affects the urinaryexcretion pattern of the other.

Both sulfamethoxazole and trimethoprim distribute to sputum, vaginal fluid and middle ear fluid;trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk.

Geriatric Pharmacokinetics: The pharmacokinetics of sulfamethoxazole 800 mg and trimethoprim160 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 subjectscompared with young adult subjects.[3]

Microbiology

Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para- aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid fromdihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with both sulfamethoxazole and trimethoprim in combination than with either sulfamethoxazole ortrimethoprim alone.

Sulfamethoxazole and trimethoprim have been shown to be active against most strains of thefollowing microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

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
influenzae
Morganella
morganii
Proteus
mirabilis
Proteus
vulgaris
Shigella
flexneri
Shigella
sonnei

6. Pharmaceutical particulars

6.1 List of excipients

Nipagin (Methyl Paraben)	0.36mg
Nipasol (Propyl Paraben)	0.18mg
Gum Acacia B.P.	1.50mg
Corn Starch B.P. (Paste)	26.00mg
Corn Starch B.P. (Bulk)	48.50mg
Corn Starch B.P. (Lubricant)	15.00mg
Talcum B.P.	2.00mg
Magnesium Stearate	2.00mg
Purified Water	q.s.

6.2 Incompatibilities

None known

6.3 Shelf life

3 years for tablets in polypropylene or polyethylene containers.
3 years for tablets in blister strip packs .

6.4 Special precautions for storage

Store in the original package in order to protect from light

Do not store above 30°C

6.5 Nature and contents of container

White HDPE plastic securi container with red press on cap containing 1000 tablets and blister strips of 100 x 10 tablets per carton

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Vitabiotics Nigeria Limited
35, Mobolaji Johnson Avenue,
Oregun Industrial Estate,
Ikeja, Lagos,
Nigeria.