1. NAME OF THE MEDICINAL PRODUCT
COTRIKRIS 480 CAPLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains**:**
Sulphamethoxazole B.P----------400mg
Trimethoprim B.P----------80mg
Excipients----------Q.S

Excipients with known effect:
Maize Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Sodium Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Tablet
Round shaped, White color, uncoated tablet one side middle line other side embossed with COTRIKRIS 480.

4. Clinical particulars

4.1 Therapeutic indications

Co-Trimoxazole tablets are indicated in adults and children over 12 years for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

• Treatment and prevention of *Pneumocystis jirovecii* pneumonitis or " PJP" .

• Treatment and prophylaxis of toxoplasmosis.

• Treatment of nocardiosis.

The following infections may be treated with Co-Trimoxazole where there is bacterial evidence of sensitivity to Co-Trimoxazole and good reason to prefer the combination of antibiotics in Co-Trimoxazole to a single antibiotic:

• Acute uncomplicated urinary tract infection.

• Acute otitis media.

• Acute exacerbation of chronic bronchitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Standard dosage recommendations for acute infections

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days therapy, the patient should be reassessed.

Adults and children over 12 years:

STANDARD DOSAGE: 2 tablets every 12 hours

The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses.

As an alternative to Standard Dosage for acute uncomplicated lower urinary tract infections, short-term therapy of 1 to 3 days duration has been shown to be effective.

Elderly patients:

See Special Warnings and Precautions for Use (Section 4.4). Unless otherwise specified standard dosage applies.

Impaired hepatic function:

No data are available relating to dosage in patients with impaired hepatic function.

Impaired renal function:

Dosage recommendation*:*

Adults and children over 12 years:

Creatinine Clearance (ml/min)	**Recommended Dosage**
>30	2 tablets every 12 hours
15 to 30	1 tablet every 12 hours
<15	Not recommended

No information is available for children aged 12 years and under with renal failure. See section 5.2 for the pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ.

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of Co-Trimoxazole. If the concentration of total sulfamethoxazole exceeds 150 microgram/ml then treatment should be interrupted until the value falls below 120 microgram/ml.

Pneumocystis jirovecii pneumonitis

Treatment - Adults and children over 12 years:

A higher dosage is recommended, using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of **greater than or equal to** 5 microgram/ml (verified in patients receiving 1-hour infusions of intravenous Co-Trimoxazole). (See 4.8 Undesirable Effects).

Prevention - Adults and children over 12 years:

The following dose schedules may be used:

160 mg trimethoprim/800 mg sulfamethoxazole daily 7 days per week.

160 mg trimethoprim/800 mg sulfamethoxazole three times per week on alternate days.

320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times per week on alternate days.

The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day, given in two equally divided doses.

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Nocardiosis - Adults (>18 years old):

There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used.

Toxoplasmosis:

There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience. For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jirovecii* pneumonitis may be appropriate.

Method of administration:

Oral.

It may be preferable to take Co-Trimoxazole with some food or drink to minimise the possibility of gastrointestinal disturbances.

Method of administration

Tablet for oral administration

4.3 Contraindications

- Hypersensitivity to the active substance(s) sulphonamides, trimethoprim, co-trimoxazole or to any of the excipients listed in section 6.1.
- Co-Trimoxazole should not be given to patients with severe impairment of liver function.
- Contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Co-trimoxazole should not be given to infants during the first 6 weeks of life.
- Co-Trimoxazole should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- Co-Trimoxazole should not be given to patients with acute porphyria.

4.4 Special warnings and precautions for use

Life threatening adverse reactions

Fatalities, although very rare, have occurred due to severe reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

• Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of Co-Trimoxazole.

• Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS, TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, Co-Trimoxazole treatment should be discontinued (see section 4.8).

• The best results in managing SJS, TEN and DRESS come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

• If the patient has developed SJS, TEN and DRESS with the use of Co-Trimoxazole, Co-Trimoxazole must not be re-started in this patient at any time.

• At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of Co-Trimoxazole alone or in combination with other drugs.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary

infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Elderly patients

Particular care is *always* advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other drugs.

Patients with renal impairment

For patients with known renal impairment special measures should be adopted (see section 4.2).

Urinary output

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Folate

Regular monthly blood counts are advisable when Co-Trimoxazole is given for long periods, or to folate deficient patients or to the elderly; since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. Supplementation with folinic acid

may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

Patients with glucose-6-phosphate dehydrogenase deficiency

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.

Patients with severe atopy or bronchial asthma

Co-Trimoxazole should be given with caution to patients with severe atopy or bronchial asthma.

Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci

Co-Trimoxazole should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic *streptococci*; eradication of these organisms from the oropharynx is less effective than with penicillin.

Phenylalanine metabolism

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

Patients with or at risk of porphyria

he administration of Co-Trimoxazole to patients known or suspected to be at risk of porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Patients with hyperkalaemia and hyponatraemia

Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

Metabolic acidosis

Co-Trimoxazole has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Patients with serious haematological disorders

Except under careful supervision Co-Trimoxazole should not be given to patients with serious haematological disorders (see 4.8 Undesirable Effects). Co-Trimoxazole has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral

blood.

The combination of antibiotics in Co-Trimoxazole should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interaction with other medicinal products and other forms of interaction

Its use is advised against in people being concomitantly treated with:

ACE inhibitors like captopril, enalapril, lisinopril, perindopril, and ramipril due to the potential for additive hyperkalaemic effects

Prilocaine — additive risk of methaemoglobinaemia

Antiarrhythmics like amiodarone (increased risk of ventricular arrhythmias) and dofetilide (increased risk of QT interval prolongation)

Antibacterials like dapsone (increases plasma levels of both drugs), methenamine (increased risk of crystalluria) and rifampicin (as it may lead to an increased plasma level of rifampicin and lower plasma levels of trimethoprim)

Anticoagulants like warfarin and acenocoumarol — anticoagulant effects of either drug is potentiated by this combination

Sulfonylureas — effects enhanced

Phenytoin, half-life of phenytoin is increased

Antifolates like pyrimethamine, proguanil and methotrexate increase the risk of associated side effects like bone marrow toxicity, folic acid supplementation should be considered. A significant risk of megaloblastic anaemia exists with doses of pyrimethamine in excess of 25 mg/wk.

Antivirals, more specifically, lamivudine (increased plasma concentrations of lamivudine), zalcitabine (increased plasma concentrations of zalcitabine) and zidovudine (increased risk of haematological reactions)

Procainamide and/or amantadine may have their plasma concentrations increased bilaterally or unilaterally.

Clozapine and other antipsychotics — increased risk of haematological side effects

Nucleoside analogue antineoplastics like azathioprine and mercaptopurine — increased risk of haematological toxicity

Digoxin — increase in digoxin levels in a proportion of elderly patients

Diuretics — elderly patients receiving thiazide diuretics are at a heightened risk for developing thrombocytopaenia while on co-trimoxazole

Ciclosporin — patients who have received a kidney transplant and are receiving co-trimoxazole and ciclosporin concomitantly are at an increased risk of having a reversible deterioration in their kidney function.

Spironolactone — concurrent use can increase the likelihood of hyperkalemia, especially in the elderly. The trimethoprim portion acts to prevent potassium excretion in the distal tubule of the nephron.[23]

Potassium aminobenzoate — effects of sulfonamides (like Sulfamethoxazole) inhibited.

Laboratory tests — trimethoprim and sulfonamides have been reported to interfere with diagnostic tests, including serum-methotrexate and elevated serum creatinine levels,[24] also urea, urinary glucose and urobilinogen tests.

4.6 Pregnancy and Lactation

Its use during pregnancy is contraindicated, although it has been placed in Australian pregnancy category C. Its use during the first trimester (during organogenesis) and 12 weeks prior to pregnancy has been associated with an increased risk of congenital malformations, especially malformations associated with maternal folic acid deficiency (which is most likely related to the mechanism of action of co-trimoxazole) such as neural tube defects such as spina bifida, cardiovascular malformations (e.g. Ebstein's anomaly), urinary tract defects, oral clefts, and club foot in epidemiological studies. Its use later on during pregnancy also increases the risk of preterm labour (odds ratio: 1.51) and low birth weight (odds ratio: 1.67). Animal studies have yielded similarly discouraging results.

It appears to be safe for use during breastfeeding as long as the baby is healthy

Babies Its use in those less than 2 months of age is not recommended due to the risk of adverse side effects.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of Co-Trimoxazole on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the

pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of Co-Trimoxazole should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency.

Tabulated list of adverse reaction

The following convention has been used for the classification of adverse events in terms of frequency: Very common ≥ 1/10, common ≥ 1/100 and <1/10, uncommon ≥ 1/1000 and <1/100, rare ≥ 1/10,000 and <1/1000, very rare <1/10,000, not known - cannot be estimated from the available data

System Organ Class	Frequency	Side effects
Infections and infestations	Common	Overgrowth fungal.
	Very rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Very rare	Leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anaemia megaloblastic, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients.
Immune system disorders	Very rare	Serum sickness, anaphylactic reaction, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus. Severe hypersensitivity reactions associated with PJP*, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.
Metabolism and nutrition disorders	Very common	Hyperkalaemia.
sychiatric disorders	Very rare	Depression, hallucination.
	Not known	Psychotic disorder.
Nervous system disorders	Common	Headache.
	Very rare	Meningitis aseptic *, convulsions, neuropathy peripheral, ataxia, dizziness.
Ear and labyrinth disorders	Very rare	Vertigo, tinnitus
Eye disorders	Very rare	Uveitis.
Respiratory, thoracic and mediastinal disorders	Very rare	Cough *, dyspnoea*, lung infiltration*.

Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, pancreatitis.
patobiliary disorders	Very rare	Transaminases increased, blood bilirubin increased, cholestatic jaundice, hepatic necrosis.
Skin and subcutaneous tissue disorders*	Common	Rash.
	Very rare	Photosensitivity reaction, angiodema, dermatitis exfoliative, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) *, toxic epidermal necrolysis (TEN) *. Acute generalised exanthematous pustulosis (AGEP).
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), Drug reaction with eosinophilia and systemic symptoms (DRESS)*
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia, myalgia.
Renal and urinary disorders	Very rare	Renal impairment (sometimes reported as renal failure), tubulointerstitial nephritis and uveitis syndrome, renal tubular acidosis

* see description of selected adverse reactions

Description of selected adverse reactions

Aseptic meningitis

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

Pulmonary hypersensitivity reactions

Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Hepatobiliary disorders

Jaundice cholestatic and hepatic necrosis may be fatal.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening (see section 4.4).

As with any other drug, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the drug. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed (see section 4.4).

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management

Severe hypersensitivity reactions, rash, pyrexia, neutropenia, thrombocytopenia, hepatic enzyme increased, hyperkalaemia, hyponatraemia, rhabdomyolysis.

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. Severe hypersensitivity reactions have been reported in PJP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days.

Rhabdomyolysis has been reported in HIV positive patients receiving trimethoprim-sulfamethoxazole for prophylaxis or treatment of PJP.

4.9 Overdose

Likely signs of toxicity include:

- Nausea
- Vomiting
- Dizziness
- Headache
- Mental depression
- Confusion
- Thrombocytopenia
- Uremia
- Bone marrow depression
- Loss of appetite
- Colic
- Drowsiness
- Unconsciousness

The recommended treatment for overdose includes:[3]

- Administration of activated charcoal
- Stomach pumping
- General supportive measures
- Haemodialysis, which is moderately effective in clearing co-trimoxazole from the plasma.
- Calcium folinate treatment in cases of blood dyscrasias
- Forcing oral fluids

Alkalinisation of the urine may reduce the toxicity of sulfamethoxazole, but it may increase the toxic effects of trimethoprim

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterials for systemic use - Sulfonamides and trimethoprim, incl. derivatives; ATC code: J01EE01

Mechanism of Action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. 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 less than for the corresponding bacterial enzyme.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out- compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-

mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

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

Many common pathogenic bacteria are susceptible *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the 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 susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

Susceptibility testing breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing) limits

Enterobacteriaceae: S≤ 2 R> 4

S. maltophilia: S≤ 4 R> 4

Acinetobacter: S≤ 2 R> 4

Staphylococcus: S≤ 2 R> 4

Enterococcus: S≤ 0.032 R> 1

Streptococcus ABCG: S≤ 1 R> 2

Streptococcus pneumoniae: S≤ 1 R> 2

Hemophilus influenza: S≤ 0.5 R> 1

Moraxella catarrhalis: S≤ 0.5 R >1

Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant. *These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.

Trimethoprim: sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration.

Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

Commonly susceptible species:
Gram-positive aerobes: *Staphylococcus aureus* *Staphylococcus saprophyticus*

Streptococcus pyogenes
Gram-negative aerobes: *Enterobacter cloacae* *Haemophilus influenzae* *Klebsiella oxytoca* *Moraxella catarrhalis* *Salmonella* spp. *Stenotrophomonas maltophilia*
Yersinia spp.
Species for which acquired resistance may be a problem:
Gram-positive aerobes: Enterococcus faecalis Enterococcus faecium Nocardia spp. Staphylococcus epidermidis Streptococcus pneumoniae
Gram-negative aerobes: Citrobacter spp. Enterobacter aerogenes Escherichia coli Klebsiella pneumoniae Klebsiella pneumonia Proteus mirabilis
Proteus vulgaris Providencia spp. Serratia marcesans
Inherently resistant organisms:
Gram-negative aerobes: Pseudomonas aeruginosa Shigella spp. Vibrio cholera

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound.

Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 66% of sulfamethoxazole in the plasma is protein bound. The concentration of active sulfamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid,

sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulfamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in elderly patients compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely.

The half-life of sulfamethoxazole in man is approximately 9 to 11 hours in the presence of normal renal function.

There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25 ml /minute.

The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of Co-Trimoxazole should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulfamethoxazole.

Elderly patients

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

Paediatric population

See special dosage regimen (see section 4.2).

5.3 Preclinical safety data

At doses in excess of 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

Maize Starch, Microcrystalline Cellulose, Sodium Starch Glycolate, Sodium Methyl Paraben, Propyl Paraben, Magnesium Stearate, Purified Talc

6.2 Incompatibilities

See section 4.2

6.3 Shelf-life

Blisters: 36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

The tablets are packed in Alu/PVC blister and inserted in a carton. Pack sizes: 10X10 Tablets

6.6 Special precautions for disposal and other handling

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. Functional inhibition of the renal tubular secretion of creatinine may product a spurious fall in the estimated rate of creatinine clearance.

7. Manufactured by:

Krishat Pharma Industries Limited
KM 15, Lagos-Ibadan Expressway, Ibadan, Oyo State,
NIGERIA.
Email: info@krishatpharma.com

Company contacts details

operations@krishatpharma.com