1. NAME OF THE MEDICINAL PRODUCT
Avrotrim Paediatric Dispersible Tablet 20/100mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: 20mg Trimethoprim BP and 100mg Sulfamethoxazole BP.
Excipients:
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
White uncoated tablets.
White, circular, biconvex uncoated tablets, plain on one face and embossed with identifying letters on either side of a central division line on the reverse.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Avrotrim Paediatric Dispersible tablets are indicated for the treatment of the following infections when owing to sensitive organisms (see section 5.1):
- Treatment and prevention of *Pneumocystis jiroveci* pneumonitis.
- Treatment and prophylaxis of toxoplasmosis
- Treatment of nocardiosis and melioidosis.

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

Avrotrim Paediatric Dispersible tablets may also be useful for other infections: middle ear infections, lung infections in patients with chronic bronchitis, infections of the urinary system (bladder, kidneys), infectious diarrhea, treatment of toxoplasmosis, injury to the genital and / or perianal area (inguinal granuloma or donovanosis) and brucellosis.

4.2 Posology and method of administration
Posology
Standard dose

- *Adults and children over 12 years* : it is recommended to use Avrotrim Tablet 80mg / 400mg tablets or Avrotrim DS Caplet 160mg / 800mg tablets.
- *Infants and children under 12 years of age* (doses approximate 6 mg trimethoprim / 30 mg sulfamethoxazole / kg / 24 hours):
    - *6 weeks to 5 months:* 1 tablet of Avrotrim Paediatric Dispersible tablet every 12 hours.
    - *6 months to 5 years:* 2 tablets of Avrotrim Paediatric Dispersible tablet every 12 hours.
    - *6 to 12 years:* 4 tablets of Avrotrim Paediatric Dispersible tablet every 12 hours.

If after 7 days of treatment there is no clinical improvement, the patient will be reevaluated.

As an alternative to the standard dose, a treatment of 5mg trimethoprim / 2 mg sulfamethoxazole / kg in children every 12 hours for three days is appropriate for the treatment of infections of the urinary and infectious diarrhea.

Special dosages

Patients with renal failure :
Information is not available for children under 12 years of age

Pneumocystis *jiroveci* (*P. carinii*)

Treatment

Children: 20mg of trimethoprim and 100mg of sulfamethoxazole / kg / day, in two or more divided doses, for two weeks.

Prophylaxis (prevention)

Children
The following dosage regimens can be used:

- *6 weeks to 5 months* : it is recommended to use 1 tablet Avrotrim Paediatric Dispersible tablet twice a day, 7 days a week, or 3 times per week on alternate days or 3 times a week on consecutive days.
- *6 months to 5 years* : 2 tablets of Avrotrim Paediatric Dispersible tablet twice a day, 7 days a week, or 3 times a week on alternate days or 3 times a week on consecutive days.
- *6 to 12 years* : 4 tablets of Avrotrim x Paediatric Dispersible tablet twice a day, 7 days a day week, or 3 times a week on alternate days or 3 times a week on consecutive days.

The doses indicated above can also be administered in a single dose, 3 times a week on consecutive days. The daily dose administered in one day of treatment approximates 150 mg of trimethoprim / m^2 / day and 750 mg of sulfamethoxazole / m^2 / day. The total daily dose should not exceed 320 mg of trimethoprim and 1,600 mg of sulfamethoxazole (16 tablets of Avrotrim Paediatric Dispersible tablets).

Toxoplasmosis

Primary prophylaxis (primary prevention)

Children : 150 mg trimethoprim / m^2 body surface area / day and 750 mg sulfamethoxazole / m^2 body surface area / day in two doses. The total daily dose should not exceed 320 mg of trimethoprim and 1,600 mg of sulfamethoxazole (16 tablets of Avrotrim Paediatric Dispersible tablets)..

Treatment

Children : no data available

Brucellosis

Adults and children older than 8 years : it is recommended to use Avrotrim tablets or Avrotrim DS Caplet

Children under 8 years of age (in this age group it is considered first choice treatment):
10 mg / kg / day of trimethoprim and 50 mg / kg / day of sulfamethoxazole divided into two doses (ie, 5 mg / kg trimethoprim / 25 mg / kg sulfamethoxazole / 12 hours) for 6 weeks.

Melioidosis
8 mg / kg trimethoprim and 40 mg / kg sulfamethoxazole (maximum 320 mg trimethoprim / 1,600 mg sulfamethoxazole) every 12 hours for 3-6 months.

If you take more Avrotrim Pediatric Dispersible tablets than you should

Overdose symptoms include: nausea, vomiting, dizziness and confusion.
In acute overdose with trimethoprim, bone marrow depression has been observed.
In case the vomit does not appear, it must be induced. Gastric lavage should be performed. Depending on the state of renal function, fluid administration is recommended if urine elimination is low.
Both substances, trimethoprim and sulfamethoxazole are dialysable by hemodialysis.Peritoneal dialysis is not effective.

If you forget to take Avrotrim Pediatric Dispersible tablets

Do not take a double dose to make up for forgotten doses.

Method of administration:
Oral.
Add a tablet to a little water (5 to 10ml), Mix water and tablet well If your child is between 6 to 11 months, give them the medicine with a spoon.
If your child is between 12 months to 12 years, give them the medicine in a cup.
It may be preferable to take Co-Trimoxazole with some food or drink to minimize the possibility of gastrointestinal disturbances.

4.3 Contraindications
• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Contra-indicated in patients showing marked liver parenchymal damage.
• 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
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) and 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, TEN or DRESS is within the first weeks of treatment.
- If symptoms or signs of SJS, TEN or DRESS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, co-trimoxazole treatment should be discontinued (see 4.8 Undesirable Effects).
- 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 or TEN with the use of co-trimoxazole, co-trimoxazole must not be re-started in this patient at any time.
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.
For patients with known renal impairment special measures should be adopted (see section 4.2).

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulfonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.
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. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity.
In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.
Co-trimoxazole should be given with caution to patients with severe allergy or bronchial asthma.
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.
Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.
The administration of co-trimoxazole to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulfonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.
Close monitoring of serum potassium is warranted in patients at risk of hyperkalaemia.
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.
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
Interaction with laboratory tests: 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%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.
Zidovudine: in some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.
Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.
Rifampicin: concurrent use of rifampicin and Co-Trimoxazole results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.
When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.
Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.
Pyrimethamine: occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co- trimoxazole be prescribed concurrently.
Warfarin: co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with Co-Trimoxazole is advisable.

Phenytoin: co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.
Digoxin: concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.
Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If Co-Trimoxazole is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4).
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.
Lamivudine: administration of trimethoprim /sulfamethoxazole 160 mg/800 mg (co- trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.
Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.
Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulfamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.
Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.
Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulfamethoxazole. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.
Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.
Azathioprine: There are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulfamethoxazole, resulting in serious haematological abnormalities.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are not any adequate data from the use of co-trimoxazole in pregnant women. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.
Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see 5.3 Preclinical Safety Data).
Co-trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if co-trimoxazole is used in pregnancy.
Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when co-trimoxazole is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6-phosphate dehydrogenase deficiency.

Lactation
The components of co-trimoxazole (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of co-trimoxazole should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of co-trimoxazole should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

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 patient's ability to operate machinery.

4.8 Undesirable effects
Like all medicines, Avrotrim Pediatric Dispersible tablets can cause side effects, although not everybody gets them.

The described adverse effects of Avrotrim Pediatric Dispersible tablets are classified in order of frequency and are as follows:

- Very common (*may affect more than 1 in 10 people*): hyperkalemia (high potassium level).

- Common (*may affect up to 1 in 10 people*): candidiasis (overgrowth of candida fungus), headache, nausea, diarrhea and skin rashes.

- Uncommon (*may affect up to 1 in 100 people*): vomiting.

- Rare (*may affect up to 1 in 1,000 people*): hypersensitivity reactions with eosinophilia (increase in a certain type of white blood cells) and systemic symptoms.

- Very rare (*may affect up to 1 in 10,000 people*): leukopenia (decrease in the number of white blood cells), neutropenia (decrease in the number of a certain type of white blood cells), thrombocytopenia (decrease in the number of platelets), agranulocytosis (decrease in the number of a certain type of white blood cell), anemia megaloblastic (decrease in the number of red blood cells and increase in their size), aplastic anemia (failure of the marrow to produce different types of cells), hemolytic anemia (characterized by an insufficient number of red blood cells), methemoglobinemia (inability to hemoglobin to transport oxygen), eosinophilia (abnormally high amount of a certain type of white blood cells), purpura (reddish patches on the skin), hemolysis (rupture of red blood cells) in certain susceptible patients deficient in G-6-PD .
Serum disease (hypersensitivity reaction similar to an allergy), anaphylaxis (severe allergic reaction), allergic myocarditis (allergic reaction affecting the heart), angioedema (fluid retention in the skin and mucous membranes), fever, allergic vasculitis resembling purpura of Schoenlein-Henoch (inflammation that affects especially the small veins), periarteritis nodosa (vascular disease), systemic lupus erythematosus (immune-type disease).
Hypoglycemia (decreased blood glucose), hyponatremia (decreased blood sodium), anorexia (metabolic disorder). Depression, hallucinations, aseptic meningitis, seizures, peripheral neuritis (injury and deterioration of peripheral nerves), ataxia (loss of coordination), vertigo, tinnitus (ringing in the ear), dizziness, cough, shortness of breath, pulmonary infiltrates, glossitis (inflammation of the tongue), stomatitis (lesions in the mouth), pseudomembranous colitis (inflammation of the colon), pancreatitis (inflammation of the pancreas), hepatobiliary disorders (impaired liver function), photosensitivity (skin reaction caused by the interaction with light)), exfoliative dermatitis (severe inflammation of the entire surface of the skin), fixed drug eruption (allergic reaction), erythema multiforme (allergic reaction that affects the skin), arthralgia (joint pain), myalgia (muscle pain), impaired renal function, uveitis (inflammation of the eye). Skin rashes may appear that can threaten the patient's life (Stevens Johnson syndrome, toxic epidermal necrolysis) (see section 2: Warnings and precautions).

- Frequency not known (cannot be estimated from the available data): In

In some cases, skin rashes that may threaten the patient's life have been observed (acute febrile neutrophilic dermatosis or sweet syndrome) (see section 2: Warnings and precautions).

- Very rare side effects (*may affect up to 1 in 10,000 people*) related to the treatment of *Pneumocystis jiroveci pneumonitis* (*P.carinii*): severe hypersensitivity reactions, rashes, fever, neutropenia (decrease in the number of a certain type of blood cells) whites), thrombocytopenia (decreased number of platelets), increased liver enzymes, hyperkalemia (high potassium level), hyponatremia (decreased blood sodium) and rhabdomyolysis (destruction or muscle inflammation that leads to severe muscle pain and weakness) .
If you experience side effects, consult your doctor or pharmacist, even if they are side effects not listed in this leaflet.

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.
The majority of haematological changes are mild and reversible when treatment is stopped. Most of the changes cause no clinical symptoms although they may become severe in isolated cases, especially in the elderly, in those with hepatic or renal dysfunction or in those with poor folate status. Fatalities have been recorded in at-risk patients and these patients should be observed carefully (see 4.3 Contra-indications). Close supervision is recommended when co-trimoxazole is used in elderly patients or in patients taking high doses of co-trimoxazole as these patients may be more susceptible to hyperkalaemia and hyponatraemia.

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) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management.
Very rare: 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. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). 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
Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.
If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependent on the status of renal function, administration of fluids is recommended if urine output is low.
Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives;
ATC code: J01EE01

Mode of Action

Co-trimoxazole is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) 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.

Breakpoints

EUCAST

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).
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, 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.
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

Reproductive toxicology: 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

Povidone K.30
Crospovidone
Avicel PH 101
Aspartame
Dry Tutti Frutti Flavour
Magnesium Stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C in a dry place.
Protect from light.

6.5 Nature and contents of container

The product is supplied in Alu/PVC blister packs in cartons.
Pack size: 20's, 100's and 1000's.

6.6 Special precautions for disposal and other handling

Not applicable.

7. APPLICANT/MANUFACTURER

Avro Pharma Limited
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