Name of the medicinal product

EMTRIM DSPERSIBLE TABLET 20/100MG

2. Qualitative and quantitative composition

Each tablet contains: Trimethoprim BP 20mg /Sulfamethoxazole BP 100MG

3. Pharmaceutical form

White uncoated tablets,with emtrim embossed on one side of the tablet.

4. Clinical particulars

4.1 Therapeutic indications

Emtrim Tablet is indicated in children below 12 years.

Emtrim Tablet is 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.

The following infections may be treated with Emtrim Tablet where there is bacterial evidence of sensitivity to Emtrim Tablet and good reason to prefer the combination of antibiotics in Emtrim Tablet 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

Method of administration: oral

It may be preferable to take Emtrim Tablet with some food or drink to minimise the possibility of gastrointestinal disturbances.

Standard dosage recommendations for acute infections

Adults

Tablets	2 every 12 hours

This dosage for children is equivalent to approximatly 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day.

Paediatric population (over 12 years)

The schedules for children are according to the child's age and body weight provided in the table below:

12 years and over OR Weighing 53kg or above	Two tablets in a morning and two tablets in an evening

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.

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.

The elderly:

See Special Warnings and Precautions for Use. Unless otherwise specified standard dosage applies.

Impaired hepatic function:

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

Special Dosage Recommendations

(Standard dosage applies unless otherwise specified)

Where dosage is expressed as "tablets" this refers to the adult tablet, i.e. 80 mg Trimethoprim BP and 400 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Impaired renal function:

Adults and children over 12 years (no information is available for children under 12 years of age):

Creatinine Clearance (ml/min)	Recommended Dosage
>30	STANDARD DOSAGE
15 to 30	Half the STANDARD DOSAGE
<15	Not recommended

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 jiroveci pneumonitis:

Treatment: 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: 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.

Children:

The following dose schedules may be used for the duration of the period at risk (see Standard dosage recommendations for acute infections subsection of 4.2):

- Standard dosage taken in two divided doses, seven days per week

- Standard dosage taken in two divided doses, three times per week on alternate days

- Standard dosage taken in two divided doses, three times per week on consecutive days

- Standard dosage taken as a single dose, three times per week on consecutive days

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.

Emtrim Tabletshould not be given to infants during the first 6 weeks of life.

Nocardiosis: 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 jiroveci* pneumonitis may be appropriate.

4.3 Contraindications

• Emtrim Tablet should not be given to patients with a history of hypersensitivity to sulfonamides, trimethoprim, Emtrim Tablet or any excipients of co-trimoxazole.

• 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.

• Emtrim Tabletshould not be given to infants during the first 6 weeks of life.

4.4 Special warnings and precautions for use

Fatalities, although very rare, have occurred due to severe reactions including 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, Emtrim Tablettreatment 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, Emtrim Tabletmust 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.

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 Emtrim Tablet 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.

Emtrim Tabletshould be given with caution to patients with severe allergy or bronchial asthma.

Emtrim Tabletshould 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 Emtrim Tabletto 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.

Except under careful supervision Emtrim Tabletshould not be given to patients with serious haematological disorders (see 4.8 Undesirable Effects). Emtrim Tablethas 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 Emtrim Tabletshould 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

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.

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.

Reversible deterioration in renal function has been observed in patients treated with Emtrim Tabletand cyclosporin following renal transplantation.

Concurrent use of rifampicin and Emtrim Tabletresults 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.

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should Emtrim Tabletbe prescribed concurrently.

Emtrim Tablet 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 Emtrim Tabletis advisable.

Emtrim Tablet 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.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Emtrim Tablet may increase the free plasma levels of methotrexate. 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.

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 sulfonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.

If Emtrim Tablet is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are not any adequate data from the use of Emtrim Tabletin 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).

Emtrim Tabletshould not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Emtrim Tabletis 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 Emtrim Tabletis 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 Emtrim Tablet(trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Emtrim Tabletshould 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 Emtrim Tabletshould 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 Emtrim Tablet 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 Emtrim Tabletshould be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

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.

The following convention has been used for the classification of adverse events in terms of frequency:- Very common ≥1/10, common ≥1/100 and 01/10, uncommon ≥1/1000 and 01/100, rare ≥1/10,000 and 01/1000, very rare 01/10,000.

Infections and Infestations

Common:	Monilial overgrowth

Blood and lymphatic system disorders

Very rare	Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients

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).

Immune system disorders

Very rare:	Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus

Metabolism and nutrition disorders

Very common:	Hyperkalaemia
Very rare:	Hypoglycaemia, hyponatraemia, anorexia

Close supervision is recommended when Emtrim Tabletis used in elderly patients or in patients taking high doses of Emtrim Tabletas these patients may be more susceptible to hyperkalaemia and hyponatraemia.

Psychiatric disorders

Very rare:	Depression, hallucinations

Nervous system disorders

Common:	Headache
Very rare:	Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

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

Respiratory, thoracic and mediastinal disorders

Very rare:	Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Gastrointestinal disorders

Common:	Nausea, diarrhea
Uncommon:	Vomiting
Very rare:	Glossitis, stomatitis, pseudomembranous colitis, pancreatitis

Eye Disorders

Very rare:	Uveitis

Hepatobiliary disorders

Very rare:	Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal.

Skin and subcutaneous tissue disorders

Common:	Skin rashes
Very rare:	Photosensitivity, exfoliative dermatitis, fixed drug eruption,erythema multiforme, severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4)
Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders

Very rare:	Arthralgia, myalgia

Renal and urinary disorders

Very rare:	Impaired renal function (sometimes reported as renal failure), interstitial nephritis

Effects associated with *Pneumocystis jiroveci* Pneumonitis (PCP) management.

Very rare:	Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia

At the high dosages used for PCP 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 PCP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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. Dependant 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

Emtrim Tabletis 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 binds to and reversibly inhibits bacterial dihydrofolate reductase (DHFR) and blocks the production of 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.

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

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.

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.

Approximately 50% of trimethoprim in the plasma is protein bound. The half-life 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 the elderly 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.

Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in a variety of body fluids is of the order of 20 to 50% of the plasma concentration.

Approximately 66% of sulfamethoxazole in the plasma is protein bound. The half-life 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. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Paediatric population

The pharmacokinetics in the pediatric population with normal renal function of both components of Co-trimoxazole, trimethoprim and sulfamethoxazole are age dependent. Elimination of trimethoprim and sulfamethoxazole is reduced in neonates, during the first two months of life, thereafter both trimethoprim and sulfamethoxazole 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).

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.

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