SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIMAC 200mg/40mg Suspension

2. QUALITY AND QUANTITATIVE COMPOSITION

Qualitative Composition:

Each 5 ml contains:

Sulfamethoxazole.....200mg

Trimethoprim.....40mg

Excipients……Q.S.

Colour: Pale Yellow to white yellow

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	Ph. Eur.
2	Polysorbate 80	Ph. Eur.
3	Methyl Paraben	Ph. Eur.
4	Propyl Paraben	Ph. Eur.
5	Sorbitol	Ph. Eur.
6	Banana Flavour	Ph. Eur.
7	Vanilla Flavour	Ph. Eur.
8	Sodium Lauryl Sulphate	Ph. Eur.

Quantitative Composition:

Each 5 ml contains:

Sulfamethoxazole.....200mg

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TRIMAC SUSPENSION

Trimethoprim.....40mg

Excipients……Q.S.

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6	Banana Flavour	Ph. Eur.
7	Vanilla Flavour	Ph. Eur.
8	Sodium Lauryl Sulphate	Ph. Eur.

3. PHARMACEUTICAL FORM

Oral Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trimac Suspension is indicated in children aged 12 years and under (≥6 weeks) for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

Trimac suspension arc indicated for the treatment of the following infections

• Treatment and prevention of *Pneumocystis jirovecii* pneumonitis (PJP).

• Treatment and prophylaxis of toxoplasmosis.

• Treatment of nocardiosis.

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

• Acute uncomplicated urinary tract infection.

• Acute otitis media.

• Acute exacerbation of chronic bronchitis.

Infections associated with other lung conditions like COPD and Cystic fibrosis. These are chronic lung conditions which can sometimes make your lungs more prone to infections

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.

Children aged 12 years and under

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. For severe infections, the dosage shown for children may be increased by 50%. The schedules for children are according to the child's age and provided in the table below:

STANDARD DOSAGE	
Age	**Paediatric Suspension**
6 to 12 years	10 ml every 12 hours
6 months to 5 years	5 ml every 12 hours
6 weeks to 5 months	2.5 ml every 12 hours

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.

Special populations

Impaired hepatic function renal impairment

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	10 ml every 12 hours
15 to 30	5 ml 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

Children aged 12 years and under:

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 section 4.8).

Prevention

Children aged 12 years and under:

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 schedules according to the child's age that may be used for the duration of the period at risk are provided in the table below:

Age	Paediatric Suspension
6 to 12 years	10 ml every 12 hours, seven days per week
6 to 12 years	10 ml every 12 hours, three times per week on alternative days
6 to 12 years	10 ml every 12 hours, three times per week on consecutive days
6 to 12 years	20 ml once a day, three times per week on consecutive days
6 months to 5 years	5 ml every 12 hours, seven days per week
6 months to 5 years	5 ml every 12 hours, three times per week on alternative days

6 months to 5 years	5 ml every 12 hours, three times per week on consecutive days
6 months to 5 years	10 ml once a day, three times per week on consecutive days
6 weeks to 5 months	2.5 ml every 12 hours, seven days per week
6 weeks to 5 months	2.5 ml every 12 hours, three times per week on alternative days
6 weeks to 5 months	2.5 ml every 12 hours, three times per week on consecutive days
6 weeks to 5 months	5 ml once a day, 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.

Method of administration

Oral

It may be preferable to take Trimac suspension food or drink to minimise the possibility of gastrointestinal disturbances.

4.3 Contraindications

Hypersensitivity to the active substance(s) sulphonamides, trimethoprim, co-trimoxazole or to any of the excipients listed in section 6.1.

- Severe impairment of liver. Patients with severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.
- Trimac Suspension should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulphonamides.
- Trimac Suspension should not be given to patients with acute porphyria.
- Trimac Suspension should not be given to infants during the first 6 weeks of life.

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 Trimac suspension, Trimac suspension 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 Trimac Suspension alone or in combination with other drugs.

Hemophagocytic 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, hypofibrinogenemia, 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 older 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 Trimac Suspension is given for long periods, or to folate deficient patients or to older patients; 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

Trimac Suspension should be given with caution to patients with severe atopy or bronchial asthma.

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

Trimac Suspension 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

The administration of Trimac Suspension 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 and sodium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

Metabolic acidosis

Trimac Suspension 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 Trimac Suspension should not be given to patients with serious haematological disorders (see section 4.8). Trimac Suspension 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 Trimac Suspension 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.

TRIMAC SUSPENSION

Diuretics (thiazides)

In older 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

Trimac Suspension 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

Trimac Suspension 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 older patients.

Methotrexate

Trimac Suspension 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

Trimethoprim and sulfamethoxazole cross the placenta and their safety in pregnant women has not been established. 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 section 5.3).

Trimac Suspension should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Trimac Suspension 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 Trimac Suspension 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.

Breast-feeding

The components of Co-Trimoxazole (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Trimac Suspension 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 Trimac Suspension 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 Trimac Suspension 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 Trimac Suspension should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

Summary of the safety profile

As Trimac Suspension contains trimethoprim and a sulfonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

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. In addition, adverse events may vary in their incidence depending on the indication.

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,

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TRIMAC SUSPENSION

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.
	Very rare	Hypoglycaemia, hyponatraemia, decreased appetite, metabolic acidosis
Psychiatric disorders	Very rare	Depression, hallucination.
	Not known	Psychotic disorder
Nervous system disorders	Common	Headache.
	Very rare	Meningitis aseptic *, seizure, neuropathy peripheral, ataxia, dizziness.
Ear and labyrinth disorders	Very rare	Vertigo, tinnitus
Eye disorders	Very rare	Uveitis.
Vascular disorders	Not known	Circulatory shock*

Respiratory, thoracic and mediastinal disorders	Very rare	Cough*, dyspnoea *, lung infiltration*.
Gastrointestinal disorders	Common	Nausea, diarrhoea.
	Uncommon	Vomiting.
	Very rare	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	Very rare	Jaundice cholestatic *, hepatic necrosis* Transaminases increased, blood bilirubin increased.
Skin and subcutaneous tissue disorders*	Common	Rash.
	Very rare	Photosensitivity, dermatitis exfoliative, angioedema, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome (SJS) and 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 (see section 4.4).

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 and 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 co-trimoxazole for prophylaxis or treatment of PJP.

Circulatory shock

Cases of circulatory shock, often accompanied by fever and not responding to standard treatment for hypersensitivity, have been reported with sulfamethoxazole + trimethoprim, mainly in immunocompromised patients.

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions is essential for continuous monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the Swipha Pharmacovigilance online ADR form www.swiphanigeria.com/adr_form . See Section 7 for more info.

4.9 Overdose

Symptoms and Signs

Nausea, vomiting, Stomach pain, dizziness, drowsiness, depression and confusion, blood in urine and loss of consciousness are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

Treatment

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: Antibacterials for systemic use

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.

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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.

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.

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TRIMAC SUSPENSION

Trimethoprim/sulfamethoxazole susceptibilities 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 older 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. In older patients there is a reduced renal clearance of sulfamethoxazole.

Pharmacokinetics in special patient populations

The pharmacokinetics in the paediatric population with normal renal function of both components of Trimac Suspension, 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).

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. 0 Pharmaceutical Particulars

6.1 List of excipients

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	Ph. Eur.
2	Polysorbate 80	Ph. Eur.
3	Methyl Paraben	Ph. Eur.
4	Propyl Paraben	Ph. Eur.
5	Sorbitol	Ph. Eur.
6	Banana Flavour	Ph. Eur.
7	Vanilla Flavour	Ph. Eur.
8	Sodium Lauryl Sulphate	Ph. Eur.

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C, protect from light.

Keep medicines out of reach of children.

Store in the original package.

Bottles of suspension already in use can be stored at room temperatures or under refrigeration

6.5 Nature and contents of container

Pack size: 50ml and 100ml Amber coloured bottle with Aluminium Robb caps with a 5ml plastic spoon

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER/ REGISTRANT

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9. MARKETING AUTHORIZATION NUMBERS

A4-7555

10. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

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10. DATE OF REVISION OF THE TEXT
