SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FECTRIM FORTE/Co-Trimoxazole 160/800 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160 mg of trimethoprim and 800 mg of sulphamethoxazole

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, capsule-shaped tablet, engraved ‘DDSA/Fectrim Forte’ on one side and scored on the other side

4.1 Therapeutic indications

Co-trimoxazole Adult Tablets are indicated in children (>12 to <18 years old) and adults (>18 years old) for treatment of the following infections when owing to sensitive organisms (see section 5.1):

- Treatment and prophylaxis of Pneumocystis jirovecii pneumonia (PJP).
- Treatment and prophylaxis of toxoplasmosis
- Treatment of nocardiosis

The following infections may be treated with FECTRIM/ Co-trimoxazole where there is bacterial evidence of sensitivity to FECTRIM/ Co-trimoxazole and good reason to prefer this combination of antibiotics in Co-trimoxazole to a single antibiotic.

- Acute uncomplicated urinary tract infections
- Acute otitis media
- Acute exacerbations of chronic bronchitis

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

4.2 Posology and method of administration

Posology:

General dosage recommendations

Where dosage is expressed as "tablets" this refers to the adult Fectrim /Co-trimoxazole tablet, i.e 160 mg Trimethoprim BP and 800 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Standard dosage recommendation for acute infections:

Adults (>18 years old):

STANDARD DOSAGE	
Age	**Tablets**
>18 years old	1 tablets every 12 hours

Children over 12 years old (>12 to <18 years old):

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

Age	**Tablets**
>12 to <18 years old	1 tablets every 12 hours

Treatment should be continued until the patient has been symptom-free for two (2) 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.

Elderly patients:

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

Impaired Hepatic Function

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

Impaired Renal Function

Dosage recommendation:

Children (>12 to <18 years old) and adults (>18 years old):

Creatinine Clearance (ml/min)	**Recommended Dosage**
>30	1 tablet every 12 hours
15 to 30	1 tablet per day
< 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 FECTRIM/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 Fectrim/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 (>12 to <18 years old) and adults (>18 years old):*

A higher dosage is recommended using 20 mg Trimethoprim and 100 mg Sulfamethoxazole per kg bodyweight per day in 2 or more divided doses for 2 weeks. The aim is to obtain peak plasma or serum level of Trimethoprim greater than or equal to 5 micrograms per ml (verified in patients receiving 1-hour infusions of intravenous Co-Trimoxazole). (See section 4.8 Undesirable effects).

Prevention: Adults (>18 years old):

The following dosing schedules may be used:

- 160 mg trimethoprim/800 mg sulfamethoxazole daily, 7 days per week.
- 160 mg trimethoprim/800 mg sulfamethoxazole three times a week on alternate days.
- 320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times a week on alternate days.

Prevention Children (>12 to <18 years old:):

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	**Tablets**

>12 to to < 18 years old	1 tablet every 12 hours, seven days per week
>12 to to < 18 years old	1 tablet every 12 hours, three time per week on alternative days
>12 to to < 18 years old	1 tablet every 12 hours, three times per week on consecutive days
>12 to to < 18 years old	2 tablets 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.

Nocardiosis:- Adults (>18 years old):

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

Toxoplasmosis:

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

Method of administration:

Oral.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Life threatening adverse reactions

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

- Life-threatening cutaneous reactions including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms have been reported with the use of Fectrim/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 or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. fever, eosinophilia) are present, Fectrim/Co-trimoxazole treatment should be discontinued (see Section 4.8).
- The best results in managing SJS and TEN or 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 or DRESS with the use of Fectrim Forte, Fectrim Forte must not be re-started in this patient at any time.
- At the start of treatment, the occurrence of a generalised febrile erythema associated with pustules, should raise the suspicion of acute generalised exanthematous pustulosis (AGEP) (see section 4.8); it requires cessation of treatment and contraindicates any new administration of Co-Trimoxazole alone or in combination with other drugs.

Haemophagocytic lymphohistiocytosis (HLH)

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

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

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

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

Urinary output
An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulfonamide 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 FECTRIM/Co-Trimoxazole is given for long periods, or to folate deficient patients or to the elderly; since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate.. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy (see section 4.5).

Patients with glucose-6-phosphate dehydrogenase deficiency
Haemolysis may occur in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency patients.

Patients with severe atopy or bronchial asthma
Fectrim/Co-trimazole should be given with caution in patients with severe atopy or bronchial asthma.

Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci
Fectrim/Co-trimaxole should not be use 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 phenylketonuria patients on appropriate dietary restriction.

Patients with or at risk of porphyria
The administration of Fectrim/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.

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

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

Patients with serious haematological disorders
Except under careful supervision Fectrim/Co-Trimoxazole should not be given to patients with serious haematological disorders (see section 4.8). Fectrim/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 Fectrim/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.

Anti viral (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.

Immunosuppressants*(Cyclosporin):*
Reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and ciclosporin following renal transplantation.

Anti-Bacterial drug (Rifampicin) *:*
Concurrent use of rifampicin and Fectrim/Co-Trimaxole 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.

Anti-arrhythmic (Procainamide, Amantadine):
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.

Anit-malarial (Pyrimethamine):
Occasional reports suggest that Patients receiving pyrimethamine at dosage in excess of 25 mg weekly may develop megaloblastic anaemia should co-trimoxazole be prescribed concurrently.

Anti-coagulants (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 anti-coagulant therapy during treatment with Fectrim is advisable.

Anti-epiletics (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.

Cardiac glycoside (Digoxin):
Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Antineoplastics (Methotrexate):
Co-trimoxazole may increase the free plasma levels of methotrexate. If Fectrim/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 potassiumsparing 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 failure 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 establised. 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). Fectrim/Co-Trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate/Co-trimoxazole supplementation should be considered if Fectrim/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 Fectrim/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.

Breast feeding

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

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reaction

The following convention has been used for the classification of adverse events in terms of frequency: Very common ≥1/10, common ≥1/100 and 01/10, uncommon ≥1/1000 and 01/100, rare ≥1/10,000 and 01/1000, very rare 01/10,000, Not known – cannot be estimated from the available data.

System Organ Class	Frequency	Side effect
Infections and Infestations	Common	Overgrowth fungal
	Very rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Very rare	Leucopenia, neutropenia, Thrombocytopenia, agranulocytosis, , megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients
Immune system disorders	Very rare	Serum sickness, anaphylactic reactions, allergic myocarditis, , drug fever, allergic myocarditis, hypersensitivity vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus (SLE) 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, hallucinations
	Not known:	Psychotic disorder
Nervous system disorders	Common:	Headache
	Very rare:	Meningitis aseptic*, convulsions, neuropathy peripheral, ataxia, dizziness

Ear and labyrinth disorders	Very rare	Vertigo, tinnitus
Eye disorder	Very rare	Uveitis
Respiratory, thoracic and mediastinal disorders	Very rare:	Cough*, dyspnoea*, pulmonary infiltrates*
Vascular disorders	Not known	Circulatory shock
Gastrointestinal disorders	Common	Nausea, diarrhoea
	Uncommon:	Vomiting
	Very rare:	Glossitis, stomatitis, pancreatiti
Hepatobiliary disorders	Very rare	Transaminases increase, blood bilirubin incease, cholestatic jaundice, hepatic necrosis
Skin and subcutaneous tissue disorders	Common	Rash
	Very rare	Photosensitivity reaction, angioedema, exfoliative dermatitis, 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.

Hepatobiliary disorders
Jaundice cholestatic and hepatic necrosis may be fatal.

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

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

Effects associated with Pneumocystis jirovecii Pneumonitis (PJP) management.

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

At the high dosages used for PJP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy.

Severe hypersensitivity reactions have been reported in PJP patients on reexposure to co-trimoxazole, sometimes after a dosage interval of a few days.

Rhabdomyolysis has been reported in HIV positive patients receiving cotrimoxazole 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

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:
Nausea, vomiting, dizziness and confusion 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

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

Mechanism of Action

Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (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 Sulfamethoxazole and Trimethoprim 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 several different mechanisms. Bacterial mutations cause an increased production 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 of dihydropteroate synthetase, the enzyme inhibited by sulfonamides, to a less sensitive form, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

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

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

Many common pathogenic bacteria are susceptible in vitro to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, in vitro activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

Susceptibility testing breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing) limits
Enterobacteriaceae: S≤ 2 R> 4
S. maltophilia: S≤4 R> 4
Acinetobacter: S≤ 2 R> 4
Staphylococcus: S≤ 2 R> 4
Enterococcus: S≤ 0.032 R> 1
Streptococcus ABCG: S≤ 1 R> 2
Streptococcus pneumoniae: S≤ 1 R>
2 *Hemophilus influenza*: S≤ 0.5 R>
1 *Moraxella catarrhalis*: S≤0.5 R >1
Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*
S = susceptible, R = resistant. *These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.
Trimethoprim: sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration.

Antibacterial Spectrum
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only

an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not. Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

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

5.2 Pharmacokinetic properties

Absorption

After oral administration Sulfamethoxazole and Trimethoprim 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, spetum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sullfamethoxazole 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 the elderly compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of a 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 recovered in urine is in the active form.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-trimoxazole, trimethoprim and sulfamethoxazole, are age dependent. Elimination of trimethoprim-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).
In elderly patients there is a reduced renal clearance of sulfamethoxazole.

Special patient population

Renal impairment

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

Hepatic impairment

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

Elderly patients

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

Paediatric population

See special dosage regimen (see section 4.2).

5.3 Preclinical safety data

At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K25

Crospovidone

Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

Containers: 48 months

6.4 Special precautions for storage

Store below 25°C in a dry place in well closed containers.

6.5 Nature and contents of container

High density polystyrene or polypropylene containers with polythene or polypropylene lids and polyurethane/polythene inserts.
High density polyethylene containers with polyolefin (a combination of polyethylene and polypropylene) lids and PET/Al/PE foil laminated closure liner. Pack size: 100

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Hualan Pharmaceuticals Limited
16/17 College Green
Dublin
D02 V078
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 52104/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29//01/2009

10 DATE OF REVISION OF THE TEXT

14/07/2025