SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bactrim forte 800 mg/160 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 800 mg sulfamethoxazole and 160 mg trimethoprim.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White to off-white, biconvex tablet, approx. 19 mm long and 9 mm wide, marked with 'BACTRIM 800+160' on one side and with a score line on the other side.
The tablet may be divided into two equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bactrim forte is indicated for adults, adolescents and children aged 6 years and above in the following indications:
Upper urinary tract infection. Complicated lower urinary tract infection. Prostatitis. Severe infections originating in the urinary tract. Acute exacerbation of chronic bronchitis. Shigellosis. Typhoid and paratyphoid fever. Prevention and treatment of infections caused by *Pneumocystis jirovecii,* especially in severely immunocompromised patients.

Consideration should be given to official guidelines concerning proper use of antibacterial drugs and local occurrence of resistance.

4.2 Posology and method of administration

Treatment should continue until the patient has been symptom-free for 2 days and should not normally exceed 7 days. In fulminant infections the dose can be increased by 50% in all age groups.

Adults and children over 12 years: 1 Bactrim forte tablet in the morning and evening. The maximum dose in fulminant infections is 1½ Bactrim forte tablets in the morning and evening.

Children 6–12 years: The standard dose is ½ Bactrim forte tablet in the morning and evening.

Exacerbations of chronic bronchitis: Patients who do not respond satisfactorily to 5–7 days of treatment with Bactrim forte require reassessment, whereupon other medical treatment should be considered.

Prophylaxis against Pneumocystis jirovecii: Adults: ½-1 Bactrim forte tablet once a day or 1–2 Bactrim forte tablets given in 1–2 divided doses 3 times per week.

Treatment of Pneumocystis jirovecii pneumonia: 20 mg trimethoprim and 100 mg sulfamethoxazole per kg body weight per day given in two or more doses. The aim is to achieve a serum trimethoprim concentration >5 µg/ml.

Impaired renal function:
Patients with impaired renal function should be dosed according to the following schedule:

Creatinine clearance Normal value 60–120 ml/min	Serum creatinine Normal value 45–115 µmol/l	Dosage in patients with impaired renal function
>30 ml/min.	<320 µmol/l	Same dosage as for patients with normal renal function.
15-30 ml/min.	320–405 µmol/l	1 Bactrim forte tablet every 12 hours for 3 days, then 1 Bactrim forte tablet every 24 hours for as long as the control analysis allows.
<15 ml/min.	>405 µmol/l	The drug can only be given to patients receiving regular dialysis treatment. 1 Bactrim forte tablet every 24 hours for as long as the control analysis allows.

In patients with impaired renal function (creatinine clearance <30 ml/min) the total plasma sulfamethoxazole concentration must be measured every third treatment day, 12 hours after the last dose. Treatment with Bactrim forte must be discontinued if the total plasma sulfamethoxazole concentration exceeds 600 µmol/l. Once the total concentration is less than 500 µmol/l (e.g. in patients on haemodialysis), treatment can continue and control analyses are performed every third day.
Peritoneal dialysis results in minimal clearance of administered sulfamethoxazole + trimethoprim and their use is therefore not recommended in these patients.

4.3 Contraindications

Hypersensitivity to sulfamethoxazole and trimethoprim or to any excipient.
Severe liver damage, blood dyscrasias (megaloblastic haematopoiesis).
Must not be given to infants under 6 weeks of age (see 4.6 Pregnancy and lactation).
Must not be given to patients with creatinine clearance <15 ml/min (see section 4.2), unless the patient is receiving regular haemodialysis treatment.
Sulfamethoxazole + trimethoprim must not be given concomitantly with dofetilide (see 4.5 Interactions).

4.4 Special warnings and precautions for use

Caution should be exercised in patients with renal insufficiency, suspected or confirmed folate deficiency, dehydration or malnutrition, as well as in very elderly patients and those with a severe allergy or bronchial asthma.

To minimise the risk of adverse reactions treatment time must be kept as short as possible. Treatment must be stopped if skin rashes occur.

Severe adverse reactions
Although very rare, cases with a fatal outcome have been reported in connection with adverse reactions such as blood dyscrasia, severe cutaneous adverse reactions (SCARs – such as widespread exudative erythema multiforme [Stevens-Johnson syndrome (SJS)], toxic epidermal necrolysis [TEN], drug rash with eosinophilia and systemic symptoms [DRESS] and acute generalised exanthematous pustulosis [AGEP] and fulminant necrosis of the liver.

Patients must be informed about signs and symptoms of skin reactions and monitored closely with regard to these skin reactions. They are at greatest risk of developing SJS, DRESS, AGEP or TEN during the first few weeks of the treatment. If symptoms or signs of SJS, DRESS, AGEP or TEN (e.g. progressive skin rashes, often with blisters or mucosal lesions) are present, treatment with sulfamethoxazole + trimethoprim must be discontinued.

The best results in preventing progression of SJS, DRESS, AGEP or TEN come from early diagnosis and immediate discontinuation of the drug that is suspected of causing the symptoms. Early discontinuation usually means a better prognosis.

If a patient has developed SJS, DRESS, AGEP or TEN when using sulfamethoxazole + trimethoprim, that patient must never again be treated with sulfamethoxazole + trimethoprim.

Particular caution must be exercised when prescribing sulfamethoxazole + trimethoprim to elderly patients. In particular, the possibility of impaired renal and/or hepatic function must be considered and the dosage must be adjusted accordingly in the presence of impaired renal function (see 4.2 Posology and method of administration). Adverse events are more common in elderly patients. The risk appears to be dose-related and increases with treatment time.

More frequent monitoring of blood levels at weekly intervals is recommended when treating elderly patients and patients predisposed to folate deficiency. Folate supplements should also be considered in patients on long-term treatment with sulfamethoxazole + trimethoprim at high doses.

Patients with seriously impaired renal function (i.e. creatinine clearance 15-30 ml/min) who are receiving sulfamethoxazole + trimethoprim must be monitored closely for symptoms or signs of toxicity such as nausea, vomiting and hyperkalaemia.

An adequate fluid intake and urinary output should be maintained during treatment. Signs of crystalluria are rare *in vivo*, although sulfonamide crystals have been observed in cooled urine from treated patients. The risk of crystalluria may be increased in patients suffering from malnutrition. Incidence of kidney stones consisting entirely or partly of sulfamethoxazole metabolites has also been reported (see section 4.8)

Respiratory toxicity: Very rare cases of severe respiratory toxicity that in certain cases have developed into shock lung (ARDS) have been reported during treatment with sulfamethoxazole + trimethoprim. Debut of pulmonary symptoms such as cough, fever and dyspnoea, including radiological findings such as pulmonary infiltrates and worsened pulmonary function may be initial signs of ARDS. In such circumstances, the treatment with sulfamethoxazole + trimethoprim should be discontinued and suitable treatment given.

Patients on long-term therapy must be followed up closely. The follow-up should consist of regular checks on clinical and laboratory parameters, including haematology, blood chemistry and liver-function testing. Changes attributable to folic acid deficiency can be reversed by administering folinic acid (leucovorin) 5–10 mg/day without impairing the antibacterial effect.

When Bactrim forte is used concomitantly with antiepileptics, e.g. phenytoin, primidone and barbiturates, patients on long-term therapy must have their folic-acid levels measured. It should be noted that folic-acid metabolism disorders can occur even without a reduction in serum folic-acid levels.

The high doses of trimethoprim given to patients with *Pneumocystis jirovecii* pneumonia have been shown to induce a progressive but reversible increase in serum potassium concentrations. Even treatment at recommended doses can cause hyperkalaemia in patients with a potassium metabolism disorder, renal insufficiency or when other hyperkalaemia-inducing drugs are administered concomitantly. Close monitoring of serum potassium is justified in these patients.

Although sulfamethoxazole + trimethoprim can cause haemolysis in certain susceptible G6PD-deficient patients, this does not appear to be dose-related.

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* may occur. Patients with diarrhoea must therefore be monitored closely.

Hemophagocytic lymphohistiocytosis (HLH): Very rare cases of HLH have been reported in patients who have been treated with sulfamethoxazole + trimethoprim. HLH is a life-threatening syndrome with pathological immune activation that is characterised by clinical signs and symptoms of severe systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenia and haemophagocytosis). Patients displaying early signs of pathological immune activation must be assessed immediately. If a diagnosis of HLH is made, treatment with sulfamethoxazole + trimethoprim must be discontinued.

Sulfamethoxazole + trimethoprim should not be given to patients known or suspected to be at risk of acute porphyria.

Sulfonamides, including sulfamethoxazole + trimethoprim, can increase urinary output, especially in patients with oedema of cardiac origin (see 4.8 Undesirable effects).

Bactrim forte contains sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, i.e. it is practically “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Bactrim may require dose adjustment:

Pharmacokinetic interactions

Trimethoprim is an inhibitor of the organic cation transporter 2 (OCT2) and the transporters MATE1 and MATE2K and it is a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9.

Drugs transported by OCT2, MATE1 and/or MATE2K
Systemic exposure to drugs transported by OCT2, MATE1 and MATE2K may increase when they are given concomitantly with sulfamethoxazole + trimethoprim. Examples include dofetilide, amantadine, memantine, metformin and lamivudine.

Sulfamethoxazole + trimethoprim must not be given in combination with dofetilide (see section 4.3). There is data suggesting that trimethoprim inhibits renal excretion of dofetilide. Administration of 160 mg trimethoprim plus 800 mg sulfamethoxazole twice daily in combination with 500 µg dofetilide twice daily for 4 days increased the AUC of dofetilide by 103% and its C_{max} by 93%. Dofetilide can cause severe ventricular arrhythmia in association with QT prolongation, including *torsade de pointes*, which is directly related to the plasma concentration of dofetilide.

Patients receiving amantadine or memantine may be at increased risk of such neurological side-effects as delirium and myoclonus.

Co-administration of trimethoprim (200 mg twice daily) with metformin increased the AUC of metformin by 30-40%. The clinical significance of this increase is unknown.

Lamivudine
Trimethoprim has been reported to inhibit renal excretion and increase blood levels of lamivudine.

Drugs metabolised by CYP2C8
Systemic exposure to drugs that are primarily metabolised by CYP2C8 may increase when they are co-administered with sulfamethoxazole + trimethoprim. Examples include paclitaxel, amiodarone, dapsone, repaglinide, rosiglitazone and pioglitazone.

As paclitaxel and amiodarone have a narrow therapeutic window, co-administration with sulfamethoxazole + trimethoprim is not advisable.

As both dapsone and sulfamethoxazole + trimethoprim can cause methaemoglobinaemia, pharmacokinetic and pharmacodynamic interactions are therefore both possible. Patients receiving both dapsone and sulfamethoxazole + trimethoprim must be monitored for methaemoglobinaemia. Consideration should be given to alternative treatments if possible.

Patients receiving repaglinide, rosiglitazone or pioglitazone must be regularly monitored for hypoglycaemia.

Drugs metabolised by CYP2C9
Systemic exposure to drugs primarily metabolised by CYP2C9 may increase during co-administration with sulfamethoxazole + trimethoprim. Examples include coumarins (warfarin,

acenocoumarol, phenprocoumon), phenytoin and sulfonylurea derivatives (glibenclamide, gliclazide, glipizide, chlorpropamide and tolbutamide).

Coagulation must be monitored in patients receiving coumarins.

Trimethoprim inhibits the metabolism of phenytoin. Following treatment with a standard dose of sulfamethoxazole + trimethoprim the half-life of phenytoin increased by 39% and its clearance decreased by 27%. Patients receiving phenytoin must be monitored for signs of phenytoin toxicity.

Pharmacodynamic interactions and interactions of unknown mechanism

Clozapine
Co-administration with clozapine, a drug with the potential to cause agranulocytosis, must be avoided.

Cyclosporin
Reversible deterioration of renal function has been observed in kidney-transplant patients who were treated concomitantly with sulfamethoxazole + trimethoprim and cyclosporin.

Tacrolimus
Co-administration with tacrolimus may increase the risk of nephrotoxic side-effects. Patients receiving sulfamethoxazole + trimethoprim concomitantly with tacrolimus must therefore be monitored for renal function.

Digoxin
Increased levels of digoxin in the blood can occur when it is co-administered with Bactrim, especially in elderly patients. Serum levels of digoxin must be monitored.

Zidovudine
Zidovudine – and, less commonly, sulfamethoxazole + trimethoprim – are known to cause haematological side-effects. Consequently, there is a possibility that the pharmacodynamic effect may be potentiated. Patients receiving combination therapy with sulfamethoxazole + trimethoprim and zidovudine must be monitored for haematological toxicity and dose adjustment may be required.

Azathioprine and mercaptopurine
Co-administration with azathioprine or mercaptopurine may increase the risk of haematological side-effects, especially in patients who receive sulfamethoxazole + trimethoprim over a long period or have an increased risk of folic acid deficiency. Alternatives to sulfamethoxazole + trimethoprim must therefore be considered for patients receiving azathioprine or mercaptopurine. If sulfamethoxazole + trimethoprim is given in combination with azathioprine or mercaptopurine, patients should be monitored for haematological side-effects.

Hyperkalaemia-inducing drugs
Care should be exercised when co-administering sulfamethoxazole + trimethoprim with other drugs that may increase serum potassium, such as ACE inhibitors, angiotensin-receptor blockers, potassium-sparing diuretics and prednisolone, because of the potassium-sparing

effects of sulfamethoxazole + trimethoprim. Regular checks on serum potassium are recommended, especially in patients with underlying potassium disturbances or impaired renal function or those receiving high doses of sulfamethoxazole + trimethoprim (see section 4.4). Prednisolone is expected to reduce the occurrence of trimethoprim-induced hyperkalaemia as the mineralocorticoid effect that is exerted on distal tubules by glucocorticoid therapy results in an acute transient kaliuresis. Nevertheless, 39% of the patients treated with sulfamethoxazole + trimethoprim plus prednisolone in a retrospective study developed hyperkalaemia compared with 0% (i.e. none) of patients treated with sulfamethoxazole + trimethoprim alone. The authors hypothesised that the increased occurrence of hyperkalaemia could be related to the catabolic effect of concomitantly administered prednisolone in patients with reduced potassium excretion induced by trimethoprim.

Contraceptives
In isolated cases certain antibiotics might reduce the effectiveness of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the gut and thus also the reabsorption of unconjugated steroid. This would result in a reduction in the plasma levels of active steroid. Although negative studies with trimethoprim-sulfa are available, there is very little study material.

Methotrexate
Sulfonamides, including sulfamethoxazole, may inhibit protein binding and renal transport of methotrexate and thereby potentiate its effect. Cases of pancytopenia have occurred when trimethoprim and methotrexate are combined. Trimethoprim has low affinity for human dihydrofolate reductase but may increase the toxicity of methotrexate, especially in the presence of other risk factors such as advanced age, hypoalbuminaemia, impaired renal function and decreased bone marrow reserve, as well as in patients receiving high doses of methotrexate. High-risk patients must be treated with folic acid or calcium folinate in order to counteract the effects of methotrexate on haematopoiesis.

Tricyclic antidepressants
Based on isolated case reports, the possibility cannot be excluded that efficacy of tricyclic antidepressants may be reduced in patients treated concomitantly with sulfamethoxazole + trimethoprim .

Pyrimethamine
Isolated reports suggest that patients who receive pyrimethamine for the prevention of malaria at doses in excess of 25 mg per week may develop megaloblastic anaemia if treated with a combination of sulfamethoxazole and trimethoprim.

Thiazides
There appears to be an increased risk of thrombocytopenia in elderly patients who are treated concomitantly with diuretics (especially thiazides). Platelets must be monitored in patients receiving diuretics.

4.6 Pregnancy and lactation

Pregnancy

Trimethoprim and sulfamethoxazole cross the placenta. Their safety in pregnant women has not been established. Sulfamethoxazole + trimethoprim must be avoided during pregnancy, especially during the first trimester, unless the benefit to the mother outweighs the potential risk to the fetus.

An observational study of more than 165,000 pregnancies within the Quebec Pregnancy Cohort identified a 2.72-fold increase in the risk of spontaneous abort in women treated with trimethoprim in combination with sulfamethoxazole before week 20 of pregnancy compared with no use of antibiotics over the same period. An observational study of more than 930,000 pregnancies in Denmark identified a 2.04-fold increase in the risk of miscarriage after exposure to trimethoprim during the first trimester, which is 1.41 times higher than the risk to those not using antibiotics over the same period.

When the mother is treated during the last month of pregnancy, sulfonamides may cause kernicterus in children during the first month of life by displacing bilirubin from plasma albumin (see section 5.2).
Trimethoprim may interfere with folic-acid metabolism and it has been shown in animal studies that very high doses of sulfamethoxazole + trimethoprim given during organogenesis may cause folic acid-type teratogenic effects. It is recommended that pregnant women and those planning to become pregnant should be given 5 mg folic acid per day while they undergo treatment with Bactrim forte.

Breast-feeding
Trimethoprim and sulfamethoxazole are excreted in breast milk. Even though the amount of sulfamethoxazole + trimethoprim ingested by the breastfed child is small (see section 5.2), the mother's need for treatment with sulfamethoxazole + trimethoprim and the advantages of breast-feeding must be weighed against the potential risks to the child. Particular caution should be exercised with premature infants and those with G6PD deficit, who are at increased risk of jaundice.

4.7 Effects on ability to drive and use machines

Although no specific studies have been performed, sulfamethoxazole + trimethoprim is not expected to have any effects on the ability to drive or use machines.

4.8 Undesirable effects

The commonest side-effects are skin rashes and gastrointestinal disturbances.

Severe cutaneous adverse reactions (SCARs), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported (see section 4.4).

Side-effects reported in members of the general patient population treated with sulfamethoxazole + trimethoprim:

Organ system	**Common** ≥1/100, < 1/10	**Uncommon** ≥1/1,000, < 1/100	**Rare** ≥1/10,000, < 1/1,000	**Very rare** <1/10,000	**Frequency not known** (cannot be estimated from the available data)
Infections and infestations		Fungal infections such as candidiasis			
Blood and lymphatic system disorders			Leukopenia, granulocytopenia, thrombocytopenia, megaloblastic anaemia, haemolytic/ autoimmune anaemia, aplastic anaemia	Agranulocytosis, pancytopenia, methaemoglobinaemia	
Immune system disorders				Hypersensitivity reactions such as fever, angioneurotic oedema, anaphylactic reactions and serum sickness. Periarteritis nodosa	
Metabolism and nutrition disorders			Hypoglycaemia	Increase in serum potassium,	
Psychiatric disorders				Hallucinations	
Nervous system disorders		Convulsions	Neuropathy (including peripheral neuritis and paraesthesia)	Aseptic meningitis or meningitis-like symptoms, ataxia	
Eye disorders				Uveitis	
Ear and labyrinth disorders				Tinnitus, vertigo	
Cardiac disorders				Allergic myocarditis	
Vascular disorders				Purpura and Henoch-Schönlein purpura	Vasculitis, polyarteritis nodosa
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, pseudomembranous colitis	Stomatitis, glossitis		Acute pancreatitis
Hepatobiliary disorders	Elevated transaminases	Elevated bilirubin, hepatitis	Cholestasis	Hepatic necrosis	Vanishing bile duct syndrome

Organ system	**Common** ≥1/100, < 1/10	**Uncommon** ≥1/1,000, < 1/100	**Rare** ≥1/10,000, < 1/1,000	**Very rare** <1/10,000	**Frequency not known** (cannot be estimated from the available data)
Skin and subcutaneous tissue disorders	Recurrent drug-induced skin rash, exfoliative dermatitis, skin rash, maculopapular rashes, morbilliform rash, erythema, pruritus	Urticaria		Photosensitivity, erythema multiforme, Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)/Lyell´s syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)	Acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders				Rhabdomyolysis	Arthralgia, myalgia
Renal and urinary disorders	Elevated blood urea nitrogen, elevated serum creatinine	Impaired renal function	Crystalluria	Interstitial nephritis, increased urinary output (see 4.4)	Urolithiasis
Respiratory, thoracic and mediastinal disorders				Lung infiltration, cough, dyspnoea	
General disorders and administration site conditions			Venous pain and phlebitis		
Investigations					Hyperkalaemia, hyponatraemia

Description of selected adverse reactions

The majority of the observed haematological changes have been mild, asymptomatic and reversible following discontinuation of treatment.

As with all medicinal products, allergic reactions can occur in patients who are hypersensitive to the drug's ingredients. The commonest adverse skin reactions observed with sulfamethoxazole + trimethoprim have generally been mild and rapidly reversible following discontinuation of the drug.

High doses of trimethoprim as administered to patients with *Pneumocystis jirovecii* pneumonia give rise to a progressive but reversible increase in serum potassium concentrations in a large number of patients. Even at recommended doses, trimethoprim can cause hyperkalaemia in patients with a potassium metabolism disorder, renal insufficiency or when given concomitantly with other hyperkalaemia-inducing drugs (see section 4.4).

Cases of hypoglycaemia have been reported in non-diabetics who have been treated with sulfamethoxazole+trimethoprim, usually after several days of treatment (see section 4.5). The

risk is greater in patients with impaired renal function, liver disease, undernutrition and those who are receiving high doses of sulfamethoxazole+trimethoprim.

Cases of urinary calculus disease have occurred as a consequence of aggregation of sulfamethoxazole metabolites (either fully or partly) having been reported in patients treated with sulfametoxazol + trimetoprim. Data indicates an interaction between the medicinal product itself and other risk factors for urolithiasis.

Side-effects of Bactrim in HIV-infected patients:

Patients infected with HIV have a similar spectrum of side-effects to the rest of the patient population. However, certain side-effects occur more frequently and are accompanied by different clinical symptoms. These differences relate to the following organ classes:

Organ system	**Very common** ≥1/10	**Common** ≥1/100, < 1/10	**Uncommon** ≥1/1,000, ≤ 1/100
Blood and lymphatic system disorders	Leukopenia, granulocytopenia and thrombocytopenia		
Metabolism and nutrition disorders			Hypoglycaemia
Gastrointestinal disorders	Anorexia, nausea, vomiting, diarrhoea		Stomatitis, glossitis, diarrhoea
Hepatobiliary disorders	Elevated transaminases		
Skin and subcutaneous tissue disorders	Maculopapular skin rashes, usually with itching, pruritus		
General disorders and administration site conditions	Fever (usually associated with maculopapular eruption)		
Investigations	Hyperkalaemia		Hyponatraemia

Reporting of suspected adverse reactions
It is important to report suspected adverse reactions after the drug has been approved. This makes it possible to continuously monitor the drug's risk-benefit ratio. Health professionals are urged to report every suspected adverse reaction to the Swedish Medical Products Agency.

Läkemedelsverket
Box 26
751 03 Uppsala
www.lakemedelsverket.se

4.9 Overdose

Symptoms
Nausea, vomiting, diarrhoea, headache, dizziness, skin reactions, crystalluria, haematuria, oliguria, anuria, methaemoglobinaemia, cyanosis, liver involvement, CNS involvement. Patients receiving long-term administration of high doses may suffer bone marrow depression, manifested as thrombocytopenia or leukopenia, and other blood dyscrasias due to folic acid deficiency.

Treatment
Prevention of continued absorption, forced diuresis, alkalisation of urine, haemodialysis for anuria. Blood status, electrolyte status and liver function should be monitored and urinary output should be measured owing to the risk of oliguria and anuria.
Calcium folinate is given in order to prevent changes in blood chemistry. Methylene blue is given to patients with severe methaemoglobinaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial agent for systemic use
ATC code: J01EE01

Sulfamethoxazole is a sulfonamide which competitively inhibits synthesis of folic acid by the bacterium. Trimethoprim is a pyrimidine derivative which specifically inhibits bacterial dihydrofolic acid reductase. The combination of sulfonamide + trimethoprim therefore blocks two consecutive steps in the metabolism of folic acid and thus synthesis of purines, RNA and DNA by the microorganisms is halted. This form of sequential blockade means that this combination exerts a bactericidal effect *in vitro* at concentrations where the individual active components only exhibit a bacteriostatic effect. As the mechanism of action impedes the development of resistance, this combination is often effective against organisms that are resistant to either of the constituent components.

Antibacterial spectrum

Susceptible	*Staphylococcus aureus* and coagulase-negative Staphylococci Streptococci, Pneumococci and Enterococci *Listeria* *Moraxella catarrhalis* *Haemophilus influenzae* and *parainfluenzae* *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Morganella morganii*, *Citrobacter*, *Serratia* and *Hafnia* *Salmonella*, *Shigella* *Stenotrophomonas maltophilia* Chlamydia.

Intermediate	*Haemophilus ducreyi* *Providencia* *Acinetobacter* *Aeromonas hydrophila*.
Resistant	*Pseudomonas* *Legionella* Anaerobic bacteria including *Clostridium difficile* Mycoplasma.

Resistance occurs (1–10%) in Streptococci, Pneumococci and Staphylococci and is common (>10%) in *Haemophilus influenzae* and Gram-negative intestinal bacteria.

In addition to its antibacterial effect sulfamethoxazole + trimethoprim is effective against *Pneumocystis jirovecii*.

There is cross-resistance with trimethoprim and sulfa preparations but not with other antibiotics.

Mechanism of resistance:
Acquired, plasmid-borne resistance to both sulfa and trimethoprim mainly occurs in species of Gram-negative intestinal bacteria. Resistance to sulfa results from production of an alternative dihydropteroate synthetase that is insusceptible to sulfonamides, whereas in most cases resistance to trimethoprim results from production of an alternative trimethoprim-resistant dihydrofolate reductase. Isolates can be resistant to sulfa only or to both trimethoprim and sulfa, whereas isolates with trimethoprim resistance and susceptibility to sulfa drugs are very unusual.

Development of resistance:
The resistance situation varies geographically and information about local resistance conditions should be obtained through the local microbiology laboratory.

Breakpoints for resistance testing

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), the breakpoints for minimum inhibitory concentration are:

	MIC (µg/ml) [a]	
	Susceptible ≤	Resistant >
Enterobacteriaceae	2	4
Acinetobacter spp.	2	4
Stenotrophomonas maltophila[b]	4	4
Staphylococcus spp.	2	4
Enterococcus spp[c].	0.032	1

Streptococcus pneumoniae	1	2
Streptococcus groups A, B, C and G	1	2
Haemophilus influenzae & *Haemophilus parainfluenzae*	0.5	1
Listeria monocytogenes	0.06	0.06
Pasteurella multocida	0.25	0.25
Moraxella catarrhalis	0.5	1

[a] Trimethoprim and sulfamethoxazole in the ratio 1:19
[b] The breakpoints are based on high-dose therapy, ≥ 240 mg trimethoprim and 1.2 g sulfamethoxazole administered concomitantly twice daily.
[c] As the activity of sulfamethoxazole + trimethoprim against enterococci is unclear, the wild-type population is classified as intermediately susceptible.

5.2 Pharmacokinetic properties

Absorption
Sulfamethoxazole and trimethoprim are absorbed rapidly and completely in the upper gastrointestinal tract after oral administration. The serum concentrations of sulfamethoxazole and trimethoprim are the same, regardless of whether the two components are administered together or separately. Peak serum concentration of Bactrim forte is achieved within 2–4 hours after oral administration. The half-life is 11 hours for sulfamethoxazole and 10 hours for trimethoprim. The serum concentrations of each substance following repeated administration are 6.5 (5.2–10.3) µmol/l =1.9 (1.5–3.0) µg/ml (trimethoprim), 225 (150–300) µmol/l =56 (37.5–75) µg/ml (sulfamethoxazole). These serum concentrations exceed current bacterial MIC values by some margin.

Distribution
The distribution volume is around 1.6 l/kg for trimethoprim and around 0.2 l/kg for sulfamethoxazole. Plasma protein binding is 37% for trimethoprim and 62% for sulfamethoxazole.
In serum, sulfamethoxazole and trimethoprim are found in free, protein-bound and metabolised form. The degree of protein binding for trimethoprim and sulfamethoxazole is 45% and 70%, respectively.
The tissue concentrations of trimethoprim are usually higher than corresponding concentrations in plasma. Especially high concentrations are achieved in lung and renal tissue. The concentration of trimethoprim in bile secretions, prostatic fluid, saliva and sputum exceeds corresponding concentrations in plasma. The concentrations in spinal and cerebrospinal fluid are sufficient for an antibacterial effect. The concentration of active sulfamethoxazole in spinal fluid, bile, cerebrospinal fluid and sputum is around 30% of the plasma concentration.
The fact that trimethoprim and sulfamethoxazole are detected in human fetal tissue (placenta, liver, lung), umbilical cord blood and amniotic fluid indicates that both substances cross the placenta. Generally speaking, the concentrations of trimethoprim in the fetus are similar to

those in the mother for trimethoprim and somewhat lower for sulfamethoxazole (see section 4.6).

Both substances pass into breast milk. The concentrations in breast milk are similar to maternal plasma concentrations for trimethoprim and somewhat lower for sulfamethoxazole (see section 4.6).

Metabolism
Around 30% of the trimethoprim dose is metabolised. Results from an *in vitro* study with human liver microsomes indicate that CYP3A4, CYP1A2 and CYP2C9 are primarily responsible for the metabolism of trimethoprim. The principal trimethoprim metabolites are 1- and 3-oxides and 3- and 4-hydroxy derivatives; certain metabolites are microbiologically active. Around 80% of the sulfamethoxazole dose is metabolised in the liver, preferentially to N_4-acetyl derivatives (≈ 40% of the dose) and, to a lesser extent, by glucuronide conjugation. Sulfamethoxazole also undergoes oxidative metabolism. The first step in oxidative metabolism, which results in the formation of the hydroxylamine derivative, is catalysed by CYP2C9.

Elimination
The half-lives for the two components are very similar, with a mean value of 10 hours for trimethoprim and 11 hours for sulfamethoxazole.

Trimethoprim and sulfamethoxazole are excreted via the kidneys by glomerular filtration; trimethoprim is additionally excreted by tubular secretion. Around 20% of sulfamethoxazole is excreted as unchanged active substance, while around 60% is present in acetylated form and around 15% in glucuronidated form. Approximately two-thirds of trimethoprim is excreted unchanged in active form. Total plasma clearance of trimethoprim is 1.9 ml/min/kg and that of sulfamethoxazole is 0.32 ml/min/kg. A small portion of each substance is eliminated via the faeces.

Pharmacokinetics in specific patient groups

Paediatric population
In the paediatric population with normal renal function the pharmacokinetics of both Bactrim components, trimethoprim and sulfamethoxazole, is age-dependent. Whereas 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 together with a higher body clearance and a shorter 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).

Elderly
As trimethoprim is largely excreted renally in unchanged form and as creatinine clearance decreases physiologically with increasing age, a reduction in renal clearance and total clearance of trimethoprim can be expected. The pharmacokinetics of sulfamethoxazole should be less affected by increasing age, as renal clearance of sulfamethoxazole is equivalent to only 20% of total sulfamethoxazole clearance.

Patients with impaired renal function
The half-life of both substances is increased in patients with severely impaired renal function (creatinine clearance 15-30 ml/min) and consequently dose adjustment is required (see section 4.2).

Neither intermittent nor continuous ambulatory peritoneal dialysis contribute significantly to the elimination of trimethoprim and sulfamethoxazole. Significant amounts of trimethoprim and sulfamethoxazole are removed during haemodialysis and haemofiltration. A 50% increase in the dose of trimethoprim and sulfamethoxazole after each haemodialysis treatment has been proposed. In children with impaired renal function (creatinine clearance <30 ml/min) clearance of trimethoprim is reduced and the half-life is increased. Dosage of sulfamethoxazole + trimethoprim in these patients should be based on renal function.

Patients with impaired liver function
The pharmacokinetics of sulfamethoxazole + trimethoprim in patients with moderately or severely impaired liver function is not thought to be significantly different from that observed in healthy individuals.

Patients with cystic fibrosis
Renal clearance of trimethoprim and metabolic clearance of sulfamethoxazole are increased in patients with cystic fibrosis. Consequently, total plasma clearance of both substances is increased and their half-life is reduced.

5.3 Preclinical safety data

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K30
Sodium starch glycolate
Magnesium stearate
Docusate sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.
Maximum shelf life when using automatic dosing is 6 months.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Blister containing 50 tablets.

6.6 Special precautions for disposal and other handling

No special precautions.

7 MARKETING AUTHORISATION HOLDER

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Germany

8 MARKETING AUTHORISATION NUMBER

9259

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09-09-1977
Date of latest renewal: 01-01-2007

10 DATE OF REVISION OF THE TEXT

09-03-2023