SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bactrim 40 mg/ml + 8 mg/ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of Bactrim oral suspension contains 40 mg sulfamethoxazole and 8 mg trimethoprim.
One spoonful of 5ml contains 200 mg sulfamethoxazole and 40 mg trimethoprim.

Excipients with known effect
Sorbitol (E 420) 630 mg/ml
Methyl parahydroxybenzoate (E 218) 0.5 mg/ml
Propyl parahydroxybenzoate (E 216) 0.1 mg/ml
Propylene glycol (E 1520) 4.8 mg/ml
Ethanol 1.8 mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bactrim oral suspension is indicated for adults, adolescents, children and infants from the age of 6 weeks in the following indications (see sections 4.2, 4.3, 4.4, 4.8 and 5.1):
Upper urinary tract infections. Complicated lower urinary tract infections. Prostatitis. Serious infections originating from the urinary tract. Acute exacerbation of chronic bronchitis. Shigellosis. Typhoid and paratyphoid fever. Treatment of infections caused by *Pneumocystis jirovecii; Prophylaxis of infections caused by Pneumocystis jirovecii,* particularly in immunocompromised patients.

Consideration should be given to official guidance on the appropriate use of antibacterial agents and the local resistance situation.

4.2 Posology and method of administration

Posology

Adults and adolescents over 12 years of age with difficulties swallowing tablets:
Bactrim oral suspension is recommended in adults and adolescent above 12 years of age only if there are difficulties in swallowing tablets.

Children: The dosage for children is equivalent to a dose of approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day. Dosing by body weight may be used in cases where this is deemed more accurate by the prescribing physician.

Local therapeutic guidelines should be adhered to.

Standard dosage recommendations:
Adults and children over 12 years of age: 20 ml (4 spoons) Bactrim oral suspension every 12 hours (i.e. morning and evening).

Children from 6 years to 12 years of age: 10 ml (2 spoons) Bactrim oral suspension every 12 hours (i.e. morning and evening).

Children from 6 months to 5 years of age: 5 ml (1 spoon) Bactrim oral suspension every 12 hours (i.e. morning and evening).
Children from 6 weeks up to 5 months of age: 2.5 ml (one half of a spoon) Bactrim oral suspension every 12 hours (i.e. morning and evening).

In case of fulminant infections, the dose can be increased by 50% in all age groups.

Specific cases:
Prophylaxis of Pneumocystis jirovecii pneumonia:
Adults and adolescents over 12 years of age: 10-20 ml (2-4 spoons) Bactrim oral suspension between three and seven times a week (once daily).

Children: the recommended dose is 150 mg/m^2/day trimethoprim with 750 mg/m^2/day sulfamethoxazole given orally in equally divided doses twice a day, on 3 consecutive days per week. More frequent dosing, up to seven days a week (daily) may be considered if required. This corresponds to approximately 5 mg/kg/day trimethoprim and 25 mg/kg/day sulfamethoxazole. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Treatment of Pneumocystis jirovecii pneumonia:
Adults, adolescents over 12 years of age, children: 20 mg trimethoprim and 100 mg sulfamethoxazole per kg body weight per day divided in two or more dosage administrations.

Impaired renal function:
In case of impaired renal function the dosage should be administered according to the following schedule:

Creatinine clearance Normal value 60– 120 ml/min	Serum creatinine Normal value 45– 115 micromol/L	Dosage in impaired renal function
> 30 ml/min.	< 320 micromol/L	Dosage as for patients with normal renal function.
30-15 ml/min.	320-405 micromol/L	20 ml oral suspension every 12 hours (i.e. morning and evening) for 3 days, thereafter 20 ml oral suspension every 24 hours for as long as control analyses permit.
< 15 ml/min.	> 405 micromol/L	The product may only be given to patients undergoing regular dialysis treatment. 20 ml oral suspension every 24 hours for as long as control analyses permit.

In patients with impaired renal function (creatinine clearance <30 ml/min), the total plasma concentration of sulfamethoxazole must be determined every third day of treatment, 12 hours after the last dose. If the total plasma concentration exceeds 600 micromol/L, treatment with Bactrim should be interrupted. If the total concentration falls below 500 micromol/L (e.g. in patients on haemodialysis), treatment can be continued and control analyses can be performed every third day.
Peritoneal dialysis results in minimal clearance of administered sulfamethoxazole+trimethoprim and their use is therefore not recommended in these patients.

Duration of treatment

Treatment should be continued until the patient has been symptom-free for 2 days and the treatment should normally not exceed 7 days. If it is not evident clinical improvement after 7 days of therapy, the patient should be reassessed.

Exacerbations of chronic bronchitis: Patients who do not respond satisfactorily to 5–7 days' treatment with Bactrim should be reassessed, and other medical treatment should be considered.

Method of administration
For oral use.
A measuring spoon is supplied for use with this oral suspension. Use only the measuring spoon included in the outer packaging. The measuring spoon is graduated 1.25 ml, 2.5 ml, and 5 ml.
Shake the bottle before each use.
See section 6.6.

4.3 Contraindications

Hypersensitivity to sulfamethoxazole and trimethoprim or to any of the excipients as specified in Section 6.1.
Severe hepatic damage, blood dyscrasias (megaloblastic haematopoiesis).
Shall not be given to infants under 6 weeks of age (see 4.6 Pregnancy and lactation).
Deficit of glucose-6-phosphate dehydrogenase including breastfed children due to the risk of triggering hemolysis.
Shall not be given to patients with creatinine clearance <15 ml/min (see section 4.2), unless the patient is undergoing regular haemodialysis treatment.

Sulfamethoxazole+trimethoprim should not be given together with dofetilide (see 4.5 Interaction).

4.4 Special warnings and precautions for use

Caution should be observed in the case of renal impairment, suspected or confirmed folate deficiency, dehydration, malnutrition or advanced age, as well as in severe allergy and bronchial asthma.

The treatment period must be kept as short as possible to minimise the risk of side effects. Treatment should be discontinued if skin rash occurs.

Severe adverse skin reactions (SCARs – such as major exudative erythema multiforme (Stevens-Johnson syndrome, SJS), drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN, Lyell's syndrome) and acute generalized exanthematous pustulosis (AGEP)) have been reported with the use of sulfamethoxazole+trimethoprim.

Patients should be advised of the signs and symptoms of skin reactions and monitored closely for these skin reactions. The highest risk for occurrence of SJS, DRESS, TEN and AGEP is within the first weeks of treatment. If symptoms or signs of SJS, DRESS, TEN or AGEP (e.g. progressive skin rash, often with blisters or mucosal lesions) occur, treatment with sulfamethoxazole+trimethoprim should be discontinued.

The best results in preventing the progress of SJS, DRESS, TEN and AGEP come from early diagnosis and immediate discontinuation of any drug suspected of causing the symptoms. Early withdrawal is generally associated with a better prognosis.

If a patient has developed SJS, DRESS, TEN or AGEP with the use of sulfamethoxazole+trimethoprim, the patient must never be treated with sulfamethoxazole+trimethoprim again.

Fatal outcome has also been reported, although rarely, in relation to adverse reactions such as blood dyscrasias, and fulminant hepatic necrosis.

Cutaneous or haematological manifestations require immediate and definitive discontinuation of treatment.

More regular blood counts at weekly intervals are recommended in the treatment of older patients and patients predisposed to folate deficiency. Folate supplementation should also be considered during long-term treatment with high doses of sulfamethoxazole+trimethoprim.

Patients should be monitored closely during long-term treatment. Follow-up should consist of regular monitoring of clinical and laboratory parameters, including haematology, blood chemistry and liver function tests. Changes that relate to a deficiency of available folic acid can be reversed by administration of folinic acid (see the summary of product characteristics of drugs containing folinic acid) without adverse impact on the antibacterial effect.

Particular caution should be observed when prescribing sulfamethoxazole+trimethoprim to older patients. In particular, the possibility of impaired renal and/or hepatic function should be considered and the dosage in impaired renal function adapted accordingly (see 4.2 Posology and method of administration). The incidence of adverse reactions is increased in older patients. The risk is dose-related and increases with the length of the treatment period.

Particular biological monitoring should be carried out in the event of hepatic insufficiency (transaminases and bilirubin), haematological history (blood count, platelets, reticulocytes), and renal insufficiency (creatinine clearance).

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

Close monitoring of serum potassium and renal function is necessary in patients receiving a high dose of sulfamethoxazole+trimethoprim, such as in Pneumocystis jirovecii pneumonia, as well as in patients receiving a standard dose of sulfamethoxazole+trimethoprim who have underlying potassium metabolism or renal impairment (see section 4.8), and in HIV-infected patients, the elderly, and patients receiving other potassium-increasing drugs (see section 4.5).

If a significant reduction in blood counts is noted, treatment with sulfamethoxazole+trimethoprim must be discontinued. Except in exceptional cases, sulfamethoxazole+trimethoprim should not be administered to patients with severe haematological disorders.

Cases of haemophagocytic lymphohistiocytosis (HLH) have been reported very rarely in patients treated with sulfamethoxazole+trimethoprim. 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, sulfamethoxazole+trimethoprim treatment should be discontinued.

Very rare, severe cases of respiratory toxicity, sometimes progressing to acute respiratory distress syndrome (ARDS), have been reported during sulfamethoxazole+trimethoprim 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, sulfamethoxazole+trimethoprim should be discontinued and appropriate treatment given.

As with all sulfonamide-containing drugs, caution is recommended in patients with thyroid dysfunction.

Adequate hydration and urinary output should be maintained during treatment. Signs of crystalluria *in vivo* are rare, although sulphamethoxazole crystals have been observed in cooled urine from treated patients. The risk of crystalluria may be increased in malnourished patients. Formation of renal calculi composed wholly or in part of sulfamethoxazole metabolites has also been observed (see section 4.8).

Patients should be informed of the risk of photosensitivity reactions (see section 4.8). Exposure to the sun or UV radiation should be avoided and the wearing of clothing to protect against significant direct exposure to the sun is recommended for the duration of treatment and for up to three days after stopping.

Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

On co-administration with antiepileptics such as phenytoin, primidone and barbiturates, folic acid levels should be determined in long-term therapy. It should be noted that disorders of folic acid metabolism can occur even without a reduction in serum folic acid levels.

High doses of trimethoprim given to patients with *Pneumocystis jirovecii* pneumonia have been shown to induce a progressive but reversible increase in serum potassium levels. Even

treatment with recommended doses can cause hyperkalaemia in patients with a disorder of potassium metabolism, renal impairment or in whom other hyperkalaemic drugs are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* occurs. Patients with diarrhoea should therefore be monitored closely.
Sulfamethoxazole+trimethoprim should not be given to patients with a known or suspected risk of acute porphyria.

Sulfonamides including sulfamethoxazole+trimethoprim can induce increased urine output, particularly in patients with anaemia of cardiac origin (see 4.8 Undesirable effects).

This medicine contains sorbitol (E 420), methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), propylene glycol (E 1520), alcohol (ethanol) and sodium.

This medicine contains 630 mg of sorbitol per ml.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and the intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

This medicine contains 24 mg of propylene glycol per 5 ml equivalent to 4.8 mg / ml.

This medicine contains 9 mg of alcohol (ethanol) per 5 ml equivalent to 1.8 mg/ml. The amount per 5 ml of this medicine is equivalent to less than 0.23 ml of beer or 0.10 ml of wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per ml and is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with Bactrim may require a dose adjustment:

Pharmacokinetic interactions

Trimethoprim is an inhibitor of the organic cation transporter 2 (OCT2), the MATE1/2-K transporters and is a weak inhibitor of CYP2C8. Sulfamethoxazole is a weak inhibitor of CYP2C9.

Medicinal products transported by OCT2, MATE1 and/or MATE2-K
Systemic exposure to medicinal products transported by OCT2, MATE1 and MATE2-K can increase when they are given together with sulfamethoxazole+trimethoprim. Examples include dofetilide, amantadine, memantine, metformin and lamivudine.

Sulfamethoxazole+trimethoprim should not be given in combination with dofetilide (see section 4.3). There are data to the effect that trimethoprim inhibits the renal excretion of dofetilide. Trimethoprim 160 mg in combination with sulfamethoxazole 800 mg was given twice daily together with dofetilide 500 micrograms twice daily for 4 days, which resulted in an increase of AUC for dofetilide by 103% and C_{max} increased by 93%. Dofetilide can cause severe ventricular arrhythmia associated with QT prolongation, including *torsade de pointes*, which is directly related to the plasma concentration of dofetilide.

Patients receiving amantadine or memantine can have an increased risk of neurological adverse reactions such as delirium and myoclonus.

On co-administration of trimethoprim (200 mg twice daily) and metformin, metformin AUC increased about 30%-40%. The clinical relevance of this increase is not known.

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

Medicinal products metabolised by CYP2C8
Systemic exposure to medicinal products predominantly metabolised by CYP2C8 can increase when they are given with sulfamethoxazole+trimethoprim. Examples include paclitaxel, amiodarone, dapsone, repaglinide, rosiglitazone and pioglitazone.

Paclitaxel and amiodarone have a narrow therapeutic window, therefore co-administration with sulfamethoxazole+trimethoprim is not recommended.

Both dapsone and sulfamethoxazole+trimethoprim can cause methaemoglobinaemia and both pharmacokinetic and pharmacodynamic interactions are therefore possible. Patients receiving both dapsone and sulfamethoxazole+trimethoprim should be monitored for methaemoglobinaemia. Alternative treatments should be considered if possible.

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

Medicinal products metabolised by CYP2C9
Systemic exposure to medicinal products predominantly metabolised by CYP2C9 can increase on co-administration with sulfamethoxazole+trimethoprim. Examples include coumarins (warfarin, acenocoumarol, phenprocoumon), phenytoin and sulphonylurea derivatives (glibenclamide, gliclazide, glipizide, chlorpropamide and tolbutamide).

Coagulation should be monitored in patients receiving coumarins.

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

Pharmacodynamic interactions and interactions with an unknown mechanism

Clozapine

Concomitant treatment with clozapine, a medicinal product that has a possible potential to cause agranulocytosis, should be avoided.

Ciclosporin
A reversible deterioration of renal function has been observed in renal transplant patients treated concomitantly with sulfamethoxazole+trimethoprim and ciclosporin.

Tacrolimus
Concomitant treatment with tacrolimus can increase the risk of nephrotoxic adverse reactions. Patients receiving sulfamethoxazole+trimethoprim concomitantly with tacrolimus should therefore be monitored for renal function.

Digoxin
Increased blood digoxin levels can be found on concomitant treatment with Bactrim, particularly in older patients. Serum digoxin levels should be monitored.

Zidovudine
Zidovudine, and to a lesser extent sulfamethoxazole+trimethoprim, are known to induce haematological adverse reactions. There is therefore the possibility of an increased pharmacodynamic effect. Patients receiving combination treatment with sulfamethoxazole+trimethoprim and zidovudine should be monitored for haematological toxicity and a dose adjustment may be required.

Azathioprine and mercaptopurine
Concomitant treatment with azathioprine or mercaptopurine can increase the risk of haematological adverse reactions, particularly in patients receiving sulfamethoxazole+trimethoprim for a long time or who have an increased risk of folic acid deficiency. Alternatives to sulfamethoxazole+trimethoprim should 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 adverse reactions.

Hyperkalaemic medicinal products
Because of the potassium-sparing effects of sulfamethoxazole+trimethoprim, caution should be exercised when sulfamethoxazole+trimethoprim are given at the same time as other medicinal products that can increase serum potassium such as ACE inhibitors, angiotensin receptor blockers, potassium-sparing diuretics and prednisolone. Regular monitoring of serum potassium is recommended, particularly in patients with underlying potassium disorders, 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 exerted on distal tubules by glucocorticoid treatment results in acute transient kaliuresis. In a retrospective study, however, hyperkalaemia developed in 39% of patients treated with sulfamethoxazole+trimethoprim plus prednisolone versus 0% (none) in patients treated with sulfamethoxazole+trimethoprim alone. The authors' hypothesis was that the increased occurrence of hyperkalaemia could be related to the catabolic effect of co-administered prednisolone in patients with trimethoprim-induced reduced potassium excretion.

Contraceptive agents

Certain antibiotics could in rare cases reduce the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the bowel and hence the reabsorption of unconjugated steroid. Plasma levels of active steroid will decrease as a result. There are negative studies with sulfamethoxazole+trimethoprim, but the data are limited.

Methotrexate
Sulfonamides, including sulfamethoxazole, can inhibit protein binding and renal transport of methotrexate and as a result increase its effect. Cases of pancytopenia have occurred when trimethoprim was combined with methotrexate. Trimethoprim has a low affinity for human dehydrofolate reductase but can increase the toxicity of methotrexate, predominantly in the presence of other risk factors such as advanced age, hypoalbuminaemia, impaired renal function and reduced bone marrow reserve, as well as in patients receiving high doses of methotrexate. High-risk patients should be treated with folic acid or calcium folinate to prevent the effects of methotrexate on haematopoiesis.

Tricyclic antidepressants
Based on isolated case reports, a reduced effect of tricyclic antidepressants in concomitant treatment with sulfamethoxazole+trimethoprim cannot be ruled out.

Pyrimethamine
Isolated reports indicate that patients receiving pyrimethamine as malarial prophylaxis at doses exceeding 25 mg per week can develop megaloblastic anaemia in concomitant treatment with the combination of sulfamethoxazole and trimethoprim.

Thiazides
There is thought to be an increased risk of thrombocytopenia in elderly patients treated simultaneously with diuretics, predominantly thiazides. Platelets should be monitored in patients receiving diuretics.

Influence on diagnostic methods
Sulfamethoxazole+trimethoprim, particularly the trimethoprim component, may interfere with the serum methotrexate assay using the competitive protein binding technique when bacterial dihydrofolate reductase is used as a binding protein. No interference occurs, however, if methotrexate is measured by radioimmunoassay.

The presence of trimethoprim and sulfamethoxazole can also interfere with the reaction to Jaffé alkaline picrate for creatinine determination, causing an increase of approximately 10% to values in the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Trimethoprim and sulfamethoxazole pass through the placenta. The safety of use during pregnancy has not been determined. The use of sulfamethoxazole+trimethoprim during pregnancy shall be avoided, especially during the first trimester, if not the potential benefit for the mother justifies the potential risk to the fetus.

An observational study of more than 165 000 pregnancies within the Quebec pregnancy cohort suggested a 2.72-fold increased risk of spontaneous abortion in women treated with trimethoprim in combination with sulfamethoxazole before the 20th week of pregnancy compared to no use of antibiotics during the same period. An observational study of more

than 930 000 pregnancies in Denmark suggested a 2.04-fold increased risk of miscarriage after exposure to trimethoprim during the first trimester, which is a 1.41-fold higher risk compared to no use of antibiotics during the same period.

During the last month of pregnancy, sulfonamides can cause kernicterus in the neonate by removing bilirubin from albumin in the plasma (see section 5.2).
Trimethoprim may interfere with folic acid metabolism and animal experiments have shown that very high doses of sulfamethoxazole+trimethoprim given during organogenesis produce fetal malformations typical of folic acid antagonism. It is recommended that pregnant women or women planning to become pregnant should be given 5 mg of folic acid daily during their treatment with Bactrim.

Breast-feeding
Trimethoprim and sulfamethoxazole pass into breast milk. Although the quantity of sulfamethoxazole+trimethoprim ingested by a breastfed infant is small (see section 5.2), the need for the mother to be treated with sulfamethoxazole+trimethoprim and the benefits with breast-feeding must be weighed against the potential risks for the infant. Particular caution is recommended for premature children and children with G-6-PD deficiency, who are at increased risk of jaundice.

4.7 Effects on ability to drive and use machines

No specific studies have been performed, but sulfamethoxazole+trimethoprim is not expected to have any effects on the ability to drive and use machines. During treatment with sulfamethoxazole+trimethoprim, undesirable effects may occur (e.g. dizziness, convulsions, hallucinations), which may influence the ability to drive and use machines (see section 4.8). Patients should be cautious when driving or operating machinery.

4.8 Undesirable effects

The most common adverse reactions are skin rash and gastrointestinal disorders.

Severe cutaneous adverse reactions (SCARs); Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported (see section 4.4).

Adverse reactions reported from the general patient population treated with sulfamethoxazole+trimethoprim:

Organ system	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <1/100	**Rare** ≥1/10,000 to <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			

Organ system	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <1/100	**Rare** ≥1/10,000 to <1/1,000	**Very rare** <1/10,000	**Frequency not known** (cannot be estimated from the available data)
Blood and lymphatic system disorders			Leucopenia, granulocytopenia, thrombocytopenia, megaloblastic anaemia, haemolytic/ autoimmune anaemia, aplastic anaemia	Agranulocytosis, pancytopenia, methaemoglobin-aemia, eosinophilia (associated with DRESS)	
Immune system disorders				Hypersensitivity reactions such as fever, angioneurotic oedema, anaphylactic reactions and serum sickness. Periarteritis nodosa	
Metabolism and nutrition disorders			Hypoglycaemia	Increase of 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-Schoenlein purpura, necrotizing vasculitis, granulomatosis with polyangiitis	Vasculitis, polyarteritis nodosa
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, pseudomembran-ous colitis	Stomatitis, glossitis, abdominal pain		Acute pancreatitis
Hepatobiliary disorders	Transaminases increased	Bilirubin increased, hepatitis	Cholestasis	Hepatic necrosis	Vanishing bile duct syndrome

Organ system	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <1/100	**Rare** ≥1/10,000 to <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 eruption, exfoliative dermatitis, skin rash, maculopapular rash, morbilliform rash, erythema, pruritus	Urticaria		Photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis	Acute febrile neutrophilic dermatosis (Sweet's syndrome)
Musculoskeletal and connective tissue disorders				Rhabdomyolysis	Arthralgia, myalgia
Renal and urinary disorders	Blood urea nitrogen increased, serum creatinine increased	Impaired renal function	Crystalluria	Interstitial nephritis, urine output increased (see 4.4)	Urolithiasis
Respiratory, thoracic and mediastinal disorders				Pulmonary infiltrate, cough, breathlessness	
Investigations					Hyperkalaemia, hyponatraemia

Description of selected adverse reactions

The majority of the observed haematological changes were mild, asymptomatic and reversible after discontinuation of treatment.

As with all medicinal products, allergic reactions can occur in patients who are hypersensitive to the ingredients of the medicinal product. The most common adverse skin reactions observed with sulfamethoxazole+trimethoprim were generally mild and rapidly reversible after discontinuation of the medicinal product.

High doses of trimethoprim given to patients with *Pneumocystis jirovecii* pneumonia induce a progressive but reversible increase in serum potassium levels in a large number of patients. Even at recommended doses, trimethoprim can cause hyperkalaemia in patients with a disorder of potassium metabolism, renal impairment or in whom other hyperkalaemic drugs are given concomitantly (see section 4.4).

Cases of hypoglycaemia have been reported in non-diabetics treated with sulfamethoxazole+trimethoprim, usually after a few days of treatment (see section 4.5). Patients with impaired renal function, liver disease, malnutrition or those receiving high doses of sulfamethoxazole+trimethoprim are at additionally high risk.

Cases of urolithiasis formed by aggregation of sulfamethoxazole metabolite crystals (either 100% or partial) have been reported in patients treated with sulfamethoxazole+trimethoprim. The data suggest an interplay between the drug itself and other risk factors for urolithiasis.

Effects of Bactrim in HIV-infected patients:

Patients infected with HIV have a similar spectrum of adverse reactions to the remaining patient population. Certain adverse reactions, however, occur with greater frequency and with other clinical symptoms. These differences concern the following organ classes:

Organ system	**Very common** ≥1/10	**Common** ≥1/100 to <1/10	**Uncommon** ≥1/1,000 to <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	Transaminases increased		
Skin and subcutaneous tissue disorders	Maculopapular skin rash, usually with itching, pruritus		
General disorders and administration site conditions	Fever usually associated with maculopapular rash		
Investigations	Hyperkalaemia		Hyponatraemia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Nausea, vomiting, diarrhoea, headache, dizziness, skin reactions, crystalluria, haematuria, oliguria, anuria, methaemoglobinaemia, cyanosis, hepatic disorders, CNS disorders. Following long-term administration of high doses, bone marrow suppression can occur, manifesting as thrombocytopenia or leucopenia, and other blood dyscrasias due to folic acid deficiency.

Treatment
Prevention of continued absorption (gastric lavage (in case of recent intake) should be considered to prevent further absorption of the drug), forced diuresis, urinary alkalinisation, haemodialysis in the case of anuria. Blood status, electrolyte status, liver function should be monitored, urine output should be measured as there is a risk of oliguria or anuria.

Calcium folinate is given to prevent blood count changes. Methylthionine is given in the event of severe methaemoglobinaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification
Pharmacotherapeutic group: Antibacterials for systemic use
ATC code J01EE01

Mechanism of action
Sulfamethoxazole is a sulfonamide that competitively inhibits bacterial folic acid synthesis. Trimethoprim is a pyrimidine derivative and specifically inhibits dihydrofolic acid reductase in the micro-organisms. The combination of sulfonamide+trimethoprim blocks two consecutive steps in folic acid metabolism and thereby interrupts the synthesis of purine, RNA and DNA by the micro-organisms. This form of sequential blockade involves an in vitro bactericidal effect of the combination at concentrations at which the active components by themselves exert only a bacteriostatic effect. The mechanism of action interferes with the development of resistance and means that the combination is often effective against organisms that are resistant to one or other of the components involved.

Resistance
Resistance occurs (1–10%) in streptococci, pneumococci and staphylococci and is common (>10%) in *Haemophilus influenzae* and gram-negative intestinal bacteria.

Cross-resistance exists with trimethoprim and sulfa products but not with other antibiotics.

Mechanism of resistance:
Acquired, plasmid-borne resistance to both sulfa and trimethoprim occurs predominantly in species belonging to gram-negative intestinal bacteria. Resistance to sulfa is based on the production of an alternative dihydropteroate synthetase that is insensitive to sulfonamides, while resistance to trimethoprim is usually due to production of an alternative trimethoprim-resistant dihydrofolate reductase. Isolates resistant to sulfa alone or to both trimethoprim and sulfa are found, whereas isolates with trimethoprim resistance and sulfa susceptibility are very uncommon.

Resistance development:
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.

Breakpoints for resistance determination

Minimum inhibitory concentration breakpoints according to the “European Committee on Antimicrobial Susceptibility Testing” (EUCAST) are:

	MIC (µg/ml) [a]	
	Susceptible≤	Resistant >
Enterobacteriaceae	2	4
Acinetobacter spp.	2	4
Stenotrophomonas maltophila[b]	0.001	4
Staphylococcus spp.	2	4
Enterococcus spp[c].	-	-
Streptococcus pneumoniae	1	2
Streptococcus groups A, B, C and G	1	2
Haemophilus influenzae	0.5	1
Listeria monocytogenes	0.06	0.06
Pasteurella multocida	0.25	0.25
Moraxella catarrhalis	0.5	1
Kingella kingae	0.25	0.25
Aeromonas spp	2	4
Burkholderia pseudomallei	0.001	4

[a] Trimethoprim:sulfamethoxazole in the ratio of 1:19. Breakpoints are expressed as the trimethoprim concentration.
[b] The breakpoints are based on high-dose treatment, ≥ 240 mg trimethoprim and 1.2 g sulfamethoxazole administered jointly twice daily.
[c] The activity of trimethoprim and sulfamethoxazole+trimethoprim is uncertain against *enterococci*, and it is not possible to predict clinical outcome.

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

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

5.2 Pharmacokinetic particulars

Absorption
Sulfamethoxazole and trimethoprim are rapidly and completely absorbed in the upper part of the gastrointestinal tract after oral administration. Serum concentrations of sulfamethoxazole and trimethoprim are the same, regardless of whether the two components are given together or separately. The peak serum concentration of Bactrim is reached within 2–4 hours after oral administration. The half-life is 11 hours for sulfamethoxazole and 10 hours for trimethoprim. The serum concentrations of the respective substances on repeated administration are 6.5 (5.2–10.3) micromol/L =1.9 (1.5–3.0) micrograms/ml (trimethoprim), 225 (150–300) micromol/L =56 (37.5–75) micrograms/ml (sulfamethoxazole). These serum concentrations far exceed the current bacterial MIC values.

Distribution
The volume of distribution is about 1.6 l/kg for trimethoprim and about 0.2 l/kg for sulfamethoxazole. Plasma protein binding is up to 37% for trimethoprim and 62% for sulfamethoxazole.
Sulfamethoxazole and trimethoprim are found in serum in the free, protein-bound and metabolised form. The degree of protein binding for trimethoprim and sulfamethoxazole is 45 and 70%, respectively. Tissue levels of trimethoprim are usually higher than corresponding plasma levels. Especially high concentrations are found in lung and kidney tissue. Trimethoprim concentrations in, for example, bile, prostatic fluid, saliva and sputum exceeds the corresponding plasma concentrations. Concentrations in the aqueous humour and cerebrospinal fluid are adequate for an antibacterial effect. The concentration of active sulfamethoxazole in aqueous humour, bile, cerebrospinal fluid and sputum is about 30% of the plasma concentration.
In humans, trimethoprim and sulfamethoxazole are detected in fetal tissue (placenta, liver, lung), umbilical cord blood and amniotic fluid, indicating that both substances cross the placenta. The concentration of trimethoprim in the fetus is generally similar to that in the mother for trimethoprim and slightly lower for sulfamethoxazole (see section 4.6).

Both substances are excreted in breast milk. The concentrations in breast milk are generally similar to plasma concentrations in the mother for trimethoprim and slightly lower for sulfamethoxazole (see section 4.6).

Metabolism
About 30% of the trimethoprim dose is metabolised. Results from an *in-vitro* study with human liver microsomes show that CYP3A4, CYP1A2 and CYP2C9 are predominantly responsible for the metabolism of trimethoprim. The main metabolites of trimethoprim are 1-and 3-oxides and 3- and 4-hydroxy derivatives; certain metabolites are microbiologically active.
About 80% of the sulfamethoxazole dose is metabolised in the liver, preferentially to the N_4-acetyl derivative (≈ 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-life of the two components is the same (a mean of 10 hours for trimethoprim and 11 hours for sulfamethoxazole).

Trimethoprim and sulfamethoxazole are eliminated via the kidneys by glomerular filtration; trimethoprim is also eliminated by tubular secretion. Sulfamethoxazole is 20% eliminated as unchanged active substance, while about 60% is present in the acetylated form and about 15% in the glucuronated form. Approximately two thirds of trimethoprim is excreted unchanged in the active form. Total plasma clearance of trimethoprim is 1.9 ml/min/kg and for sulfamethoxazole 0.32 ml/min/kg. A small proportion of each substance is eliminated via the faeces.

Pharmacokinetics in special patient groups

Paediatric population
The pharmacokinetics for both components of Bactrim, trimethoprim and sulfamethoxazole, are age-dependent in the paediatric population with normal renal function. While elimination of trimethoprim and sulfamethoxazole is reduced in neonates during the first two months, thereafter both trimethoprim and sulfamethoxazole exhibit higher elimination with a higher body clearance and shorter half-life. The differences are most apparent in young infants (>1.7 months up to 24 months) and decrease with age, compared with 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 eliminated to a large extent renally in the unchanged form and in view of the fact that creatinine clearance decreases physiologically with age, a reduction in renal and total clearance of trimethoprim is to be expected. The pharmacokinetics of sulfamethoxazole should be less affected by increasing age as renal clearance of sulfamethoxazole accounts for only 20% of total sulfamethoxazole clearance.

Patients with impaired renal function
In patients with severely impaired renal function (creatinine clearance 15-30 ml/min), the half-life of both substances is prolonged, necessitating a dose adjustment (see section 4.2).

Intermittent or continuous ambulatory peritoneal dialysis does not contribute significantly to the elimination of trimethoprim and sulfamethoxazole. Trimethoprim and sulfamethoxazole are eliminated to a significant extent during haemodialysis and haemofiltration. In children

with impaired renal function (creatinine clearance <30 ml/min), clearance of trimethoprim is reduced and the half-life is prolonged. The dose of sulfamethoxazole+trimethoprim in these patients should be based on renal function.

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

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

5.3 Preclinical safety data

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420), microcrystalline cellulose, carmellose sodium, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), polysorbate 80, banana flavouring (contains propylene glycol (E 1520)), vanilla flavouring (contains ethanol) and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.
Use within 8 weeks of first opening.

6.4 Special precautions for storage

Do not store above 25 °C after first opening.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottle containing 100 ml oral suspension.
Measuring spoon graduated 1.25/2.5/5mL crystal clear

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Keep the measuring spoon with the product in the outer packaging.

7 MARKETING AUTHORISATION HOLDER

To be completed nationally

8 MARKETING AUTHORISATION NUMBER

To be completed nationally

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first approval: 1972-10-20
Date of latest renewal: 2007-01-01

10 DATE OF REVISION OF THE TEXT

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