Bactrim®

Sulfamethoxazole + trimethoprim

Composition

Active substances:

Trimethoprim (TM) and sulfamethoxazole (SMZ). The combination of the two active substances TM and SMZ has established itself under the name co-trimoxazole.

Excipients:

Bactrim tablets:
Excipients for tablets.

Bactrim Forte film-coated tablets:
Excipients for coated tablets.

Bactrim syrup for children:
Flavouring agents: vanillin and others; preservatives: E216, E218; excipients for suspension.

Pharmaceutical form and quantity of active substance per unit

Bactrim tablets:
white scored tablets, 80 mg TM and 400 mg SMZ.

Bactrim Forte film-coated tablets:
beige-white scored film-coated tablets, 160 mg TM and 800 mg SMZ.

Bactrim syrup for children:
oral suspension, 40 mg TM and 200 mg SMZ/5 ml.

Indications and potential uses

Infections due to co-trimoxazole-sensitive organisms, such as:

Upper and lower respiratory tract and ear infections: acute exacerbations of chronic bronchitis, bronchiectasis, pneumonia (including *Pneumocystis carinii* pneumonia), sinusitis, otitis media.

Urogenital infections: acute and chronic cystitis, pyelonephritis, urethritis, prostatitis.

Gastrointestinal infections including typhoid and paratyphoid fever (including treatment of chronic carriers) and cholera (as an adjunct to fluid and electrolyte replacement).

Other bacterial infections due to sensitive organisms: acute brucellosis, nocardiosis, mycetoma (except when caused by true fungi), South American blastomycosis (*Paracoccidioides brasiliensis*).

In osteomyelitis as a last-line drug (e.g. when vancomycin is contraindicated), for multiresistant organisms shown to be sensitive to co-trimoxazole.

Official recommendations on the appropriate use of antibiotics should be followed, especially usage recommendations to prevent the increase in antibiotic resistance.

Dosage and administration

Usual dosage

Bactrim is administered every 12 hours. Adults and children over 12 years are generally treated with tablets or Forte film-coated tablets, children under 12 years with syrup for children.

Table 1: Usual dosage for adults and children over 12 years of age

	Tablets		Forte film-coated tablets	
	morning	evening	morning	evening
Standard dosage	2	2	1	1
Minimum dosage and dosage for long-term therapy (more than 14 days)	1	1	½	½
High dosage (for severe cases)	3	3	1 ½	1 ½

Table 2: Usual dosage for children up to 12 years of age

	Syrup number of measuring spoons – every 12 hours
6 weeks to 5 months	½ (2.5 ml)
6 months to 5 years	1 (5 ml)
6 years to 12 years	2 (10 ml)

The pediatric doses shown in Table 2 are approximately equivalent to a daily dose of 6 mg TM and 30 mg SMZ per kg body weight. In severe infections the dosage for children may be increased by 50%.

Special dosage instructions

Acute uncomplicated urinary tract infections

For treatment of women with acute uncomplicated urinary tract infections, a single dose of 2–3 Forte tablets is recommended. These are best taken in the evening after a meal or before going to bed.

Patients with Pneumocystis carinii *pneumonia*

The recommended dosage is up to 20 mg TM per kg and 100 mg SMZ per kg orally per 24 hours, given in equal divided doses every 6 hours for 14 days.

Table 3 below is a general guideline for the upper dosage limit, based on body weight in patients with *Pneumocystis carinii* pneumonia:

Table 3

Body weight [kg]	Dose – every 6 hours		
	Measuring spoons of syrup	Tablets	Forte film-coated tablets
8	1 (5 ml)	-	-
16	2 (10 ml)	1	-
24	3 (15 ml)	1½	-
32	4 (20 ml)	2	1
40	5 (25 ml)	2½	-
48	6 (30 ml)	3	1½
64	8 (40 ml)	4	2
80	10 (50 ml)	5	2½

Pneumocystis carinii *pneumonia prophylaxis*

The recommended dosage for prophylaxis of *Pneumocystis carinii* pneumonia in adolescents and adults is 1 Forte film-coated tablet 3 times weekly or 1 standard tablet daily. (For a comparison of the two options, see under *Properties and effects*, *Clinical efficacy*.)

The recommended dosage for prophylaxis of *Pneumocystis carinii* pneumonia in children is 150 mg/m^2/day of TM and 750 mg/m^2/day of SMZ orally, divided into two equal daily doses on three consecutive days per week. The maximum daily dose should not exceed 320 mg of TM and 1600 mg of SMZ.

The following table is a general guideline for achieving the recommended dosage, based on body surface area (BSA), for prophylaxis of *Pneumocystis carinii* pneumonia in children.

Table 4

Body surface area (m^2)	Dose – every 12 hours	
	Measuring spoons of syrup	Tablets
0.26	½ (2.5 ml)	
0.53	1 (5 ml)	$^1/_2$
1.06	2 (10 ml)	1

The optimum prophylactic dosage has not been determined.

Patients with nocardiosis

The recommended dosage for adults with nocardiosis is 3–4 Forte film-coated tablets daily for at least 3 months. This dosage recommendation should be adapted to the patient's age, weight and renal function, and to the severity of the disease. There have been reports of long-term treatment for 18 months.

Patients with renal impairment

Dose recommendation for patients with renal impairment:

Table 5

Creatinine clearance	Recommended dosage schedule
>30 ml/min	Standard dosage
15–30 ml/min	Half the standard dosage
<15 ml/min	Use not recommended

Hemodialysis patients

When Bactrim is indicated in hemodialysis patients, it should be given the first time at the standard dose, then at half or a third of the standard dose every 24–48 hours. The serum concentration of the drug should be monitored and the dosage adjusted accordingly.

Method and duration of use

Bactrim is best taken with plenty of fluid after a meal.

In acute infections treatment with oral Bactrim should continue for at least 5 days.

Contraindications

- Hypersensitivity to the active substances, to sulfonamides or trimethoprim, or to any of the constituent excipients.
- Marked parenchymal liver disease.
- Severe renal impairment (creatinine clearance <15 ml/min) unless TM and SMZ plasma concentrations can be determined repeatedly.
- Megaloblastic anemia due to folic acid deficiency.
- Use in premature infants or neonates during the first 6 weeks of life, as this may increase the risk of kernicterus.
- Use in the last trimester of pregnancy (see *Pregnancy and lactation*).
- Combination with dofetilide (see *Interactions*).

Warnings and precautions

Bactrim should be used with caution in patients with a history of allergy or bronchial asthma.

Depending on dosage and duration of treatment, there is an increased risk of severe adverse reactions in elderly patients, in patients with complicating conditions such as renal and/or hepatic impairment, and in patients concomitantly receiving other medicinal products. Fatal outcome, though rare, has been reported in connection with adverse reactions such as blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and fulminant liver necrosis.

Other than in exceptional cases, Bactrim should not be given to patients with serious blood dyscrasias. The product has occasionally been administered to patients receiving cytotoxic agents for the treatment of leukemia, without evidence of any adverse effect on the bone marrow or peripheral blood.

Owing to the possibility of hemolysis, Bactrim should not be given to patients with G6PD deficiency or certain hemoglobinopathies (Hb-Zurich, Hb-Cologne) unless absolutely essential, and then only in minimal doses.

Treatment should be discontinued immediately at the first appearance of skin rash or any other serious adverse reaction.

In order to minimise the risk of adverse reactions, the duration of treatment with Bactrim should be as short as possible, particularly in elderly patients. In renal impairment, dosage should be adjusted in accordance with the Special dosage instructions.

Severe persistent diarrhea during or after treatment may be indicative of pseudomembranous colitis, which requires immediate treatment. In such cases, Bactrim should be discontinued, and appropriate diagnostic and therapeutic measures initiated (e.g. oral vancomycin 250 mg 4 times daily). Antiperistaltic drugs are contraindicated.

If Bactrim is given over a prolonged period, regular blood counts are required. If a significant reduction in the count of any formed blood element to below normal levels is noted, Bactrim should be discontinued.

Urine and renal function should be monitored during long-term treatment, especially in patients with renal impairment.

An adequate fluid intake and diuresis should be ensured during treatment in order to prevent crystalluria.

Since Bactrim, like other antibiotics, can reduce the effect of oral contraceptives, female patients should be advised to take additional contraceptive measures during Bactrim treatment.

Prolonged treatment with Bactrim can lead to overgrowth of non-sensitive organisms and fungi. Appropriate treatment should be initiated immediately in the event of superinfection.

Caution is indicated in patients with porphyria or thyroid dysfunction.

In elderly patients or patients with renal impairment, hematological changes indicative of folic acid deficiency may occur. These can be reversed by folinic acid therapy.

Caution is indicated in patients with an additional risk factor for folic acid deficiency, e.g. treatment with phenytoin or other folic acid antagonists, malnutrition.

Cases of pancytopenia have been reported in patients given the combination of trimethoprim and methotrexate (see *Interactions*).

Trimethoprim has been found to have an adverse effect on phenylalanine metabolism. However, this has no relevance to patients with phenylketonuria who adhere to an appropriate diet.

"Slow acetylators" may be at increased risk for idiosyncratic reactions to sulfonamides.

Interactions

Pharmacokinetic and pharmacodynamic interactions

Increased digoxin blood levels can occur with concomitant co-trimoxazole therapy, especially in elderly patients.

Co-trimoxazole can inhibit the hepatic metabolism of phenytoin. A 39% increase in phenytoin half-life and a 27% decrease in the metabolic clearance rate of phenytoin have been observed following administration of co-trimoxazole at normal clinical dosages. If the two drugs are given concurrently, the possibility of an undesirably increased phenytoin effect should be borne in mind.

The efficacy of tricyclic antidepressants may be reduced if these are administered concurrently with co-trimoxazole.

Sulfonamides, including sulfamethoxazole, can displace methotrexate from plasma protein binding sites and impair the renal transport of methotrexate, thus increasing free methotrexate concentration and effect.

Co-trimoxazole may influence the required dose of oral antidiabetic agents.

Like other antibiotics, Bactrim can reduce the efficacy of oral contraceptives. Female patients should therefore be advised to take additional contraceptive measures during Bactrim treatment.

Coadministration of indomethacin and co-trimoxazole can raise sulfamethoxazole blood levels.

Observed interactions

An increased incidence of thrombocytopenia with purpura has been observed in elderly patients concurrently receiving certain diuretics, primarily thiazides.

It has been reported that co-trimoxazole may prolong prothrombin time in patients receiving the anticoagulant warfarin. This interaction should be borne in mind when Bactrim is given to patients already receiving anticoagulants. In such cases, the prothrombin time should be redetermined.

Reversible deterioration of renal function, as detected by raised serum creatinine levels, has been observed in patients treated with co-trimoxazole and ciclosporin following renal transplantation. This interaction is thought to be due to the TM component.

Cases of pancytopenia have been reported in patients given the combination of trimethoprim and methotrexate (see *Warnings and precautions*). Trimethoprim has a low affinity for human dihydrofolate reductase, but can potentiate the side effects of methotrexate and lead to undesirable hematological interactions with methotrexate, particularly in the presence of other risk factors such as advanced age, hypoalbuminemia, renal impairment and reduced bone marrow reserve. Such adverse drug reactions can occur in particular when high doses of methotrexate are administered.

Such patients should be treated with folic acid or calcium folinate in order to counteract the effects on hematopoiesis (rescue).

Isolated reports suggest that patients receiving pyrimethamine-containing preparations as malaria prophylaxis in doses exceeding 25 mg pyrimethamine weekly may develop megaloblastic anemia if co-trimoxazole is prescribed concurrently.

Toxic delirium has been reported after coadministration of Bactrim and amantadine.

There is evidence that TM can interact with dofetilide by inhibiting the renal transport system. Coadministration of trimethoprim 160 mg in combination with sulfamethoxazole 800 mg twice daily and dofetilide 500 µg twice daily for 4 days increased the area under the concentration-time curve (AUC) of dofetilide by 103% and the peak plasma concentration (C_{max}) by 93%. Dofetilide may cause serious ventricular arrhythmias associated with QT interval prolongation, including torsades de pointes, which are directly related to the plasma concentration of dofetilide. Coadministration of dofetilide and trimethoprim is contraindicated.

Pregnancy and lactation

Pregnancy

Bactrim should not be used in pregnancy unless it is clearly necessary, since both TM and SMZ cross the placental barrier and may thus interfere with fetal folic acid metabolism.

In animal experiments, very high doses of co-trimoxazole induced malformations typical of folic acid antagonism.

On the basis of studies in pregnant women, literature reviews and spontaneous reports of malformations, co-trimoxazole appears to present no significant risk of teratogenicity in humans.

Supplementary folic acid (5 mg/day) is recommended for pregnant women who require Bactrim treatment. Bactrim should be avoided as far as possible during the last trimester, as it can increase the risk of kernicterus in the neonate.

Lactation

Both TM and SMZ pass into breast milk. Although the amount of drug ingested by a breast-fed infant is extremely small, the benefit to the mother should be carefully weighed against the risk to the infant (kernicterus, hypersensitivity) (see *Contraindications*).

Effects on ability to drive and use machines

Bactrim has no direct effects on the ability to drive or operate machinery. However, undesirable effects are possible that could impair these abilities, in some cases severely (see *Undesirable effects*).

Undesirable effects

The main undesirable effects are skin reactions and mild gastrointestinal upsets, which occurred in approximately 5% of treatment periods.

The following undesirable effects were reported (arranged by frequency and MedDRA system organ classes):

"*Very common*" (≥1/10), "*common*" (≥1/100, <1/10), "*uncommon*" (≥1/1000, <1/100), "*rare*" (≥1/10,000, <1/1000), "*very rare*" (<1/10,000).

Infections and infestations

Very rare: Fungal infections such as candidiasis.

Blood and lymphatic system

Rare: Leukopenia, granulocytopenia, thrombocytopenia.

Very rare: Agranulocytosis, anemia (megaloblastic, immunohemolytic, aplastic), methemoglobinemia, pancytopenia. Most of the observed hematological changes were mild, asymptomatic and reversible on discontinuing the product.

Immune system disorders

Very rare: Allergic reactions such as fever, angioedema, anaphylactoid reactions and serum sickness, periarteritis nodosa, allergic myocarditis.

Metabolic and nutritional disorders

Very common: Increase in serum potassium level: High-dose TM as used in patients with *Pneumocystis carinii* pneumonia induces a progressive but reversible increase in serum potassium concentration in a substantial proportion of patients. In patients with disorders of potassium metabolism or renal insufficiency or given drugs that induce hyperkalemia, TM can cause hyperkalemia very frequently (in up to over 60% of patients), even at the recommended doses. Close monitoring of serum potassium should be ensured in these patients.

Hyponatremia.

Hypoglycemia in non-diabetic patients, usually occurring in the first few days of treatment. Patients with renal dysfunction, liver disease or malnutrition and those receiving high doses of TM-SMZ are at particular risk.

Psychiatric disorders

Very rare: Hallucinations. Delirium and psychosis, particularly in elderly patients.

Nervous system

Very rare: Neuropathy (including peripheral neuritis and paresthesia), uveitis. Aseptic meningitis or meningitis-like symptoms, ataxia, convulsions, vertigo, tinnitus.

Respiratory organs

Very rare: Pneumonitis with eosinophilic infiltration.

Gastrointestinal disorders

Common: Nausea (with or without vomiting).

Rare: Stomatitis, glossitis, diarrhea.

Very rare: Pseudomembranous enterocolitis, acute pancreatitis in severely ill patients.

Hepatobiliary system

Very rare: Elevated transaminases and bilirubin, hepatitis, cholestasis, hepatic necrosis, vanishing bile duct syndrome.

Skin

Common: Rashes. These side effects are generally mild and rapidly reversible after withdrawal of the drug.

Like many other medicinal products that contain sulfonamides:

Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), purpura, Henoch-Schoenlein purpura, photosensitivity.

Musculoskeletal system

Very rare: Arthralgia, myalgia, rhabdomyolysis.

Kidneys and urinary tract

Very rare: Renal impairment and failure, interstitial nephritis, elevated blood urea nitrogen (BUN), elevated serum creatinine, crystalluria. Sulfonamides, including Bactrim, can increase diuresis, particularly in patients with cardiac edema.

Undesirable effects in HIV-infected patients

HIV-infected patients with frequent comorbidities and their treatments usually receive longer prophylaxis or treatment of *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia with higher doses of Bactrim. Apart from a small number of additional side effects, the side effect profile in these patients is similar to that in the non-HIV-infected general population. However, certain side effects occur more frequently (in about 65%) and are often more severe, necessitating interruption or cessation of Bactrim therapy in 20–25% of patients.

The following undesirable effects, in particular, have been observed additionally or with greater frequency:

Blood and lymphatic system

Very common: Mainly neutropenia, but also anemia, leukopenia, granulocytopenia and thrombocytopenia.

Very rare: Agranulocytosis.

Immune system disorders

Very common: Fever, usually in association with skin rashes.

Very rare: Allergic reactions such as angioedema, anaphylactoid reactions and serum sickness.

Metabolic and nutritional disorders

Very common: Hyperkalemia. Close monitoring of serum potassium should be ensured in these patients.

Uncommon: Hyponatremia, hypoglycemia.

Psychiatric disorders

Very rare: Acute psychosis.

Nervous system

Very rare: Neuropathy (including peripheral neuritis and paresthesia), hallucinations, uveitis. Aseptic meningitis or meningitis-like symptoms, ataxia, convulsions, Parkinson-

like resting tremor, sometimes combined with apathy, ankle clonus and broad-based gait. Vertigo, tinnitus.

Respiratory organs
Very rare: Pneumonitis with eosinophilic infiltration.

Gastrointestinal disorders
Very common: Anorexia, nausea with or without vomiting and diarrhea.

Rare: Stomatitis, glossitis.

Very rare: Pancreatitis.

Hepatobiliary system
Common: Liver enzyme/transaminase elevation, cholestatic jaundice.

Very rare: Sometimes severe hepatitis.

Skin
Very common: Maculopapular rash that eventually causes itching and is rapidly reversible after withdrawal of the drug, usually with pruritus.

Rare: Photosensitivity.

Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), Henoch-Schoenlein purpura.

Musculoskeletal system
Very rare: Arthralgia, myalgia, rhabdomyolysis.

Kidneys and urinary tract
Uncommon: Renal impairment, azotemia, elevated serum creatinine, crystalluria.

Very rare: Sulfonamides, including Bactrim, can increase diuresis, particularly in patients with cardiac edema.

Overdosage

Symptoms

In *acute* overdosage the following signs and symptoms may occur: nausea, vomiting, headache, vertigo, dizziness, mental and visual disturbances; crystalluria, hematuria and anuria can occur in severe cases.
In *chronic* overdosage: bone marrow depression manifested as thrombocytopenia, leukopenia or other blood dyscrasias due to folic acid deficiency.

Management

Depending on the signs and symptoms, the following measures should be considered: avoidance of further absorption, acceleration of renal elimination by forced diuresis (alkalinisation of the urine accelerates the elimination of SMZ), hemodialysis (N.B.: peritoneal dialysis is ineffective), monitoring of blood count and electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Calcium folinate, 3–6 mg i.m. for 5–7 days, may be given to counteract the effect of TM on hematopoiesis.

Properties and effects

ATC code: J01EE01.

Mechanism of action/Pharmacodynamics

Bactrim contains two active ingredients acting synergistically by blockade of two enzymes that catalyse successive steps in the biosynthesis of folinic acid in the microorganism. This mechanism usually results in bactericidal activity *in vitro* of co-trimoxazole at concentrations at which the individual substances are only bacteriostatic. In addition, co-trimoxazole is often effective against organisms that are resistant to one of the two components. Furthermore, the risk of development of widespread resistance is minimised by this dual action.

The antibacterial action of co-trimoxazole *in vitro* covers both gram-positive and gram-negative pathogens including the following organisms, though sensitivity can depend on geographical area:

Generally sensitive organisms (MIC_{90} ≤2 mg/l [TM]; ≤38 mg/l [SMZ])

Cocci: *Moraxella catarrhalis.*
Gram-negative rods: *Haemophilus parainfluenzae*, *Citrobacter freundii*, other *Citrobacter* spp., *Klebsiella oxytoca*, other *Klebsiella* spp., *Enterobacter cloacae*, *Enterobacter aerogenes*, *Hafnia alvei*, *Serratia marcescens*, *Serratia liquefaciens*, other *Serratia* spp., *Yersinia enterocolitica*, other *Yersinia* spp., *Vibrio cholerae.*

Miscellaneous gram-negative rods: *Edwardsiella tarda, Alcaligenes faecalis, Burkholderia pseudomallei.*

Based on clinical experience, the following organisms have also to be considered as sensitive: *Brucella, Listeria monocytogenes, Nocardia asteroides, Pneumocystis carinii, Cyclospora cayetanensis.*

Partially sensitive organisms (MIC_{90} = 4 mg/l [TM]; = 76 mg/l [SMZ])

Cocci: *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant), *Staphylococcus* spp. (coagulase-negative), *Streptococcus pneumoniae* (penicillin-sensitive, penicillin-resistant).

Gram-negative rods: *Haemophilus influenzae* (β-lactamase-positive, β-lactamase-negative), *Haemophilus ducreyi*, *E. coli*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, other *Providencia* spp., *Salmonella typhi*, *Salmonella enteritidis*, *Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia*).

Miscellaneous gram-negative rods: *Acinetobacter lwoffi*, *Acinetobacter anitratus*

(especially *A. baumanii*), *Aeromonas hydrophila*.

Resistant organisms (MIC_{90} ≥8 mg/l [TM]; ≥152 mg/l [SMZ])

Burkholderia (*Pseudomonas*) *cepacia*, *Pseudomonas aeruginosa*, *Mycoplasma* spp., *Mycobacterium tuberculosis*, *Shigella* spp., *Treponema pallidum*, *Neisseria gonorrhoeae*, *Bacteroides*, other strictly anaerobic organisms.

The local prevalence of resistance to co-trimoxazole among bacteria relevant to the infection treated should be known when Bactrim is prescribed on an empirical basis.

In infections due to moderately sensitive organisms, sensitivity testing should be performed in order to exclude resistance.

Sensitivity to co-trimoxazole can be determined by standardised methods such as the disk or dilution tests recommended by the Clinical and Laboratory Standards Institute (CLSI). The following sensitivity criteria are recommended by the CLSI:

Table 6

	Disk test*, diameter of inhibition zone [mm]	Dilution test **, MIC (mg/l) TM + SMZ
Sensitive	≥16	≤2 + ≤38
Partially sensitive	11–15	4 + 76
Resistant	≤10	≥8 + ≥152

* Disk: 1.25 µg TM and 23.75 µg SMZ

** TM and SMZ in a ratio of 1 to 19.

Development of resistance, cross-resistance

Resistance to co-trimoxazole develops only rarely during treatment. Cross-resistance exists between all sulfonamides; cross-resistance to chemically unrelated antibiotics does not develop as a result of acquisition of resistance to co-trimoxazole.

Synergism, antagonism

There is marked synergism between sulfamethoxazole and trimethoprim. This synergism generally exists even when resistance to one of the two components is present.

Clinical efficacy

The clinical efficacy of Bactrim in the commonest approved indications (see *Indications and potential uses*) has been demonstrated in numerous clinical studies.

This also applies to the recently added indication, prophylaxis of *Pneumocystis jiroveci* pneumonia (former name: *Pneumocystis carinii* pneumonia, PCP) in HIV-infected patients:
A Dutch randomised study with a median follow-up of one year compared Bactrim tablets (80/400 mg) with Bactrim Forte tablets (160/800 mg) in 260 HIV-infected patients

with CD4 cell counts below 200 cells/µl and no history of PCP. No patient in either group developed PCP. More undesirable effects requiring withdrawal of TM-SMX occurred in the group treated with Bactrim Forte (hazard ratio 1.4; 95% confidence interval [CI] 0.95–2.02).
A randomised multicentre study with a median follow-up of approximately two years compared daily with thrice-weekly administration of Bactrim Forte tablets in 2625 HIV-infected patients with CD4 cell counts below 200 cells/µl, some of whom had a history of PCP. Intention-to-treat analysis showed similar annual PCP incidences in the two groups: 3.5 and 4.1 (relative risk 0.82; 95% CI 0.69–1.09). On-treatment analysis showed a lower PCP risk with daily administration (relative risk 0.59; 95% CI 0.37–0.95). Discontinuation of TM-SMX due to undesirable effects was more frequent with daily administration (relative risk 2.14; 95% CI 1.73–2.66).

Pharmacokinetics

The clinically relevant pharmacokinetic properties of TM and SMZ are broadly similar.

Absorption

TM and SMZ are absorbed rapidly and almost completely (bioavailability: 80–100 %) in the upper gastrointestinal tract after oral administration. Following a single dose of 160 mg TM + 800 mg SMZ, peak plasma concentrations of 1.5–3 mg/l for TM and 40–80 mg/l for SMZ are reached in 1–4 hours. If administration is repeated every 12 hours, the steady-state peak plasma concentrations of SMZ and TM are generally 50–100% higher than after a single oral dose. Plasma levels are dose-proportional. The effect of food on the kinetics of the active components of Bactrim has not been investigated. When a trimethoprim suspension is taken on a full stomach, the extent of absorption is less than when taken on an empty stomach, though the rate of absorption was not affected by a standard meal.

Distribution

The volumes of distribution of TM and SMZ are approximately 1.2–1.5 l/kg and 0.15–0.36 l/kg, respectively.

At the above concentrations 42–46% of TM and 66% of SMZ are bound to plasma proteins.

Studies in both animals and man have shown that diffusion of co-trimoxazole into the tissues is good. Large amounts of TM and smaller amounts of SMZ pass from the bloodstream into the interstitial fluid and other extravascular body fluids. The concentrations of TM and SMZ may be increased in inflamed tissues.

TM and SMZ have been detected in the fetal placenta, cord blood, amniotic fluid and fetal tissues (liver, lungs), indicating that both substances cross the placental barrier. As a rule, fetal TM concentrations are similar to those in the maternal circulation, while fetal levels of SMZ are lower.

Both substances are excreted in breast milk. Concentrations in breast milk are similar to (TM) or lower than (SMZ) those in the maternal plasma.

Metabolism

Some 50–70% of TM and 10–30% of SMZ are eliminated in the urine in unchanged form. The principal TM metabolites are 1- and 3-oxides and 3'- and 4'-hydroxy derivatives; some of the metabolites are active. SMZ is metabolised in the liver, predominantly via N_4-acetylation and to a lesser extent via glucuronidation; its metabolites are inactive.

Elimination

With normal renal function, the half-lives of the two components are very similar (mean of 10 hours for TM and 11 hours for SMZ).

Total clearance levels are around 100 ml/min for TM and 20 ml/min for SMZ.

The elimination half-life of TM in children is approximately half that in adults, while no corresponding significant difference applies to SMZ.

Both substances and their metabolites are eliminated predominantly via the kidneys both by glomerular filtration and by tubular secretion. The concentrations of TM and SMZ in the urine are some 100 and 5 times higher, respectively, than the corresponding plasma levels.

Renal clearance levels are 20–80 ml/min for trimethoprim and 1–5 ml/min for sulfamethoxazole.

Both substances are detected to a slight extent in the feces.

Pharmacokinetics in special patient groups

In the elderly and in patients with renal impairment, the elimination half-lives of both components are prolonged and appropriate dose adjustment is required.

Although the kinetics, particularly for TM, are not markedly altered in patients with hepatic impairment, caution is nevertheless indicated when Bactrim is administered at high doses in severe hepatic impairment. Blood level determination and dose adjustment are required with hemodialysis.

Preclinical data

TM also inhibits folic acid reductase in mammalian cells, but this requires concentrations many orders of magnitude higher than in bacteria. Several studies have shown that high-dose combinations of TM with sulfonamides lead to malformations and embryolethality in rats. Folic acid antagonism evidently exists under these experimental conditions. However, the doses employed were a factor of 10–100 above therapeutic human doses. TM is mutagenic *in vitro*.

SMZ induces thyroid carcinomas in rats. This result appears to be species-specific and is probably of no clinical significance in humans.

Additional information

Influence on diagnostic methods

Co-trimoxazole, particularly the TM component, can interfere with a serum methotrexate assay based on the competitive binding protein technique when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by radioimmunoassay.

The presence of TM and SMZ may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, causing values in the normal range to be overestimated by about 10%.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the container.

Packs

Tablets (scored)	20, 100
Forte film-coated tablets (scored)	10, 20, 50
Syrup for children	50 ml, 100 ml

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at November 2007

Syrup:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by CENEXI SAS, Fontenay-sous-Bois, France

Tablets, Forte film-coated tablets:

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel