Enterococcus faecalis, non-ß-hemolytic streptococci, Streptococcus pneumoniae (penicillin-sensitive).

Gram-negative

Current clinical experience has also shown Brucella, Chlamydia trachomatis*, Nocardia asteroides, Toxoplasma gondii and Pneumocystis carinii to be amenable to treatment with Bactrim.

Current clinical experience suggests that, in a hospital setting, susceptibility testing is advisable for these organisms.

Partially Sensitive Organisms
Streptococcus pneumoniae: penicillin-resistant, E. coli Klebsiella pneumoniae, other Klebsiella spp., other Providencia spp., Pseudomonas cepacia.

Resistant Organisms
Most pseudomonas. Xanthomonas maltophilia, anaerobes, Campylobacter fetus, ureaplasmas and mycoplasmas, Mycobacterium tuberculosis and Treponema pallidum are resistant. In the case of infections caused by moderately sensitive pathogens susceptibility testing is recommended in order to exclude any resistance.

Sensitivity to Bactrim can be determined by standardized methods such as the disk or dilution tests recommended by the National Committee for...
Clinical Laboratory Standards (NCCLS). The following criteria for susceptibility are recommended by the NCCLS:

<table>
<thead>
<tr>
<th>Disk test*</th>
<th>Dilution test**</th>
</tr>
</thead>
<tbody>
<tr>
<td>diameter of inhibition zone (mm)</td>
<td>MIC (µg/ml) TM + SMZ</td>
</tr>
<tr>
<td>Sensitive</td>
<td>≥16</td>
</tr>
<tr>
<td>Moderately sensitive</td>
<td>11-15</td>
</tr>
<tr>
<td>Resistant</td>
<td>≤10</td>
</tr>
</tbody>
</table>

* 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 treatment is rare.

Cross-resistance exists between all sulfonamides; cross-resistance with chemically unrelated antibiotics does not occur by the acquisition of resistance to co-trimoxazole.

Synergism, Antagonism
Marked synergism exists between sulfamethoxazole and trimethoprim. This synergism is particularly prevalent when resistance to one of the two components is present.

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

Absorption
TM and SMZ are rapidly and almost completely (bioavailability: 80-100%) absorbed 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 µg/ml for TM and 40-80 µg/ml 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. The 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, although the rate of absorption was not affected by a standard meal.

Distribution
The volumes of distribution of TM and SMZ are approx. 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 Bactrim 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 can be increased in tissues with inflammatory changes.

TM and SMZ have been detected in the fetal placenta, cord blood, amniotic fluid and fetal tissues (liver, lungs), thus 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 (TM) to or lower (SMZ) than those in the maternal plasma.

Metabolism
Some 50-70% of TM and 10-30% of SMZ are eliminated 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 metabolized in the liver, predominantly via N4-acetylation and, to a lesser extent, glucuronidation; its metabolites are inactive.

Elimination
With normal renal function the half-lives of the two components are very similar (means 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, as well as their metabolites, are eliminated predominantly via the kidneys, by glomerular filtration and tubular secretion; the con-
Concentrations of both active ingredients in the urine are higher than the corresponding blood levels. 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.

Kinetics in special clinical situations
The elimination half-lives of both components are prolonged in the elderly and in patients with restricted renal function, and the dosage should be adjusted accordingly. Although the kinetics, particularly for TM, are not significantly altered in patients with liver dysfunction, caution is nevertheless indicated when high-dose Bactrim treatment is administered in severe liver dysfunction. Dose adjustments are indicated with hemodialysis.

Indications
Infections due to co-trimoxazole-sensitive organisms, e.g.:
Upper and lower respiratory infections: acute and chronic bronchitis, bronchiectasis, pneumonia (including Pneumocystis carinii pneumonia); pharyngitis, tonsillitis (in infections due to group A β-hemolytic streptococci the antibacterial effect is not entirely satisfactory), sinusitis, otitis media.
Urogenital infections: acute and chronic cystitis, pyelonephritis, urethritis, including gonococcal urethritis and prostatitis.
Gastrointestinal infections: including typhoid and paratyphoid fever (incl. treatment of chronic carriers); bacillary dysentery; cholera (as an adjunct to fluid and electrolyte replacement).
Skin and soft tissue infections: pyoderma, furuncles, abscesses and wound infections.
Other bacterial infections: acute and chronic osteomyelitis, acute brucellosis, septicemia due to susceptible organisms, nocardiosis, mycetoma (except when caused by the true fungi), South American blastomycosis.

Contraindications
Bactrim is contraindicated in patients with marked liver parenchymal damage. It is also contraindicated in patients with severe renal impairment (creatinine clearance <15 ml/mm) when repeated determinations of the plasma concentration cannot be made. Bactrim is also contraindicated in the presence of hypersensitivity to sulfonamides or trimethoprim and in megaloblastic anemia due to folic acid deficiency. Bactrim should not be administered to premature or term neonates during the first 6 weeks of life.

Side Effects
The following effects have been reported (in order of frequency):
Gastrointestinal side effects: nausea (with or without vomiting), stomatitis, diarrhea, rare cases of cholestatic hepatitis and isolated cases of pseudomembranous enterocolitis or acute pancreatitis, the latter particularly in patients in a poor state of health, e.g. AIDS. Focal or diffuse hepatic necroses have been observed in very rare cases.
Drug-induced skin rashes: These are generally mild and quickly reversible after withdrawal of medication. Like many other drugs, Bactrim has in rare cases been linked to photosensitivity. Severe skin reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell’s syndrome) occur in rare instances with, very rarely, a fatal outcome.
Kidneys: Kidney failure and impairment have been associated with co-trimoxazole therapy in rare cases (e.g. interstitial nephritis), as has crystalluria. Sulfonamides, including Bactrim, can increase diuresis, particularly in patients with cardiac edema.
Blood: Most of the hematological changes observed have been mild and asymptomatic and have proved to be reversible on withdrawal of the therapy. The changes most commonly seen were leukopenia, neutropenia and thrombocytopenia. Very rarely, agranulocytosis, megaloblastic, hemolytic or aplastic anemia, pancytopenia or purpura may occur.
Hypersensitivity reactions: As with any other drug,
the event of renal impairment, dosage should be adjusted according to the Special dosage instructions. If Bactrim is given over a prolonged period, regular blood counts are required. If a significant reduction in any formed blood element to below normal levels is noted, Bactrim should be discontinued.

Other than in exceptional cases, Bactrim should not be given to patients with serious hematological disorders. The combination 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. Since Bactrim can reduce the effect of oral contraceptives, female patients should be asked to take additional contraceptive precautions during Bactrim treatment.

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

Owing to the possibility of hemolysis, Bactrim should not be given to patients with a 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 elderly patients or patients with renal impairment, hematological changes indicative of folic acid deficiency may occur. These are reversible by folinic acid therapy.

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

Patients undergoing long-term treatment with Bactrim (in particular, patients with renal impairment) should be monitored regularly for urine values and kidney function.

An adequate fluid intake should be ensured during treatment in order to prevent crystalluria.
**Pregnancy, Nursing Mothers**

Animal studies with very high co-trimoxazole doses have shown the development of anomalies typical of folic acid antagonism.

Studies with pregnant women, literature reviews and spontaneous reports of malformations do not appear to show any significant risk of a teratogenic effect for Bactrim in humans.

Since TM and SW cross the placental barrier, with potential effects on fetal folic acid metabolism, Bactrim should only be administered during pregnancy if the expected therapeutic benefit outweighs the risk to the fetus. Supplementary folic acid (5-10 mg/day) is recommended for pregnant women requiring Bactrim treatment. If possible, Bactrim should not be used during the last trimester as this is associated with an increased risk of neonatal kernicterus.

TM and SW pass into the breast milk. Although the quantity of drug consumed by the breastfed infant is extremely small, the benefit for the mother should be carefully weighed against the risk to the infant (kernicterus, hypersensitivity).

**Overdosage**

In acute overdosage the following signs and symptoms are possible: nausea, vomiting, headache, dizziness, lightheadedness, mental and visual disturbances; crystalluria, hematuria and anuria can occur in severe cases.

In chronic overdosage: bone marrow depression manifested in the form of thrombocytopenia, leukopenia or other blood dyscrasias as a result of folic acid deficiency.

Depending on the signs and symptoms involved, the following measures should be considered: gastric lavage, provoked emesis, acceleration of renal elimination by forced diuresis (alkalinization of the urine accelerates the elimination of SW), hemodialysis (NB. peritoneal dialysis is ineffective), monitoring of blood count and serum electrolytes. A definite blood dyscrasia or jaundice should be treated specifically. Calcium folinate, 3-6 mg I.M. for 5-7 days, may be administered as an antidote to counteract the effect of TM on hematopoiesis.

**Special Remarks**

*Interference with diagnostic laboratory tests*

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

The presence of TM and SW 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 medicine should not be used after the expiry date (EXP) shown on the pack.

**Drug 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 the prothrombin time in patients receiving the anticoagulant warfarin. This interaction should be borne in mind when Bactrim is given to patients already on anticoagulant therapy. In such cases, the coagulation time should be determined anew.

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, it is important to watch for an excessive phenytoin effect.

Sulfonamides, including sulfamethoxazole, can displace methotrexate from plasma protein binding sites, thus impairing its renal transport and increasing free methotrexate concentrations.

Co-trimoxazole may also affect the required dose of hypoglycemic drugs.

Occasional reports suggest that patients receiving pyrimethamine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic
Dosage for children under 12 years: daily dose approximately 2 ml/5 kg, in two equally divided doses, mornings and evenings. Thus, the recommended basis for dosage in children is 6 mg TM plus 30 mg SMZ per kg daily.

Duration of Therapy
As a general rule, Bactrim should be given by the parenteral route only for as long as the patient is unable to take the drug orally.

The standard dosage should not be given for more than 5 consecutive days or the maximum dosage for more than 3 consecutive days.

In acute infections treatment with oral Bactrim should continue for at least 5 days, or until the patient has been free of symptoms for 2 days.

Special Remarks
Infusion: Bactrim may be mixed only with the following infusion solutions: dextrose 5% and 10%, xylitol 10%, Ringer’s solution, dextran 6% in dextrose, sodium chloride 0.9%, sodium chloride 0.45% + dextrose 2.5%.

It is important to adhere to the following minimum dilution scheme, which is based on a proportion of 1 ml Bactrim ampoule solution to approximately 25-30 ml infusion solution:

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Bactrim ampoule solution to infusion solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ampoule Bactrim (5 ml)</td>
<td>125 ml infusion solution</td>
</tr>
<tr>
<td>2 ampoules Bactrim (10 ml)</td>
<td>250 ml infusion solution</td>
</tr>
<tr>
<td>3 ampoules Bactrim (15 ml)</td>
<td>500 ml infusion solution</td>
</tr>
</tbody>
</table>

These mixtures with Bactrim should be prepared immediately before use. After addition of Bactrim to the infusion solution the mixture should be shaken or swirled in order to ensure thorough mixing. Should visible turbidity or crystallization appear in the solution during the infusions, it should be replaced by a freshly prepared solution. Infusion solutions containing Bactrim must be used within 6 hours of preparation.

Dilution scheme for patients with fluid restriction
In cases where fluid restriction is desirable, 5 ml portions of Bactrim for infusion may be mixed with 75 ml of 5% dextrose, 0.9% sodium chloride or Ringer’s
solution. These solutions should be prepared immediately before use and administered within 2 hours when stored at room temperature and in subdued daylight. In order to achieve effective blood levels, the duration of the infusion, which will depend on the quantity of fluid, should not exceed 1½ hours. The normal duration is generally 30-60 minutes. Bactrim should be administered intravenously only in the form of the infusion solutions described above, and may not be injected undiluted either intravenously or direct into the infusion tube.

The prepared Bactrim infusion solution should not be mixed with other drugs or infusion solutions. Opened ampoules should be used immediately.

Special Dosage Instructions

**a. Dosage in gonorrhea**
5 tablets each morning and each evening, or 2½ forte film-coated tablets twice on one day

**b. Dosage in acute, uncomplicated urinary tract infections**
For women with acute, uncomplicated urinary tract infections, a single dose of 2-3 forte filmcoated tablets is recommended. The tablets should, ideally, be taken in the evening after a meal or before going to bed.

**c. The recommended dosage for patients with Pneumocystis carinii pneumonia is up to 20 mg TM per kg and up to 100 mg SMZ per kg I.V. or orally per 24 hours, given in equal divided doses every 6 hours for 14 days.**

**d. Dosage for children up to 12 years of age:**

<table>
<thead>
<tr>
<th>Syrup (number of measuring spoons)</th>
<th>mornings</th>
<th>evenings</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks to 5 months</td>
<td>½</td>
<td>½</td>
</tr>
<tr>
<td>6 months to 5 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6 years to 12 years</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

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

e. Dosage for patients with impaired renal function:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Recommended dosage schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 ml/mm</td>
<td>Standard dosage</td>
</tr>
<tr>
<td>15-30 ml/mm</td>
<td>Half the standard dosage</td>
</tr>
<tr>
<td>&lt;15 ml/mm</td>
<td>Use of Bactrim not recommended</td>
</tr>
</tbody>
</table>