

Trimethoprim-sulfamethoxazole (co-trimoxazole):

Class: Antibiotic.

Indications:

Oral: Treatment of urinary tract infections due to *E. coli*, *Klebsiella* and *Enterobacter* sp, *M. morgani*, *P. mirabilis* and *P. vulgaris*; acute otitis media; acute exacerbations of chronic bronchitis due to susceptible strains of *H. influenzae* or *S. pneumoniae*; treatment and prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP); traveler's diarrhea due to enterotoxigenic *E. coli*; treatment of enteritis caused by *Shigella flexneri* or *Shigella sonnei*

I.V.: Treatment of *Pneumocystis jirovecii* pneumonia (PCP); treatment of enteritis caused by *Shigella flexneri* or *Shigella sonnei*; treatment of severe or complicated urinary tract infections due to *E. coli*, *Klebsiella* and *Enterobacter* spp, *M. morgani*, *P. mirabilis*, and *P. vulgaris*.

Available dosage form in the hospital: 240MG/5ML SUSP, 480MG TAB, 960MG TAB, 96MG/ML AMP.

Trade Names:

Dosage:

Dosage recommendations are based on the trimethoprim component. double-strength tablets are equivalent to sulfamethoxazole 800 mg and trimethoprim 160 mg.

-General dosing guidelines:

-Oral: 1-2 double-strength tablets (sulfamethoxazole 800 mg; trimethoprim 160 mg) every 12-24 hours

-I.V.: 8-20 mg TMP/kg/day divided every 6-12 hours

-Chronic bronchitis (acute): Oral: One double-strength tablet every 12 hours for 10-14 days

-Cyclosporiasis (unlabeled use): Oral, I.V.: 160 mg TMP twice daily for 7-10 days. Note: AIDS patients: Oral: One double-strength tablet 2-4 times/day for 10 days, then 1 double-strength tablet 3 times/week for 10 weeks (Pape, 1994; Verdier, 2000).

-Granuloma inguinale (donovanosis) (unlabeled use): Oral: One double-strength tablet every 12 hours for at least 3 weeks and until lesions have healed (CDC, 2010)

-Isosporiasis (*Isospora belli* infection) in HIV-positive patients (unlabeled use; CDC, 2009):

-Treatment: Oral, I.V.: 160 mg TMP 4 times/day for 10 days **or** 160 mg TMP 2 times/day for 7-10 days. May increase dose and/or duration up to 3-4 weeks if symptoms worsen or persist

- Secondary prophylaxis (in patients with CD4+ count <200 /microL): Oral: 160 mg TMP 3 times/week (preferred) **or** alternatively, 160 mg TMP daily **or** 320 mg TMP 3 times/week
- Meningitis (bacterial): I.V.: 10-20 mg TMP/kg/day in divided doses every 6-12 hours
- Nocardia* (unlabeled use): Oral, I.V.:
 - Cutaneous infections: 5-10 mg TMP/kg/day in 2-4 divided doses
 - Severe infections (pulmonary/cerebral): 15 mg TMP/kg/day in 2-4 divided doses for 3-4 weeks, then 10 mg TMP/kg/day in 2-4 divided doses. Treatment duration is controversial; an average of 7 months has been reported.

Note: Therapy for severe infection may be initiated I.V. and converted to oral therapy (frequently converted to approximate dosages of oral solid dosage forms: 2 DS tablets every 8-12 hours). Although not widely available, sulfonamide levels should be considered in patients with questionable absorption, at risk for dose-related toxicity, or those with poor therapeutic response.
- Osteomyelitis due to MRSA (unlabeled use): Oral, I.V.: 3.5-4 mg TMP/kg/dose every 8-12 hours for a minimum of 8 weeks with rifampin 600 mg once daily (Liu, 2011)
- Pneumocystis jirovecii* pneumonia (PCP): Oral: Manufacturer's labeling:
 - Prophylaxis: 160 mg TMP daily
 - Treatment: 15-20 mg TMP/kg/day divided every 6 hours for 14-21 days
- Pneumocystis jirovecii* pneumonia (PCP) prophylaxis and treatment in HIV-positive patients (CDC, 2009): **Note:** Sulfamethoxazole and trimethoprim is the preferred regimen for this indication.
 - Prophylaxis: Oral: 80-160 mg TMP daily **or** alternatively, 160 mg TMP 3 times/week
 - Treatment:
 - Mild-to-moderate: Oral: 15-20 mg TMP/kg/day in 3 divided doses for 21 days **or** alternatively, 320 mg TMP 3 times/day for 21 days
 - Moderate-to-severe: Oral, I.V.: 15-20 mg TMP/kg/day in 3-4 divided doses for 21 days
- Prosthetic joint infection (unlabeled use): Oral phase treatment (after completion of pathogen-specific I.V. therapy) following debridement and prosthesis retention or 1-stage exchange:
 - Total ankle, elbow, hip, or shoulder arthroplasty: 160 mg TMP 2 times daily for 3 months. **Note:** Must be used in combination with rifampin (Cordero-Ampuero, 2007; Osmon, 2013).
 - Total knee arthroplasty: Adults: 160 mg TMP 2 times daily for 6 months. **Note:** Must be used in combination with rifampin (Cordero-Ampuero, 2007; Osmon, 2013).
- Sepsis: I.V.: 20 mg TMP/kg/day divided every 6 hours
- Septic arthritis due to MRSA (unlabeled use): Oral, I.V.: 3.5-4 mg TMP/kg/dose every 8-12 hours for 3-4 weeks (some experts combine with rifampin) (Liu, 2011)

-Shigellosis: **Note:** Due to reported widespread resistance, empiric therapy with sulfamethoxazole and trimethoprim is not recommended (CDC-NARMS, 2010; WHO, 2005).

-Oral: One double-strength tablet every 12 hours for 5 days

-I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 5 days

-Skin/soft tissue infection due to community-acquired MRSA (unlabeled use): Oral: 1-2 double-strength tablets every 12 hours for 5-10 days (Liu, 2011); Note: If beta-hemolytic *Streptococcus* spp are also suspected, a beta-lactam antibiotic should be added to the regimen (Liu, 2011)

-*Stenotrophomonas maltophilia* (ventilator-associated pneumonia): I.V.: Most clinicians have utilized 12-15 mg TMP/kg/day for the treatment of VAP caused by *Stenotrophomonas maltophilia*. Higher doses (up to 20 mg TMP/kg/day) have been mentioned for treatment of severe infection in patients with normal renal function (Looney, 2009; Vartivarian, 1989; Wood, 2010)

-*Toxoplasma gondii* encephalitis (unlabeled use; CDC, 2009): Oral:

-Primary prophylaxis: Oral: 160 mg TMP daily (preferred) or 160 mg TMP 3 times/week or 80 mg TMP daily

-Treatment (alternative to sulfadiazine, pyrimethamine and leucovorin calcium): Oral, I.V.: 5 mg/kg TMP twice daily

-Travelers' diarrhea: Oral: One double-strength tablet every 12 hours for 5 days

-Urinary tract infection:

-Oral: One double-strength tablet every 12 hours

-Duration of therapy: Uncomplicated: 3-5 days; Complicated: 7-10 days

Pyelonephritis: 14 days

Prostatitis: Acute: 2 weeks; Chronic: 2-3 months

-I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 14 days with severe infections

Renal Impairment :

-Oral, I.V.:

-Manufacturer's recommendation: Children and Adults:

-Cl_{cr} >30 mL/minute: No dosage adjustment required

-Cl_{cr} 15-30 mL/minute: Administer 50% of recommended dose

-Cl_{cr} <15 mL/minute: Use is not recommended

-Alternate recommendations:

-Cl_{cr} 15-30 mL/minute:

-Treatment: Administer full daily dose (divided every 12 hours) for 24-48 hours, then decrease daily dose by 50% and administer every 24 hours (**Note:** For serious infections including *Pneumocystis jirovecii* pneumonia (PCP), full daily dose is given in divided doses every 6-8 hours for 2 days, followed by reduction to 50% daily dose divided every 12 hours) (Nahata, 1995).

-PCP prophylaxis: One-half single-strength tablet (40 mg trimethoprim) daily **or** 1 single-strength tablet (80 mg trimethoprim) daily or 3 times weekly (Masur, 2002).

-Cl_{cr} <15 mL/minute:

-Treatment: Administer full daily dose every 48 hours (Nahata, 1995)

-PCP prophylaxis: One-half single-strength tablet (40 mg trimethoprim) daily **or** 1 single-strength tablet (80 mg trimethoprim) 3 times weekly (Masur, 2002). While the guidelines do acknowledge the alternative of giving 1 single-strength tablet daily, this may be inadvisable in the uremic/ESRD patient.

-GFR <10 mL/minute/1.73 m²: Children: Use is not recommended, but if required, administer 5-10 mg trimethoprim/kg every 24 hours (Aronoff, 2007).

-Intermittent Hemodialysis (IHD) (administer after hemodialysis on dialysis days):

-Children: Use is not recommended, but if required, administer 5-10 mg trimethoprim/kg every 24 hours (Aronoff, 2007).

-Adults: 2.5-10 mg/kg trimethoprim every 24 hours or 5-20 mg/kg trimethoprim 3 times weekly after IHD. **Note:** Dosing is highly dependent upon indication for use (eg, treatment of cystitis versus treatment of PCP pneumonia (Heinz, 2009).

-PCP prophylaxis: One single-strength tablet (80 mg trimethoprim) after each dialysis session (Masur, 2002)

Note: Dosing dependent on the assumption of 3 times/week, complete IHD sessions.

-Peritoneal dialysis (PD):

-Use Cl_{cr} <15 mL/minute dosing recommendations. Not significantly removed by PD; supplemental dosing is not required (Aronoff, 2007):

-GFR <10 mL/minute/1.73 m²: Children: Use is not recommended, but if required 5-10 mg TMP/kg every 24 hours.

-Exit-site and tunnel infections: Oral: One single-strength tablet daily (Li, 2010)

-Intraperitoneal: Loading dose: TMP-SMX 320/1600 mg/L; Maintenance: TMP-SMX 80/400 mg/L (Aronoff, 2007; Warady, 2000)

-Peritonitis: Oral: One double-strength tablet twice daily (Li, 2010)

-Continuous renal replacement therapy (CRRT) (Heintz, 2009; Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate). The following are general recommendations only (based

on dialysate flow/ultrafiltration rates of 1-2 L/hour and minimal residual renal function) and should not supersede clinical judgment:

-CVVH/CVVHD/CVVHDF: 2.5-7.5 mg/kg of TMP every 12 hours. **Note:** Dosing regimen dependent on clinical indication. Critically-ill patients with *P. jirovecii* pneumonia receiving CVVHDF may require up to 10 mg/kg every 12 hours (Heintz, 2009).

Common side effect: nausea, vomiting, anorexia, rash or urticarial, depression, fatigue, fever, hallucinations, headache, insomnia, kernicterus (in neonates), nervousness, Hyperkalemia, hyponatremia, Abdominal pain, Agranulocytosis, aplastic anemia, eosinophilia, hemolysis (with G6PD deficiency), hemolytic anemia, hypoprothrombinemia, leukopenia, megaloblastic anemia, Arthralgia, myalgia, weakness.

Pregnancy Risk Factor: D