trimETHOPRIM and Sulfamethoxazole

Newborn use only

<table>
<tr><td>Alert</td><td>Not to be used in preterm infants until 4 weeks corrected gestational age.
Not to be used in term infants <4 weeks of age.
Term infants 4-8 weeks age: Watch for risk of kernicterus in high risk group or babies with prolonged jaundice.
Dose is expressed as trimethoprim (TMP) component.
The Antimicrobial Stewardship Team recommends this drug is listed under the following category:
Also known as co-trimoxazole.</td></tr>
<tr><td>Indication</td><td>Prophylaxis of urinary tract infections (UTI).
Treatment of mild–severe infections including UTI and acute otitis media.
Prophylaxis in HIV-exposed infants.</td></tr>
<tr><td>Action</td><td>Sulfamethoxazole is a sulfonamide that prevents the formation of dihydrofolic acid, a bacterial compound necessary for survival. Trimethoprim is a synthetic antibiotic that interferes with the production of folic acid by inhibiting the action of dihydrofolate reductase.</td></tr>
<tr><td>Drug type</td><td>Antibiotic.</td></tr>
<tr><td>Trade name</td><td>Oral: Septrin Sugar Free Oral liquid [Arrow]
IV: DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP [Pfizer]</td></tr>
<tr><td>Presentation</td><td>Oral liquid: Trimethoprim 8 mg/mL and sulfamethoxazole 40 mg/mL, 100 mL bottle
IV: Trimethoprim 16 mg/mL and sulfamethoxazole 80 mg/mL, 5mL ampoule</td></tr>
<tr><td>Dose</td><td>Dosage recommendations are based on trimethoprim component.
UTI prophylaxis
Oral: 2 mg TMP/kg/dose daily or 5 mg TMP/kg/dose twice weekly.
Prophylaxis in HIV-exposed infants <6 months of age
To commence from 4–6 weeks of age at a dose of 20 mg trimethoprim once daily (not per kg basis) (equates to 2.5 mL oral liquid daily)
Treatment of mild–severe infections (e.g. UTI, acute otitis media)
Mild to moderate infections
PO: 3–6 mg TMP/kg/dose 12 hourly (AAP Guidelines 2011).
Severe infections
IV: 2–3 mg TMP/kg/dose 6 hourly.</td></tr>
<tr><td>Dose adjustment</td><td><table>
<tr><td colspan="2">Renal Impairment Dose Adjustments</td></tr>
<tr><td>CrCl (mL/min)</td><td>Dosage</td></tr>
<tr><td>Above 25</td><td>Standard regimen</td></tr>
<tr><td>15 to 25</td><td>50% of the standard regimen</td></tr>
<tr><td>Below 15</td><td>Not recommended</td></tr>
</table></td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>Oral, IV</td></tr>
<tr><td>Preparation</td><td>Oral: Oral liquid does not require preparation.

IV: Draw up 2 mL (32 mg trimethoprim and 80 mg sulfamethoxazole) and add 48 mL of sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 50mL with a concentration of 0.64 mg/mL of TMP.

For severely fluid restricted neonates:
Draw up 2 mL (32 mg trimethoprim and 80 mg sulfamethoxazole) and add 18 mL of glucose 5%to make a final volume of 20mL with a final concentration of 1.6 mg/mL of TMP and infuse ONLY VIA A CENTRAL LINE as it is an alkaline solution. Flush the line with sufficient volume of sodium chloride 0.9% to ensure total dose is given.</td></tr>
<tr><td>Administration</td><td>Oral: Administer with feeds. Shake well before measuring dose.
IV: Infuse over 60–90 minutes. Flush the line with sufficient volume of sodium chloride 0.9% to ensure total dose is given.</td></tr>
<tr><td>Monitoring</td><td>Watch for skin reactions and blood dyscrasias.
Monitor renal function and full blood count.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to sulfonamides or trimethoprim.
Infants < 4 weeks of age</td></tr>
</table>

Precautions	Use with caution in renal impairment. Refer to dose adjustment section. In individuals with glucose-6-phosphate dehydrogenase deficiency, haemolysis may occur. Sulfamethoxazole may interfere with the serum albumin binding of bilirubin to produce kernicterus.
Drug interactions	Risk of prolonged QT interval with concurrent use of chloral hydrate, erythromycin and fluconazole. Increased effects and side effects of phenytoin (folate deficiencies) could occur when sulfamethoxazole/ trimethoprim is given concurrently. Sulfamethoxazole/trimethoprim may inhibit the hepatic metabolism of phenytoin. Concomitant use of other agents that increase serum potassium, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics and prednisolone can lead to hyperkalaemia. Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin. Cross sensitisation may exist between sulfamethoxazole/trimethoprim and some antithyroid agents, diuretics (thiazides) and oral hypoglycaemic drugs.
Adverse reactions	Gastrointestinal upset (vomiting, diarrhoea). Severe dermatologic reactions, blood dyscrasias, hepatotoxicity. Prolonged use may result in fungal or bacterial superinfection. Prolonged QT interval, torsades de pointes, ventricular tachycardias have been reported in adults. Severe cases of thrombocytopenia have been reported in adults.
Compatibility	Fluids[17]: Glucose 5%, glucose 10%, sodium chloride 0.9%, sodium chloride 0.45%. Y site (for dilutions of 1 in 25 only): Aciclovir, atracurium, dexmedetomidine, filgrastim, magnesium sulfate, morphine sulfate, piperacillin-tazobactam, vecuronium, and zidovudine. Y-site[18] (at 0.8 and 4mg/mL in glucose 5%): Aciclovir, amphotericin B liposome, azithromycin, cefepime, dexmedetomidine, filgrastim, linezolid, metronidazole, milrinone, octreotide, pamidronate, pancuronium, piperacillin-tazobactam, potassium acetate, remifentanil, sodium acetate, vecuronium, voriconazole, zidovudine.
Incompatibility	Fluids: No information.[17,18] Y site[17,18]: Amikacin, aminophylline, amiodarone, amphotericin b lipid complex, ampicillin, atropine, benzylpenicillin, calcium chloride, calcium gluconate, cefazolin, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, dexamethasone, diazepam, diazoxide, digoxin, dobutamine, dopamine, adrenaline (epinephrine), epoetin alfa, erythromycin, fentanyl, fluconazole, folic acid, furosemide, ganciclovir, gentamicin, glycopyrrolate, hydralazine, hydrocortisone, imipenem-cilastatin, indomethacin, insulin, isoprenaline, ketamine, lidocaine (lignocaine), linezolid, methylprednisolone, metoclopramide, midazolam, multiple vitamins injection, nitroprusside sodium, noradrenaline (norepinephrine), phenobarbital (phenobarbitone), phenytoin, potassium chloride, propranolol, protamine, pyridoxine, ranitidine, sodium bicarbonate, ticarcillin-clavulanate, tobramycin, urokinase, vancomycin.
Stability	IV: infusion must be completed within 2 hours of preparation. Monitor for precipitation, particularly with concentratedsolutions.
Storage	Store IV and oral preparations below 30°C. Do not refrigerate. Protect from light. IV preparation: If stored at low temperatures precipitation may occur and solutions in which precipitation has occurred should be discarded.
Excipients	IV: diethanolamine, propylene glycol, alcohol, hydrochloric acid, sodium methabisulphate, sodium hydroxide. Oral: sorbitol, preservatives methyl hydroxybenzoate and sodium benzoate, ethanol, Cherry Flavour Artif F1242 (PI 286), sunset yellow, allura red, citric acid, cellulose, glycerol, polysorbate 80, sodium carmellose, saccharin sodium.
Special comments	
Evidence	**Prophylaxis in vesicoureteric reflux** The proportion of infants with high grade vesicoureteric reflux (VUR) among all infants with febrile UTIs is small. There is no statistically significant benefit of prophylaxis in preventing recurrence of febrile UTI/pyelonephritis in infants without reflux.[1] There is benefit of prophylaxis in reducing the recurrence of infections in children with VUR but no change in renal scarring and concerns regarding multi-resistant strains among treated children.[2,3] **Treatment duration of infections**

	McMullan et al reviewed the evidence for minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections, comparing shorter courses with traditionally longer durations. In many infections, especially when clinical improvement is rapid, emerging data suggest that traditional long durations of intravenous antibiotics might be unnecessary and that intravenous to oral switch can occur earlier. In most of the other infections, evidence for routine longer courses is sparse.[4] In a Cochrane review of childhood lower urinary tract infection, no difference in persistent bacteriuria or recurrence was noted between 2–4 days and 7–14 days of oral antibiotics. Results from a subsequent Cochrane review showed that a single-dose antibiotic was associated with more persistent bacteriuria than was 10 days of antibiotics, although there was no difference in symptom duration or recurrence. A large retrospective study of infants younger than 6 months found no difference in treatment failure between intravenous antibiotics for 3 days or less and 4 days or more.[4-7] **Prophylaxis in HIV-exposed infants** All HIV-exposed infants born to mothers living with HIV must receive co-trimoxazole prophylaxis, commencing at 4–6 weeks of age (or at first encounter with the healthcare system) and continued until HIV infection can be excluded.[8]
Practice points	
References	1. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 128(3), 595–610(2011). 2. de Bessa J Jr, de Carvalho Mrad FC, Mendes EF, Bessa MC, Paschoalin VP, Tiraboschi RB, Sammour ZM, Gomes CM, Braga LH, Bastos Netto JM. Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. J Urol 2015; 193(5 Suppl):1772-7. 3. Pérez-Gaxiola G. Antibiotic prophylaxis reduced symptomatic urinary tract infection in children with vesicoureteral reflux, but not scarring. Arch Dis Child Educ Pract Ed 2015; 100:52. 4. McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, Clark JE, Cooper CM, Curtis N, Goeman E, Hazelton B, Haeusler GM, Khatami A, Newcombe JP, Osowicki J, Palasanthiran P, Starr M, Lai T, Nourse C, Francis JR, Isaacs D, Bryant PA, ANZPID-ASAP group. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis [Internet]. 2016 [cited 2016 Aug]; 16(8):e139-52. 5. Michael M, Hodson EM, Craig JC, Martin S, Moyer VA. Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children. Cochrane Database Syst Rev 2003; 1: CD003966. 6. Fitzgerald A, Mori R, Lakhanpaul M, Tullus K. Antibiotics for treating lower urinary tract infection in children. Cochrane Database Syst Rev 2012; 8: CD006857. 7. Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. Pediatrics 2010; 126: 196–203. 8. WHO. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. http://www.who.int/entity/hiv/pub/guidelines/ctxguidelines.pdf; 2006. (accessed August 15, 2016)Micromedex solutions. Accessed on 10 August 2016. 9. Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America, et al: Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep 2009; 58(RR11):1-166. 10. Van der Veen EL, Rovers MM, Albers FW, et al: Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media: a randomized, placebo-controlled trial. Pediatrics 2007; 119(5):897-904. 11. DBL Sulfamethoxazole 400 mg and Trimethoprim 80 mg Concentrate Injection BP Product Information. Accessed online via MIMS on 17 May 2021. 12. Lieberthal AS, Carroll AE, Chonmaitree T, et al: The diagnosis and management of acute otitis media. Pediatrics 2013; 131(3):e964-e999. 13. Markowitz N & Saravolatz LD: Use of trimethoprim-sulfamethoxazole in a glucose-6-phosphate dehydrogenase-deficient population. Rev Infect Dis 1987; 9(suppl 2):S218-S225. 14. Bell TAL, Foster JN, & Townsend ML: Trimethoprim-sulfamethoxazole-induced hepatotoxicity in a pediatric patient. Pharmacotherapy 2010; 30(5):539. 15. Oliver RM, Rickenbach MA, Thomas MR, et al: Intrahepatic cholestasis associated with co-trimoxazole. Br J Clin Pract 1987; 41:975-976. 16. Paap CM & Nahata MC: Trimethoprim/sulfamethoxazole dosing during renal dysfunction. Ann Pharmacother 1995; 29:1300. 17. Australian injectable drugs handbook. Accessed online on 20 May 2021. 18. Micromedex online. Accessed on 20 May 2021.

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