Meropenem
Newborn Use Only

2017

<table>
<tr><td>Alert</td><td>The Antimicrobial Stewardship Team recommends this drug is listed under the following category: Restricted.
Widespread use of carbapenems has been linked with increasing prevalence of infections caused by methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), multi-resistant Gram-negative organisms and Clostridium difficile.</td></tr>
<tr><td>Indication</td><td>Severe infections (e.g., sepsis or meningitis) caused by Gram-negative organisms resistant to other conventional antibiotics but susceptible to meropenem e.g., Extended Spectrum Beta Lactamase (ESBL)-producing organisms.
Note: Meropenem is NOT active against many resistant Gram-positive organisms, such as MRSA and most Staphylococcus epidermidis. Vancomycin is first-line therapy for these. Meropenem does have activity against penicillin-susceptible Gram-positive organisms and most anaerobic organisms. For individual advice, discuss therapy with a microbiologist or infectious diseases physician.</td></tr>
<tr><td>Action</td><td>Meropenem is a carbapenem. It inhibits cell wall synthesis.[1]

Meropenem is a better choice than imipenem for central nervous system infections. Meropenem attains a higher concentration in the cerebrospinal fluid particularly with inflamed meninges and has a lower incidence of seizures than imipenem.</td></tr>
<tr><td>Drug Type</td><td>Carbapenem antibiotic.</td></tr>
<tr><td>Trade Name</td><td>Meropenem APOTEX, Meropenem DBL, Meropenem Kabi, Meropenem Ranbaxy, Meropenem Sandoz, Merrem</td></tr>
<tr><td>Presentation</td><td>500 mg vial
1000 mg vial</td></tr>
<tr><td>Dosage / Interval</td><td>Non-CNS and Non-Pseudomonas Sepsis
<table>
<tr><th>Gestational Age at birth</th><th>Postnatal Age</th><th>Dose</th><th>Interval</th></tr>
<tr><td>$< 32^{+0}$ weeks</td><td>0–13 days</td><td>20 mg/kg</td><td>12 hourly</td></tr>
<tr><td>$< 32^{+0}$ weeks</td><td>14+ days</td><td>20 mg/kg</td><td>8 hourly</td></tr>
<tr><td>$\geq 32^{+0}$ weeks</td><td>0–13 days</td><td>20 mg/kg</td><td>8 hourly</td></tr>
<tr><td>$\geq 32^{+0}$ weeks</td><td>14+ days</td><td>30 mg/kg</td><td>8 hourly</td></tr>
</table>
Meningitis and Pseudomonas Sepsis*
<table>
<tr><th>Gestational Age at birth</th><th>Postnatal Age</th><th>Dose</th><th>Interval</th></tr>
<tr><td>Any</td><td>Any</td><td>40 mg/kg</td><td>8 hourly</td></tr>
</table>
*Assess for any renal impairment prior to using higher doses as meropenem is primarily excreted via the kidneys.</td></tr>
<tr><td>Route</td><td>IV infusion.</td></tr>
<tr><td>Maximum Daily Dose</td><td></td></tr>
<tr><td>Preparation/Dilution</td><td>Add 9.6 mL of WFI to the 500 mg powder for reconstitution to make a volume of 10 mL with a concentration of 50 mg/mL.
Draw up 2 mL (100 mg of meropenem) of solution and add 8 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 10 mg/mL.

<u>Larger doses or neonates with a fluid restriction</u>.
Add 9.6 mL of WFI to the 500 mg powder for reconstitution to make a volume of 10 mL with a concentration of 50 mg/mL.
Draw up 4 mL (200 mg of meropenem) of solution and add 6 mL sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 20 mg/mL.</td></tr>
<tr><td>Administration</td><td>IV infusion over 4 hours.
May be given over 15 to 30 minutes if longer infusion not feasible due to line access issues from other infusions.</td></tr>
<tr><td>Monitoring</td><td>Monitor renal function. Dose may need to be adjusted in impaired renal function.</td></tr>
</table>

Contraindications	Hypersensitivity to penicillins, cephalosporins and carbapenems.
Precautions	Colitis−due to risk of pseudomembranous colitis. Renal impairment.
Drug Interactions	Sodium valproate− meropenem may result in clinically significant reduction in concentration of sodium valproate, which may cause seizures.
Adverse Reactions	Injection site inflammation, diarrhoea (up to 6% in children), anaemia and eosinophilia.
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9%. Y-site: Amino acid solutions, anidulafungin, caspofungin, linezolid, atropine sulfate monohydrate, dexamethasone sodium, gentamicin, heparin sodium, metronidazole.
Incompatibility	Fluids: No information Y-site: Dolasetron, ketamine, mycophenolate mofetil, zidovudine.
Stability	Merrem: Solutions in sodium chloride are stable for 3 hours below 25°C and 24 hours at 2−8 °C. Use solutions in glucose 5% immediately. Meropenem (DBL, Kabi, Ranbaxy, Sandoz): Solutions in sodium chloride are stable for 8 hours below 25°C and 24 hours at 2−8 °C. Solutions in glucose 5% are stable for 3 hours below 25 °C and 14 hours at 2−8°C. Diluted solutions are potentially unstable, particularly glucose containing solutions and should be discarded if not used immediately.
Storage	Vial: Store at room temperature.
Special Comments	Meropenem 1 g vial contains 3.92 mmol of sodium.
Evidence summary	**Efficacy:** Carbapenems may be considered the treatment of choice for empirical treatment of patients with ESBL-producing *Enterobacteriaceae* bacteraemia. A systematic review of carbapenems for the treatment of patients with extended-spectrum β-lactamase (ESBL)-positive *Enterobacteriaceae* bacteraemia involving 1584 patients, mostly adults showed lower mortality than non-Beta-lactam/Beta-Lactam Inhibitor combination antibiotics for definitive [risk ratio (RR) 0.65, 95% CI 0.47–0.91] and empirical (RR 0.50, 95% CI 0.33–0.77) treatment. No statistically significant differences in mortality were found between carbapenems and BL/BLIs administered as definitive (RR 0.52, 95% 0.23–1.13) or empirical (RR 0.91, 95% CI 0.66–1.25) treatment (LOE 1, GOR C).[2] A retrospective case series of 100 neonates infected by extended-spectrum beta-lactamase-producing *Klebsiella* species showed higher mortality in those neonates not started on empirical meropenem or Piperacillin + tazobactam and amikacin (OR – 17.01, 95% CI 2.41–120.23) (LOE IV, GOR C).[3] A RCT reported a prolonged infusion (4 hours) of meropenem (20 mg/kg/dose every 8 hours and 40 mg/kg/dose every 8 hours in meningitis and Pseudomonas infection) in 102 neonates with gram-negative late onset infection is associated with higher rate of clinical improvement, microbiologic eradication, less neonatal mortality (14% versus 31%; p=0.03), shorter duration of respiratory support and less acute kidney injury compared with the conventional strategy (30 minute infusion) [LOE II GOR B].[5] **Pharmacokinetics:** Meropenem is primarily excreted via the kidneys. Meropenem clearance is influenced by serum creatinine and postmenstrual age in neonates.[2] A comparative pharmacokinetic study of short (30 minute) versus long (4 hour) infusion in neonates showed short infusion resulted in a higher mean drug concentration in serum (C(max)) than a prolonged infusion.[6] However, a longer infusion may have greater efficacy.[5] There is a knowledge gap in pharmacokinetic (PK) studies of neonates with renal impairment.[2,3] However, dose adjustment for renal failure may not be appropriate in cases where severe sepsis is probably responsible for acute renal failure [expert opinion].

	Dose: Multicentre, prospective PK study conducted in USA suggested a dosing strategy of 20 mg/kg every 12 hours in infants < 32 weeks GA and PNA < 14 days; 20 mg/kg every 8 hours in infants < 32 weeks GA and PNA ≥ 14 days and in infants ≥ 32 weeks GA and PNA < 14 days; and 30 mg/kg every 8 hours in infants ≥ 32 weeks GA and PNA ≥ 14 days to achieve therapeutic concentrations in infants with suspected intra-abdominal infections.[4]
References	1. Pacifici GM, Allegaert K. Clinical pharmacology of carbapenems in neonates. J Chemother 2014;26(2):67–73. 2. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. J Antimicrob Chemother 2012;67(12):2793–803. 3. Velaphi S, Wadula J, Nakwa F. Mortality rate in neonates infected with extended-spectrum b-lactamase-producing Klebsiella species and selective empirical use of meropenem. Ann Trop Paediatr 2009;29:101–10. 4. Smith PB, Cohen-Wolkowiez M, Castro LM, Poindexter B, Bidegain M, Weitkamp JH, et al, Meropenem Study Team. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J 2011;30(10):844–9. 5. Shabaan AE, Nour I, Elsayed Eldegla H, Nasef N, Shouman B, Abdel-Hady H. Conventional Versus Prolonged Infusion of Meropenem in Neonates With Gram-negative Late-onset Sepsis: A Randomized Controlled Trial. Pediatric Infectious Disease Journal. 2017;36:358-63. 6. Padari H, Metsvaht T, Korgvee LT, Germovsek E, Ilmoja ML, Kipper K, Herodes K, Standing JF, Oselin K, Lutsar I. Short versus long infusion of meropenem in very-low-birth-weight neonates. Antimicrob Agents Chemother 2012;56(9):4760–4. 7. Micromedex online. Accessed on 14 October 2017.

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