Imipenem + cilastatin

Newborn use only

2020

Alert	High risk medicine. Antimicrobial Stewardship Team recommends this drug is listed as 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*. NOT the preferred carbapenem in neonates because of possible adverse effects. Should be avoided in preterm neonates because of cilastatin accumulation.
Indication	Non-CNS sepsis caused by susceptible organisms including enteric Gram-negative rods, extended-spectrum beta-lactamase [ESBL] organisms, *Pseudomonas aeruginosa*, anaerobic organisms (including *Bacteroides fragilis*) and many Gram-positive organisms.
Action	Inhibits cell wall synthesis. Cilastatin prevents renal metabolism of imipenem. Meropenem is a better choice for central nervous system infections as it attains a higher concentration in the cerebrospinal fluid and has a lower incidence of seizures than imipenem + cilastatin.
Drug type	Carbapenem antibiotic
Trade name	Primaxin
Presentation	500 mg vial.
Dose	Dose based on imipenem component

Condition	Dose	Dosing Interval	Infusion Time
Non-*Pseudomonas aeruginosa*	25 mg/kg	12 hourly	30 minutes
Pseudomonas aeruginosa	25 mg/kg	8 hourly	90 minutes

Dose adjustment	Dose may need to be reduced in impaired renal function.
Maximum dose	75 mg/kg/day
Total cumulative dose	
Route	IV Infusion
Preparation	Add 9.2 mL of sodium chloride 0.9% to the 500 mg vial to make a 50 mg/mL solution **FURTHER DILUTE** Draw up 2 mL (100 mg of Imipenem + cilastatin) of the above solution and add 8 mL sodium chloride 0.9% to make a final volume of 10 mL with a final concentration of 10 mg/mL.
Administration	Non-*Pseudomonas aeruginosa* − IV infusion over 30 minutes. *Pseudomonas aeruginosa* − IV infusion over 90 minutes.
Monitoring	Renal function. Dose may need to be reduced in impaired renal function. Blood count and liver function.
Contraindications	Hypersensitivity to penicillins, cephalosporins or carbapenems. CNS infections.
Precautions	Seizures can occur in infants with renal impairment or central nervous system infection.
Drug interactions	Ganciclovir − risk of seizures. Do not give concomitantly unless the potential benefits outweigh the risks. Valproate − results in decreased concentrations of valproate.
Adverse reactions	Seizures, impaired renal function, impaired liver function, tachycardia, local phlebitis, urticaria, diarrhoea, pseudomembranous colitis (*Clostridium difficile*) and vomiting.
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9% Y-site: Aciclovir, amifostine, anidulafungin, aztreonam, caspofungin, cisatracurium besilate, foscarnet, granisetron, linezolid, remifentanil, tigecycline, zidovudine.
Incompatibility	Fluids**:** Hartmann's. Y-site: Amiodarone, amoxycillin, azathioprine, azithromycin, ceftriaxone, chlorpromazine, daptomycin, fluconazole, ganciclovir, haloperidol lactate, metaraminol, midazolam, milrinone, mycophenolate mofetil, palonosetron, pethidine, sodium bicarbonate, vecuronium.
Stability	Reconstituted or diluted solution stable for 4 hours below 25°C or for 24 hours at 2−8°C.

Storage	Store vial below 25°C.
Excipients	Sodium bicarbonate
Special comments	Solutions of imipenem + cilastatin range from colourless to yellow. Variations of colour within this range do not affect the potency.
Evidence	**Pharmacokinetics** Imipenem + cilastatin is excreted via kidneys, mainly though glomerular filtration. Imipenem clearance is not influenced by postnatal or postmenstrual age. Infusions (0.5 hours) of 25 mg/kg every 12 hours (50 mg/kg/day) is sufficient against common bacterial isolates in neonates. However, 1.5 hour infusions of 25 mg/kg every 8 hours (75 mg/kg/day) in neonates are required to be effective against *Pseudomonas aeruginosa*.[1] **Safety**: Seizures can occur in neonates with meningitis, other CNS infections and in patients with renal impairment.[1,4,6,9]
Practice points	
References	1. Yoshizawa K, Ikawa K, Ikeda K, Ohge H, Morikawa N. Population pharmacokinetic-pharmacodynamic target attainment analysis of imipenem plasma and urine data in neonates and children. Pediatr Infect Dis J [Internet]. 2013 [cited 2013 Nov];32(11):1208–16. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=23676856 2. Fujimura S, Nakano Y, Sato T, Shirahata K, Watanabe A. Relationship between the usage of carbapenem antibiotics and the incidence of imipenem-resistant Pseudomonas aeruginosa. J Infect Chemother [Internet]. 2007 [cited 2007 Jun];13(3):147–50. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17593500 3. Schlossberg D, Pietroski N. Carbapenems. Semin Pediatr Infect Dis [Internet]. 2002 [cited 2002 Jan];13(1):4. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12118842 4. Boswald M, Dobig C, Kandler C, Kruger C, Scharf J, Soergel F, Zink S, Guggenbichler JP. Pharmacokinetic and clinical evaluation of serious infections in premature and newborn infants under therapy with imipenem/cilastatin. Infection [Internet]. 1999 [cited 1999];27(4-5):299–304. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=10885853 5. Blumer JL. Pharmacokinetic determinants of carbapenem therapy in neonates and children. Pediatr Infect Dis J [Internet]. 1996 [cited 1996 Aug];15(8):733–7. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=8858691 6. Stuart RL, Turnidge J, Grayson ML. Safety of imipenem in neonates. Pediatr Infect Dis J [Internet]. 1995 [cited 1995 Sep];14(9):804–5. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=8559632 7. Reed MD, Kliegman RM, Yamashita TS, Myers CM, Blumer JL. Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. Antimicrob Agents Chemother [Internet]. 1990 [cited 1990 Jun];34(6):1172–7. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2393278 8. Ahonkhai VI, Cyhan GM, Wilson SE, Brown KR. Imipenem-cilastatin in pediatric patients: an overview of safety and efficacy in studies conducted in the United States. Pediatr Infect Dis J [Internet]. 1989 [cited 1989 Nov];8(11):740–4. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=2687787 9. Nalin DR, Jacobsen CA. Imipenem/cilastatin therapy for serious infections in neonates and infants. Scand J Infect Dis Suppl [Internet]. 1987 [cited 1987];5246–55. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=3331042 10. Micromedex 2.0 accessed via CIAP 4nd November 2015. 11. Australian Injectable Drugs Handbook, 6th Edition, Society of Hospital Pharmacists of Australia 2015.

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