Imipenem-cilastatin

Newborn use only

2021

<table>
<tr><td>Alert</td><td>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.</td></tr>
<tr><td>Indication</td><td>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.</td></tr>
<tr><td>Action</td><td>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.</td></tr>
<tr><td>Drug type</td><td>Carbapenem antibiotic</td></tr>
<tr><td>Trade name</td><td>Primaxin</td></tr>
<tr><td>Presentation</td><td>500 mg vial.</td></tr>
<tr><td>Dose</td><td>Dose based on imipenem component
<table>
<tr><th>Condition</th><th>Dose</th><th>Dosing Interval</th><th>Infusion Time</th></tr>
<tr><td>Non-Pseudomonas aeruginosa</td><td>25 mg/kg</td><td>12 hourly</td><td>30 minutes</td></tr>
<tr><td>Pseudomonas aeruginosa</td><td>25 mg/kg</td><td>8 hourly</td><td>90 minutes</td></tr>
</table></td></tr>
<tr><td>Dose adjustment</td><td>Dose may need to be reduced in impaired renal function.</td></tr>
<tr><td>Maximum dose</td><td>75 mg/kg/day</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV Infusion</td></tr>
<tr><td>Preparation</td><td>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 3 mL (150 mg of Imipenem component) of the above solution and add 27 mL sodium chloride 0.9% to make a final volume of 30 mL with a final concentration of 5 mg/mL.*(10,11)
*Higher concentrations (10 mg/mL) may be used in fluid restricted neonates preferably via central line (ANMF consensus)</td></tr>
<tr><td>Administration</td><td>Non-Pseudomonas aeruginosa − IV infusion over 30 minutes.
Pseudomonas aeruginosa − IV infusion over 90 minutes.</td></tr>
<tr><td>Monitoring</td><td>Renal function. Dose may need to be reduced in impaired renal function.
Blood count and liver function.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to penicillins, cephalosporins or carbapenems.
CNS infections.</td></tr>
<tr><td>Precautions</td><td>Seizures can occur in infants with renal impairment or central nervous system infection.</td></tr>
<tr><td>Drug interactions</td><td>Ganciclovir − risk of seizures. Do not give concomitantly unless the potential benefits outweigh the risks.
Valproate − results in decreased concentrations of valproate.</td></tr>
<tr><td>Adverse reactions</td><td>Seizures, impaired renal function, impaired liver function, tachycardia, local phlebitis, urticaria, diarrhoea, pseudomembranous colitis (Clostridium difficile) and vomiting.</td></tr>
<tr><td>Compatibility</td><td>Fluids (10): Glucose 5%, glucose 10%, sodium chloride 0.9%

Y-site (10): Aciclovir, aztreonam, caspofungin, cisatracurium, foscarnet, linezolid, remifentanil, tigecycline, zidovudine.</td></tr>
<tr><td>Incompatibility</td><td>Fluids (10): Hartmann’s.

Y-site (10): Amiodarone, amoxicillin, azathioprine, azithromycin, ceftriaxone, daptomycin, ganciclovir, metaraminol, midazolam, milrinone, pyridoxine, sodium bicarbonate, thiamine, vecuronium.</td></tr>
<tr><td>Stability</td><td>Reconstituted or diluted solution stable for 4 hours below 25°C or for 24 hours at 2−8°C.</td></tr>
<tr><td>Storage</td><td>Store vial below 25°C.</td></tr>
<tr><td>Excipients</td><td>Sodium bicarbonate</td></tr>
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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. 2013;32(11):1208–16. 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. 2007;13(3):147–50. 3. Schlossberg D, Pietroski N. Carbapenems. Semin Pediatr Infect Dis 2002;13(1):4. 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 1999;27(4-5):299–304. 5. Blumer JL. Pharmacokinetic determinants of carbapenem therapy in neonates and children. Pediatr Infect Dis J. 1996;15(8):733–7. 6. Stuart RL, Turnidge J, Grayson ML. Safety of imipenem in neonates. Pediatr Infect Dis J. 1995;14(9):804–5. 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 1990;34(6):1172–7. 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 1989;8(11):740–4. 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. 10. Australian Injectable Drugs Handbook, 8th Edition. Accessed on 3 April 2021.

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Authors Contribution

Original author/s	Chris Wake
Evidence Review	
Expert review	Brendan McMullan, Tony Lai, Pamela Palasanthiran
Nursing Review	Eszter Jozsa, Kirsty Minter, Samantha Hassall
Pharmacy Review	Jessica Mehegan
ANMF Group contributors	Mani Singla, Nilkant Phad, Himanshu Popat, Bhavesh Mehta, Himanshu Popat, Jing Xiao, Ushma Trivedi, Mariella De Rosa, John Sinn, Wendy Huynh, Helen Huynh, Carmen Burman, Michelle Jenkins, Thao Tran, Mani Singla
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty