

Alert	Two of the intravenous preparations of ibuprofen (Neoprofen and Pedea) are not currently registered with the Therapeutic Goods Administration (TGA). They are available for use via the Special Access Scheme (SAS). A category A SAS form will need to be completed for each course prescribed. The third available preparation, Caldolor, is registered for fever reduction, acute mild-mod or mod-severe postop pain (+ reduced morphine dose) in adults.																			
Indication	Closure of patent ductus arteriosus.																			
Action	Prostaglandin inhibitor. Prostaglandins are important in maintaining ductal patency <i>in utero</i> .																			
Drug Type	Non-steroidal anti-inflammatory drug (NSAID).																			
Trade Name	Intravenous: Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine), Pedea (ibuprofen sodium). Oral: Advil, Bugesic, Chemist's Own, Dimetapp, iProfen, , Nurofen																			
Presentation	<p>IV: Caldolor (ibuprofen arginine) 800 mg/8 mL Neoprofen (ibuprofen lysine) 20 mg/2 mL Pedea (ibuprofen sodium) 10 mg/2 mL</p> <p>Oral: 100 mg/5 mL</p>																			
Dosage/Interval	<table border="1"> <thead> <tr> <th>Post-natal Age</th> <th>Day 1</th> <th>Day 2</th> <th>Day 3</th> </tr> </thead> <tbody> <tr> <td>< 72 hours</td> <td>10 mg/kg/dose</td> <td>5 mg/kg/dose</td> <td>5 mg/kg/dose</td> </tr> <tr> <td>≥ 72 hours (Higher dose)</td> <td>20 mg/kg/dose</td> <td>10 mg/kg/dose</td> <td>10 mg/kg/dose</td> </tr> <tr> <td>≥ 72 hours (lower dose)</td> <td>10 mg/kg/dose</td> <td>5 mg/kg/dose</td> <td>5 mg/kg/dose</td> </tr> </tbody> </table> <p>Consider a second course 4 days later if duct does not close within 48 hours of the last dose or if it re-opens.</p>				Post-natal Age	Day 1	Day 2	Day 3	< 72 hours	10 mg/kg/dose	5 mg/kg/dose	5 mg/kg/dose	≥ 72 hours (Higher dose)	20 mg/kg/dose	10 mg/kg/dose	10 mg/kg/dose	≥ 72 hours (lower dose)	10 mg/kg/dose	5 mg/kg/dose	5 mg/kg/dose
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Maximum daily dose	20 mg/kg																			
Total cumulative dose	20–40 mg/kg																			
Route	IV, oral																			
Preparation/Dilution	<p>Caldolor (ibuprofen arginine) Draw up 0.5 mL (50 mg of ibuprofen) and add 19.5 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 20 mL with a concentration of 2.5 mg/mL</p> <p>Neoprofen (ibuprofen lysine) Draw up 1 mL (10 mg of ibuprofen) and add 3 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 4 mL with a concentration of 2.5 mg/mL</p> <p>Pedea (ibuprofen sodium) Can be administered undiluted. If dilution is required draw up 2 mL (10 mg of ibuprofen) and add 2 mL of sodium chloride 0.9% or glucose 5% to make a final volume of 4 mL with a concentration of 2.5 mg/mL</p>																			
Administration	<p>IV infusion: Caldolor (ibuprofen arginine) – over 30 minutes Neoprofen (ibuprofen lysine) – over 15 minutes Pedea (ibuprofen sodium) – over 15 minutes.</p> <p>Do not use chlorhexidine to disinfect the neck of the ampoule.</p> <p>Oral – give via intra-gastric tube, preferably with milk feed to minimise risk of gastrointestinal irritation. If baby is not on enteral feeds or breast milk is not available, give dose via intra-gastric tube and flush with 0.5 mL water for injection.</p>																			

Monitoring	Monitor urine output, cardiovascular status, serum biochemistry, renal function and for signs of bleeding.
Contraindications	Serious infection, active bleeding, thrombocytopenia or coagulopathy, necrotising enterocolitis or intestinal perforation, significant renal dysfunction, ductal dependent congenital heart disease, pulmonary hypertension and significant jaundice as may displace bilirubin from albumin.
Precautions	IV – nil Oral- nil
Drug Interactions	Aminoglycosides: Dose may need to be modified as ibuprofen affects renal function. Fluconazole: Metabolism of ibuprofen may be inhibited, increasing its concentration. Systemic corticosteroids: Intestinal perforation has been described in infants treated with early dexamethasone and indomethacin. Although not described with ibuprofen, caution is advised.
Adverse Reactions	Prophylactic ibuprofen is associated with renal impairment and gastrointestinal haemorrhage. (LOE I). Ibuprofen for treatment of PDA is associated with renal impairment (LOE I). There are case reports of pulmonary hypertension responsive to nitric oxide in infants treated with ibuprofen (LOE IV).
Compatibility	Fluids- Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine) and Pedeas (ibuprofen sodium): Sodium chloride 0.9%, glucose 5% Y site: Neoprofen (ibuprofen lysine): Ceftazidime, frusemide, heparin sodium, potassium chloride. Pedeas (ibuprofen sodium) and Caldolor (ibuprofen arginine): Not tested.
Incompatibility	Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine) and Pedeas (ibuprofen sodium) - regard all other IV solutions and drugs as incompatible.
Stability	Calodlor (ibuprofen arginine): Diluted solutions are stable for up to 24 hours at room temperature (20–25° C) and room lighting. Neoprofen (ibuprofen lysine) and Pedeas (ibuprofen sodium): Discard unused portion once opened.
Storage	IV – store unopened vials at room temperature (20–25°C). Oral liquid – store below 25°C.
Special Comments	Nil
Evidence summary	<p>Effectiveness: Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight infants: Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of necrotising enterocolitis and transient renal insufficiency compared to indomethacin⁴ (LOE I GOR B).</p> <p>Route: Oro-gastric administration of ibuprofen appears as effective as intravenous administration⁴ (LOE 1 GOR C).</p> <p>Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants: Prophylactic treatment exposes many infants to a drug that has renal and gastrointestinal side effects without conferring important short-term benefits and is not recommended⁵ (LOE I GOR C).</p> <p>Side effects: Prophylactic ibuprofen is associated with renal impairment and gastrointestinal haemorrhage (LOE I). There are case reports of pulmonary hypertension⁵ (LOE IV). Ibuprofen may displace bilirubin from albumin at high concentrations in vitro (200 micromol/L)⁶. This does not appear to occur in vivo at the concentrations associated with recommended doses (up to 100 micromol/L)⁷.</p> <p>Dose: Two RCTs compared higher-dose (20, 10, 10 mg/kg/day) versus lower dose (10, 5, 5 mg/kg/day) ibuprofen for patent ductus arteriosus in extremely preterm infants with an increase in ductal closure rate reported. There was no difference in side effects. Peak concentrations were 109.8 (S.D 27.2) micromol/L^{8,9}. A pharmacokinetic study has shown drug elimination increases</p>

	<p>with postnatal age and recommended ibuprofen course: 10, 5, 5 mg/kg for neonates younger than 70 hours, 14, 7, 7 mg/kg between 70–108 hours and 18, 9, 9 mg/kg between 108–180 hours¹⁰.</p> <p>Recommendation: Consider higher dose regimen (20, 10, 10 mg/kg) after postnatal day 4. Contraindicated in infants with significant jaundice (LOE II; GOR C).</p>
References	<ol style="list-style-type: none"> Allegaert K. The impact of ibuprofen or indomethacin on renal drug clearance in neonates. <i>The journal of maternal-fetal & neonatal medicine</i>. 2009;22;88–91. Hynninen VV, Olkkola KT, Leino K, Lundgren S, Neuvonen PJ, Rane A, Valtonen M, Vyyrylainen H, Laine K. Effects of the antifungals voriconazole and fluconazole on the pharmacokinetics of s-(+)- and R-(-)-Ibuprofen. <i>Antimicrobial agents and chemotherapy</i>. 2006;50:1967–72. [note adult study] Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, Donovan EF, Oh W, Bauer CR, Saha S, Poole WK, Stoll BJ, National Institute of Child H, Human Development Neonatal Research N. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. <i>National Institute of Child Health and Human Development Neonatal Research Network. The New England journal of medicine</i>. 2001;344:95–101. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. <i>The Cochrane database of systematic reviews</i>. 2015;2:CD003481. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. <i>The Cochrane database of systematic reviews</i>. 2011:CD004213. Diot C, Kibleur Y, Desfrere L. Effect of ibuprofen on bilirubin-albumin binding in vitro at concentrations observed during treatment of patent ductus arteriosus. <i>Early human development</i>. 2010;86:315–7. Desfrere L, Thibaut C, Kibleur Y, Barbier A, Bordarier C, Moriette G. Unbound bilirubin does not increase during ibuprofen treatment of patent ductus arteriosus in preterm infants. <i>The Journal of pediatrics</i>. 2012;160:258–64. Dani C, Vangi V, Bertini G, Pratesi S, Lori I, Favelli F, Ciuti R, Bandinelli A, Martano C, Murru P, Messner H, Schena F, Mosca F. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. <i>Clinical pharmacology and therapeutics</i>. 2012;91:590–6. Pourarian S, Takmil F, Cheriki S, Amoozgar H. The Effect of Oral High-dose Ibuprofen on Patent Ductus Arteriosus Closure in Preterm Infants. <i>American journal of perinatology</i>. 2015 Oct;32(12):1158–63. Hirt D, Van Overmeire B, Treluyer JM, Langhendries JP, Marguglio A, Eisinger MJ, Schepens P, Urien S. An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study. <i>British journal of clinical pharmacology</i>. 2008;65:629–36. Pedea. Summary of product characteristics. Berkshire UK: Orphan Europe (UK) Limited; 19/12/13. Accessed from www.medicines.org.uk. Accessed 09/09/15 Product Information: Caldolor intravenous, injection, ibuprofen arginine injection. Cumberland Pharmaceuticals Inc., Nashville, TN, 2014. Product Information: Neoprofen intravenous, injection, ibuprofen lysine injection. Recordati rare diseases, Lebanon, NJ, 2013. Ibuprofen arginine, Ibuprofen lysine. In: IV index. Trissel's 2 clinical pharmaceuticals database (parenteral compatibility). Greenwood Village, Colorado: Truven Health Analytics. Accessed 11/9/15. <i>Australian Injectable Drugs Handbook, 6th Edition, Society of Hospital Pharmacists of Australia</i> 2014.

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