

Alert	<p>Pedea is currently the only registered product with Therapeutic Goods Administration (TGA) for closure of patent ductus arteriosus in preterm infants <34 weeks gestation. Neoprofen is not currently registered with TGA. It is available for use via the Special Access Scheme (SAS). Caldolor is registered for fever reduction and postoperative pain in adults.</p>																			
Indication	Patent ductus arteriosus.																			
Action	Prostaglandin inhibitor. Prostaglandins are important in maintaining ductal patency in utero.																			
Drug type	Non-steroidal anti-inflammatory drug (NSAID).																			
Trade name	Intravenous: Pedea (ibuprofen sodium), Neoprofen (ibuprofen lysine). Caldolor (ibuprofen arginine), Oral: FenPaed, Advil, Bugesic, Chemist's Own, Dimetapp, iProfen, Nurofen																			
Presentation	IV: Pedea (ibuprofen sodium) 10 mg in 2 mL vial. Neoprofen (ibuprofen lysine) 20 mg in 2 mL vial. Caldolor (ibuprofen arginine) 800 mg in 8 mL vial. Oral: 100 mg/5 mL suspension																			
Dose	<p>IV/ORAL</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Post-natal Age</th> <th style="width: 25%;">Day 1</th> <th style="width: 25%;">Day 2</th> <th style="width: 25%;">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>A full course of ibuprofen may not be necessary if ductal constriction or closure is demonstrated [1,2]. A repeat course of treatment may be considered depending on continuing haemodynamic significance of the ductus arteriosus and relative contraindications to treatment [3]. Data are insufficient to determine the efficacy of a 3rd course [4].</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
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																	
Dose adjustment Therapeutic hypothermia ECMO Renal impairment Hepatic impairment	Not applicable Not applicable Current evidence is insufficient to suggest any specific dose adjustment. Not applicable																			
Maximum dose	20 mg/kg																			
Total cumulative dose	20–40 mg/kg																			
Route	IV, oral																			
Preparation	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. 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. 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.																			
Administration	<p><u>IV infusion:</u></p> <p style="padding-left: 40px;">Pedea – over 15 minutes. Neoprofen – over 15 minutes Caldolor – over 30 minutes</p> <p>Do not use chlorhexidine to disinfect the neck of the ampoule.³¹</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.
Monitoring	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	Diuretics – Ibuprofen may reduce the effect of diuretics; whilst the diuretic may increase the risk of nephrotoxicity of NSAIDs in dehydrated patients. Anticoagulants – ibuprofen may increase the effect of anticoagulants and enhance the risk of bleeding. Nitric oxide – as both medicinal products have an inhibitory effect on platelet function, their combination may in theory increase the risk of bleeding. Corticosteroids – ibuprofen may increase the risk of gastrointestinal bleeding. Other NSAIDs – the concomitant use of more than one NSAID may increase risk of adverse reactions. Aminoglycosides – since ibuprofen may decrease the clearance of aminoglycosides, their co-administration may increase the risk of nephrotoxicity and ototoxicity. 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 use of ibuprofen is associated increased risks for oliguria, increase in serum creatinine levels, and increased risk of gastrointestinal haemorrhage.[5]. [LOE I] Ibuprofen for treatment of a PDA was associated with increased oliguria and increased creatinine. [LOE I] Compared to treatment of a PDA with indomethacin, ibuprofen was associated with reduced NEC, reduced oliguria and was associated with lower creatinine levels 72 hours after initiation of treatment.[6].[LOE I] Compared to paracetamol (acetaminophen), ibuprofen was associated with a high rate of gastrointestinal bleeding, higher creatinine and bilirubin levels, and lower platelet counts and daily urine output. [7]. There have been reports of pulmonary hypertension with use of ibuprofen, [5, 6] although the rate may be similar to that reported for indomethacin.[8]. Ibuprofen may displace bilirubin from albumin at high concentrations in vitro (200 micromol/L), [9] although this does not appear to occur in vivo at the concentrations associated with recommended doses (up to 100 micromol/L). [10].
Compatibility	Fluids: Pedeia, neoprofen, caldolor - Sodium chloride 0.9%, glucose 5%. NeoProfen only- sterile water for injection. ³⁶ Y site: Pedeia : Not tested. Y site: Neoprofen: Ceftazidime, epinephrine hydrochloride, furosemide, heparin sodium, insulin, phenobarbital sodium, potassium chloride, sodium bicarbonate Y site: Caldolor: Metoprolol tartrate
Incompatibility	Caldolor (ibuprofen arginine), Neoprofen (ibuprofen lysine) and Pedeia (ibuprofen sodium) - regard all other IV solutions and drugs as incompatible.
Stability	Caldolor: Diluted solutions are stable for up to 24 hours at room temperature (20–25° C) and room lighting. Neoprofen and Pedeia: Discard unused portion once opened.
Storage	IV – store unopened vials at room temperature (20–25°C). Oral liquid – store below 25°C.

Excipients	<p>PEDEA - Each 1 ml of PEDEA contains the following inactive ingredients: trometamol (3.78 mg), sodium hydroxide (0.14 mg), sodium chloride (7.3 mg), hydrochloric acid and water for injections. The headspace within the ampoules is filled with nitrogen.</p> <p>Caldolor – Each 1 mL of Caldolor also contains 78 mg of arginine at a molar ratio of 0.92:1 arginine: ibuprofen. Hydrochloric acid is added for pH adjustment.</p> <p>Neoprofen - Each mL of NeoProfen contains 17.1 mg of ibuprofen lysine (equivalent to 10 mg of (±)-ibuprofen) in Water for Injection. The pH is adjusted to 7.0 with sodium hydroxide or hydrochloric acid.</p> <p>Fenpaed - contains glycerol, xanthan gum, maltitol, polysorbate 80, saccharin sodium, citric acid monohydrate, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, purified water and strawberry flavour.</p>
Special comments	Nil
Evidence	<p>Treatment of patent ductus arteriosus in term infants Because most term infants and children with PDA are asymptomatic, acute medical treatment before definitive closure is usually not necessary. Those with symptoms usually improve with a standard short term regimen of fluid restriction and diuretics. [11,12] Indomethacin has been reported to constrict the ductus in case series of term infants with PDA (25/41; 61%) and infants with genetic disorders and/or congenital abnormality (67/85; 79%). [12,13] There are no reports of use of ibuprofen for treatment of a PDA in term infants.</p> <p>Patent ductus arteriosus in preterm infants In preterm infants closure of the ductus is delayed, remaining open at 7 days of age in approximately 2% of infants born at 30-37 weeks' gestation, 65% of those born at 25 through 28 weeks' gestation, and 87% of those born at 24 weeks' gestation.[14] The ductus is likely to close without treatment in infants born at >28 weeks' gestation (73%),[15] in those with birth weight >1000 g (94%),[16] and in infants born at 26-29 weeks' gestation who do not have respiratory distress syndrome (93%). [17] Data from placebo arms of controlled trials demonstrate that spontaneous ductal closure among smaller, less mature infants with respiratory distress syndrome is frequent. In the Trial of Indomethacin Prophylaxis in Preterms which included infants with birth weight from 500 to 999 g, 50% of placebo recipients never developed clinical signs of a PDA. [18] In a trial of early versus late indomethacin treatment of infants born at 26-31 weeks' gestation in which PDA was confirmed by echocardiography on day 3, the ductus closed spontaneously by 9 days of age in 78% of those randomized to late intervention. [19] In a cohort of 842 infants, a haemodynamically significant PDA occurred in 70% (106/151) of infants born at 23-24 weeks and in 59% (405/691) of infants born at 25-28 weeks of gestation. [20]</p> <p>Efficacy Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants Systematic review found prophylactic ibuprofen (IV or oral) decreased the risk of PDA on day 3 or 4 (RR 0.39, 95% CI 0.31 to 0.48; NNTB 4, 95% CI 3 to 5; 9 trials; N = 1029), although in the control group, the spontaneous closure rate was 58% by day 3 to 4 of age. Ibuprofen decreased the need for rescue treatment with cyclo-oxygenase inhibitors (RR 0.17, 95% CI 0.11 to 0.26; NNTB 4; 95% CI 3 to 5), and need for surgical ductal ligation (RR 0.46, 95% CI 0.22 to 0.96; NNTB 33, 95% CI 20 to infinity; 7 trials; N = 925). Prophylactic ibuprofen decreased grade 3 or 4 IVH in infants (RR 0.67, 95% CI 0.45 to 1.00; 7 trials; N = 925), and increased risk of oliguria (RR 1.45, 95% CI 1.04 to 2.02; NNTB 17, 95% CI 9 to 100; 4 trials; N = 747). [5] For the comparison prophylactic ibuprofen versus indomethacin, only one study has been published that used oral treatment, and results were reported in 62 infants. There were no significant results apart from a significant increase in length of hospitalisation for the ibuprofen group. [21] Conclusion: Prophylactic use of ibuprofen decreases the incidence of PDA, need for rescue treatment with cyclo-oxygenase inhibitors and surgical ductal closure. Adverse effects associated with ibuprofen (IV or oral) included increased risks for oliguria, increase in serum</p>

creatinine levels, and increased risk of gastrointestinal haemorrhage. There was a reduced risk for intraventricular haemorrhage (grade III - IV) but no evidence of a difference in mortality, chronic lung disease, necrotising enterocolitis, or time to reach full feeds. In the control group, the patent ductus arteriosus had closed spontaneously by day 3 or 4 in 58% of neonates. Prophylactic treatment exposes a large proportion of infants unnecessarily to a drug that has important side effects without conferring any important short-term benefits. Current evidence does not support the use of ibuprofen for prevention of patent ductus arteriosus. [5] [LOE I GOR B]

Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight infants

The standard dosing regimen in the following analyses for ibuprofen was 10 mg/kg followed by ibuprofen 5 mg/kg 24 and 48 hours later, and indomethacin 0.2 mg/kg at 12 hour intervals for three doses.

Systematic review of RCTs found intravenous ibuprofen (3 doses) reduced failure to close a PDA compared with placebo (RR; 0.62 (95% CI 0.44 to 0.86); RD; -0.18 (95% CI -0.30 to -0.06); NNTB 6 (95% CI 3 to 17); I2 = 65% for RR and I2 = 0% for RD; 2 studies, 206 infants; moderate-quality evidence) but was associated with increased oliguria (RR 39.0, 95% CI 2.40, 633.01) and increased creatinine (MD 29.17, 95% CI 12.60, 45.74 µmol/L). There was no difference in other morbidities including pulmonary hypertension, NEC and mortality.[6]

Twenty-four studies (1590 infants) compared ibuprofen (IV or oral) with indomethacin (IV or oral). No differences in failure rate for PDA closure was found (RR 1.07, 95% CI 0.92 to 1.24; RD 0.02, 95% CI -0.02 to 0.06; I2 = 0%; moderate-quality evidence). Ibuprofen reduced NEC (18 studies, 1292 infants; RR 0.68, 95% CI 0.49 to 0.94; NNTB 25, 95% CI 14 to 100), reduced oliguria (6 studies, 576 infants; RR 0.28, 95% CI 0.14 to 0.54; NNTB 11, 95% CI 7 to 20), was associated with low creatinine levels 72 hours after initiation of treatment (11 studies, 918 infants; MD - 8.12 µmol/L, 95% CI -10.81 to -5.43) compared to indomethacin treated infants. [6]

Five studies compared treatment of PDA with paracetamol versus ibuprofen and enrolled 559 infants. There was no significant difference for failure of ductal closure after the first course of drug administration (RR 0.95, 95% CI 0.75 to 1.21; 5 trials, 559 infants). Ibuprofen was associated with a high rate of gastrointestinal bleeding (RR 0.28, 95% CI 0.12 to 0.69; NNTB 17 95% CI 11 to 50), higher creatinine and bilirubin levels, and lower platelet counts and daily urine output. There were no significant differences in the neurological outcomes at 18 to 24 months (n = 61). [7]

Higher versus lower dose of ibuprofen for treatment of patent ductus arteriosus in preterm or low birth weight infants

For the following analyses, the higher dosing regimen of ibuprofen was 20 mg/kg/day followed by ibuprofen 10 mg/kg/day for two doses compared with the standard-dose of ibuprofen 10 mg/kg/day followed by ibuprofen 5 mg/kg/day for two doses.

There was a decreased risk of failure to close a PDA with high-dose versus standard-dose of IV ibuprofen (3 studies 190 infants; RR 0.37, 95% CI 0.22 to 0.61; NNTB 4, 95% CI 3 to 7). Although neonatal morbidities including gastrointestinal and renal side effects were not significantly different, the analyses were underpowered to detect a difference. [6]

Oral ibuprofen versus intravenous ibuprofen

Prophylactic oral ibuprofen decreased the risk of PDA (RR 0.47, 95% CI 0.30 to 0.74; 4 trials, 202 infants) and increased risk of gastrointestinal bleeding (RR 2.01, 95% CI 1.17, 3.48; NNTB 7, 95% CI 4 to 25). No evidence of a difference was identified for mortality, IVH or chronic lung disease. [5] [LOE I]

For treatment of PDA, one study reported decreased failure to close a PDA after single or three doses of oral ibuprofen compared with placebo (64 infants; RR 0.26, 95% CI 0.11 to 0.62; RD - 0.44, 95% CI -0.65 to -0.23; NNTB 2, 95% CI 2 to 4) but other outcomes were not reported. [6] [LOE II]

Comparing oral ibuprofen versus intravenous ibuprofen for treatment of PDA, oral ibuprofen was associated with reduced failure to close the PDA (5 trials, 406 infants RR 0.38, 95% CI 0.26, 0.56), no difference in mortality, need for surgical closure of the ductus, duration of ventilatory support, pulmonary haemorrhage, pulmonary hypertension, chronic lung disease, IVH,

periventricular leukomalacia, necrotising enterocolitis (3 trials, 236 infants; RR 0.86, 95% CI 0.35, 2.15), intestinal perforation (2 trials, 134 infants; RR 0.32, 95% CI 0.01, 7.48), gastrointestinal bleed (2 trials, 172 infants; RR 2.89, 95% CI 0.12, 69.24), ROP or neurodevelopment at 18-24 months. Oral ibuprofen was associated with lower creatinine levels after treatment (MD -22.47, 95% CI -32.40, -12.53 $\mu\text{mol/L}$). [6] [LOE I]

Summary of treatment modalities for patent ductus arteriosus in preterm infants

A network meta-analysis of treatment modalities for patent ductus arteriosus in preterm infants included 68 RCTs of 4802 infants including 14 different variations of indomethacin, ibuprofen, acetaminophen and placebo. The overall PDA closure rate was 67.4% (2867 of 4256 infants). A high dose of oral ibuprofen [20 mg/kg followed by ibuprofen 10 mg/kg for two doses] was associated with a significantly higher odds of PDA closure versus a standard dose of intravenous ibuprofen (OR 3.59; 95% CI 1.64-8.17; RD 199, 95%CI, 95-258 more per 1000 infants) and a standard dose of intravenous indomethacin (OR 2.35, 95%CI 1.08-5.31; RD 124, 95%CI 14-188 more per 1000 infants). Based on the ranking statistics, a high dose of oral ibuprofen ranked as the best pharmacotherapeutic option for PDA closure and to prevent surgical PDA ligation. There was no significant difference in the odds of mortality, necrotizing enterocolitis, or intraventricular hemorrhage with use of placebo or no treatment compared with any of the other treatment modalities. For side effects, a continuous infusion of intravenous ibuprofen was associated with the lowest incidence of oliguria, whereas high dose ibuprofen was associated with the highest incidence of oliguria. [22]

Conclusion: A high dose of oral ibuprofen was associated with a higher likelihood of hemodynamically significant PDA closure compared to standard doses of intravenous ibuprofen or intravenous indomethacin. However, high dose ibuprofen was associated with a higher likelihood of oliguria. Placebo or no treatment did not significantly change the likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage. [22]

Safety

Compared to placebo, prophylactic use of ibuprofen is associated increased risks for oliguria, increase in serum creatinine levels, and increased risk of gastrointestinal haemorrhage.[5]

Ibuprofen for treatment of a PDA was associated with increased oliguria and increased creatinine. [6]

Compared to treatment of a PDA with indomethacin, ibuprofen was associated with reduced NEC, reduced oliguria and was associated with lower creatinine levels 72 hours after initiation of treatment. [6]

Compared to paracetamol (acetaminophen), ibuprofen was associated with a high rate of gastrointestinal bleeding (RR 3.57, 95% CI 1.45 to 8.33; NNTH 17, 95% CI 11 to 50), higher creatinine and bilirubin levels, and lower platelet counts and daily urine output. [7]

A single study (111 infants) reported use of a continuous infusion of ibuprofen of 10 mg, 5 mg and 5 mg given over 24 hours compared to IV ibuprofen of 10 mg 5 mg and 5 mg administered over 15 minutes did not have an effect on PDA closure or reopening, reduced surgical ligation of the ductus (RR 0.28, 95% CI 0.08, 0.94) and was not associated with other benefits or harms. [23] [LOE II, GOR D]

In clinical trials, pulmonary hypertension was observed in only three infants after the prophylactic use of ibuprofen [5], in one case after ibuprofen treatment, and in additional case reports for the treatment of a PDA. [6] In a cohort study, 732 infants had a PDA diagnosis, with persistent pulmonary hypertension of the newborn occurring in 19 of 306 ibuprofen treated infants (6%) and in 32 of 426 indomethacin treated infants (8%). [8]

Ibuprofen may displace bilirubin from albumin at high concentrations in vitro (200 micromol/L)[9]. This does not appear to occur in vivo at the concentrations associated with recommended doses (up to 100 micromol/L). [10] [Note 1 $\mu\text{g/mL}$ = 4.85 $\mu\text{mol/L}$].

Pharmacokinetics/pharmacodynamics

Two RCTs compared higher-dose (20, 10, 10 mg/kg/day) versus lower dose (10, 5, 5 mg/kg/day) ibuprofen for treatment of PDA in extremely preterm infants with an increase in ductal closure rate reported. There was no difference in side effects. Peak concentrations were 109.8 (SD 27.2) micromol/L [24,25]. A pharmacokinetic study has shown drug elimination increases with

	<p>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 hours. [26]</p> <p>Ibuprofen is well absorbed orally. After a single dose of 10 mg/kg oral ibuprofen, levels were detectable 1 hour after administration, peaked after 8 hours and remained in a relative plateau until 24 hours post administration. Area under the curve 0 to 24 hours was higher than levels reported with intravenous treatment. [27]</p> <p>The trough ibuprofen level >5 mg/L (25 µmol/L) after day 1 of treatment (10 mg/kg) was predictive of ductal close in a small case series. [28]</p> <p>Amikacin clearance was reduced by 21% and vancomycin by 18% during co-administration of ibuprofen. The impact of indomethacin on vancomycin clearance was significantly higher compared to ibuprofen (46 and 28%, respectively). [29]</p>
Practice points	<p>A large body of evidence demonstrates that early, routine treatment to induce closure of the ductus in preterm infants, either medically or surgically, in the first 2 weeks after birth does not improve long-term outcomes.</p> <p>The role of more selective use of medical methods for induction of ductal closure, either for defined high-risk infants in the first 2 postnatal weeks, or more generally, for older infants in whom the ductus remains patent, remains uncertain and requires further study. [30]</p> <p>Oral ibuprofen was associated a reduced failure rate to close the PDA, no difference in neonatal morbidities including intestinal perforation and gastrointestinal bleed, and lower creatinine levels after treatment compared to intravenous ibuprofen. [6] [LOE I]</p> <p>Although high dose ibuprofen (oral or intravenous) is associated with a reduced failure rate to close the PDA, there are insufficient data to assess its safety. [6]</p>
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