Indometacin (Indomethacin)

Alert
From April 2016, the international spelling for Indomethacin has been changed to Indometacin.

Indication
Closure of patent ductus arteriosus (PDA)
Prevention of severe intra-ventricular haemorrhage.

Action
Prostaglandin inhibitor. Prostaglandins are important in maintaining ductal patency in utero.

Drug Type
Non-steroidal anti-inflammatory drug (NSAID).

Trade Name
Indocid PDA, Indomethacin Agila

Presentation
1 mg powder for reconstitution.

Dosage/Interval

<table>
<thead>
<tr>
<th>Post-natal Age</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 48 hours</td>
<td>0.2 mg/kg/dose</td>
<td>0.1 mg/kg/dose</td>
<td>0.1 mg/kg/dose</td>
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<tr>
<td>&gt; 48 hours</td>
<td>0.2 mg/kg/dose</td>
<td>0.2 mg/kg/dose</td>
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</table>

Maximum daily dose
0.2 mg/kg

Total cumulative dose
0.6 mg/kg

Route
IV

Preparation/Dilution
Add 1 mL of WFI to the 1 mg powder for reconstitution. Then draw up 1 mL (1 mg) and add 9 mL WFI to make a final volume of 10 mL with a concentration of 0.1 mg/mL.

Administration
IV: Over 20—30 minutes.
Inspect visually for particulate matter and discolouration prior to administration.

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 (NEC) or intestinal perforation, significant renal dysfunction, ductal dependent congenital heart disease and pulmonary hypertension.

Precautions
Indomethacin is associated with transient renal impairment. Late and prolonged treatment of the ductus arteriosus with indomethacin may increase the incidence of NEC.

Drug Interactions
Aminoglycosides: Dose may need to be modified if indomethacin affects renal function.
Digoxin: Reduces indomethacin volume of distribution – increased dose may be required.
Diuretics: Use of furosemide in combination with indomethacin may increase the incidence of renal impairment.
Systemic corticosteroids: Intestinal perforation has been described in infants treated with early dexamethasone and indomethacin.

Adverse Reactions
Prophylactic indomethacin is associated with oliguria/anuria.
Treatment of the ductus arteriosus with indomethacin and prolonged courses of indomethacin are associated with NEC.
Gastrointestinal perforation and possibly bleeding.
Extravasation.

Compatibility
Fluids: Sodium chloride 0.9%, water for injection.
Y site: Atropine, cephalizin, cefotaxime, ceftazidime, clindamycin, dexamethasone, digoxin, fentanyl, fluconazole, furosemide, heparin, hydrocortisone, benzylpenicillin, potassium chloride, sodium bicarbonate.

Incompatibility
Fluids: Glucose 7.5%, Glucose 10%
Y-site: Amino acid solutions, adrenaline, amikacin, atracurium, aztreonam, benztrapine, buprenorphine, calcium chloride, calcium gluconate, chlorpromazine, dobutamine, dopamine, erythromycin, esmolol, gentamicin, glycopyrrolate, haloperidol lactate, hydralazine, labetalol, magnesium sulfate, metaraminol, midazolam, morphine sulfate, noradrenaline, ondansetron, penicillin, pethidine, phenylephrine, promethazine, protamine, suxamethonium, tobramycin, vancomycin, vasopressin, verapamil.

Stability
Discard unused portion. Diluted solution is stable for 6 hours at room temperature.
<table>
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<tr>
<th>Storage</th>
<th>Store unopened vials at room temperature (20–25°C)</th>
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<tbody>
<tr>
<td>Special Comments</td>
<td>Nil</td>
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**Evidence summary**

**Effectiveness:**
Prophylactic intravenous indomethacin in preterm infants has short-term benefits including a reduction in the incidence of symptomatic PDA, PDA surgical ligation and severe intraventricular haemorrhage (IVH). However, there is no evidence of effect on mortality or neurodevelopment\(^5\) (LOE I GOR C). Safety: Prophylactic indomethacin is associated with oliguria but not an increased creatinine or gastrointestinal side effects.

Indomethacin for asymptomatic patent ductus arteriosus: Treatment of an asymptomatic PDA with indomethacin reduced the incidence of symptomatic PDA, duration of supplemental oxygen, with no effect on mortality, IVH, retinopathy of prematurity, length of ventilation, or NEC. Safety: Renal and gastrointestinal toxicities and long term neurodevelopment were not reported\(^10\) (LOE I, GOR C).

Indomethacin versus ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight infants: Indomethacin is as effective as ibuprofen in closing a PDA\(^6\). Safety: Indomethacin increases the risk of NEC and transient renal insufficiency compared to ibuprofen.

Summary recommendation: Ibuprofen is as effective as indomethacin in closing a PDA and currently appears to be the drug of choice. Ibuprofen reduces the risk of NEC and transient renal insufficiency compared to indomethacin\(^6\) (LOE I GOR B).

**Dose:** Indomethacin given in total amounts for the prolonged course (6–8 doses) of 0.6–1.6 mg/kg compared with the short course 0.3–0.6 mg/kg (2–3 doses): There was no difference in efficacy between a short or prolonged course of indomethacin (LOE 1, GOR C). Safety: A prolonged course is associated with an increased risk of NEC but a decreased incidence of renal function impairment (oliguria and increased serum creatinine)\(^7\) (LOE I, GOR B). Pharmacokinetic studies reported substantial interpatient variability\(^11, 12\) in clearance related to postnatal age\(^2,12\). Bolus infusions of indomethacin are associated with alterations in renal, mesenteric and cerebral blood flow\(^13\). Ductus arteriosus closure rates are related to dose and indomethacin concentrations\(^5\)\(^11,14\).

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**References**


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<tr>
<th>Original version Date: 29/09/2015</th>
<th>Author: NeoMed Consensus Group</th>
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