North West Neonatal Operational Delivery Network
Greater Manchester, Lancashire & South Cumbria, Cheshire and Merseyside

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# Contents

# Management of Patent Ductus Arteriosus

## Background

The ductus arteriosus closes spontaneously in many preterm infants but prolonged ductal patency is a complication of extreme preterm birth [1]. A persistently patent ductus with a large ductal shunt (a 'haemodynamically significant', hsPDA) is associated with pulmonary hyper-perfusion, systemic hypo-perfusion and adverse clinical outcomes including pulmonary haemorrhage, NEC, CLD and mortality [2].

## Which babies should undergo echocardiography?

An echocardiogram should be performed in any preterm baby in whom the clinical signs and/or radiological features suggest the presence of a hsPDA. These include murmur, tachycardia, full pulses, an active praecordium, hypotension, cardiomegaly, worsening respiratory status and dependence on respiratory support.

## Diagnosis of hsPDA

Diagnosis of PDA can only be made using 2D and Doppler echocardiography; clinical signs are unreliable and should not be used in isolation to make the diagnosis. Early echocardiographic 'screening' for PDA is not routinely performed. Diagnostic echocardiography should include an initial assessment to exclude structural heart disease and, specifically, duct-dependent cardiac defects.

Assessment of hsPDA should include measures of ductal size and the magnitude and impact of the ductal shunt. The following echocardiographic indices and thresholds should be used to define a hsPDA [3]:

1. PDA diameter $\geq$ 2.0 mm (either using 2D or colour Doppler)
2. Ductal flow pattern ('growing' pattern or pulsatile with Vmax < 2 m/s and Vmax/Vmin $\geq$ 2)
3. Retrograde post ductal aortic/coeliac/SMA diastolic flow
4. La/Ao $\geq$ 2
5. LVO > 300 ml/kg/min
6. Mitral valve E/A ratio > 1

The diagnosis of hsPDA should be made in the presence of supportive clinical signs and at least 3 of the above echo indices.

# Management of babies with PDA

a. **Babies with PDA and a small ductal shunt** (i.e. not haemodynamically significant) should be managed expectantly. A repeat echo should be performed if the baby has a cardiorespiratory deterioration or if a murmur is still present prior to discharge home. Refer to cardiology if PDA is still present at discharge.

b. **Asymptomatic babies with echocardiographic criteria of hsPDA** should also be managed expectantly, but with a low threshold for repeating the echo if the baby develops any symptoms of hsPDA. Subsequently, management should follow (a) or (c), as appropriate.

c. **Symptomatic babies* with a hsPDA** may be treated with diuretics, ibuprofen and/or paracetamol (see below).

**Clinical features include persistent hypotension, pulmonary haemorrhage, prolonged dependence (or increase in) invasive or non-invasive respiratory support, feed intolerance.*

# Management strategies/therapeutic interventions (see appendix 1)

## Expectant management

This approach is used when uncomplicated spontaneous closure of the ductus arteriosus is anticipated. Management is the same as in a baby in whom the PDA is closed.

## Non-pharmacological intervention

Although there is no clear evidence of clinical efficacy, various approaches including fluid restriction, increasing PEEP, permissive hypercapnia, maintaining a high haematocrit and higher target SpO2 (89-94%) have all been used as part of a 'conservative' approach to managing a hsPDA [4].

Action:
- Follow current unit guidelines for fluid, blood transfusion and oxygen and respiratory support;
- Give information leaflet on PDA to parents.

## Diuretic therapy

There is some evidence that furosemide stimulates renal synthesis of prostaglandin E2 (a dilator of the ductus arteriosus) and delays ductal closure. The risk of PDA is greater with furosemide compared with chlorothiazide. Furosemide is associated with nephro- and ototoxicity.

Action:
- Use chlorothiazide (and not furosemide) for management of PDA-associated left heart volume overload and pulmonary oedema.

## Pharmacological closure

Although pharmacological closure of the DA is associated with decreased severe IVH and pulmonary haemorrhage, there is no convincing evidence of longer-term benefit from randomised controlled trials [5]. A conservative management approach might also be superior to early routine treatment in babies dependent on respiratory support [6].

a. **Ibuprofen**

Ibuprofen is effective in achieving ductal closure in around 70-80% of cases [7, 8]. There is some evidence that oral therapy and higher dosage regimens are associated with higher closure rates [7-9].

Action:
- Use standard dose ibuprofen (3 doses of 10, 5, 5 mg/kg at 24 hourly intervals) as routine first-line pharmacological treatment of hsPDA in babies < 21 days of age;
- Use oral (rather than IV) ibuprofen if baby is receiving full enteral feeds;
- Re-assess the ductus arteriosus and ductal shunt after 3 days;
- A second course of high dose ibuprofen (3 doses of 20, 10, 10 mg/kg at 24 hourly intervals) can be considered if baby is still under 21 days of age.

b. **Paracetamol (acetaminophen) (see appendix 3 for sample drug information sheet)**

Paracetamol has comparable efficacy to ibuprofen in ductal closure but there is limited information on long-term safety [10]. There is some evidence to support the use of paracetamol in late treatment of PDA after failure of previous NSAID therapy, although the efficacy in achieving ductal closure was only 15% [11].

Action:
- Consider using paracetamol to treat hsPDA in babies $\geq$ 21 days of age, or in babies < 21 days in whom there are contraindications to using ibuprofen (refer to drug information folder);
- Reassess the ductus arteriosus and ductal shunt after 3 days.

## Surgical closure

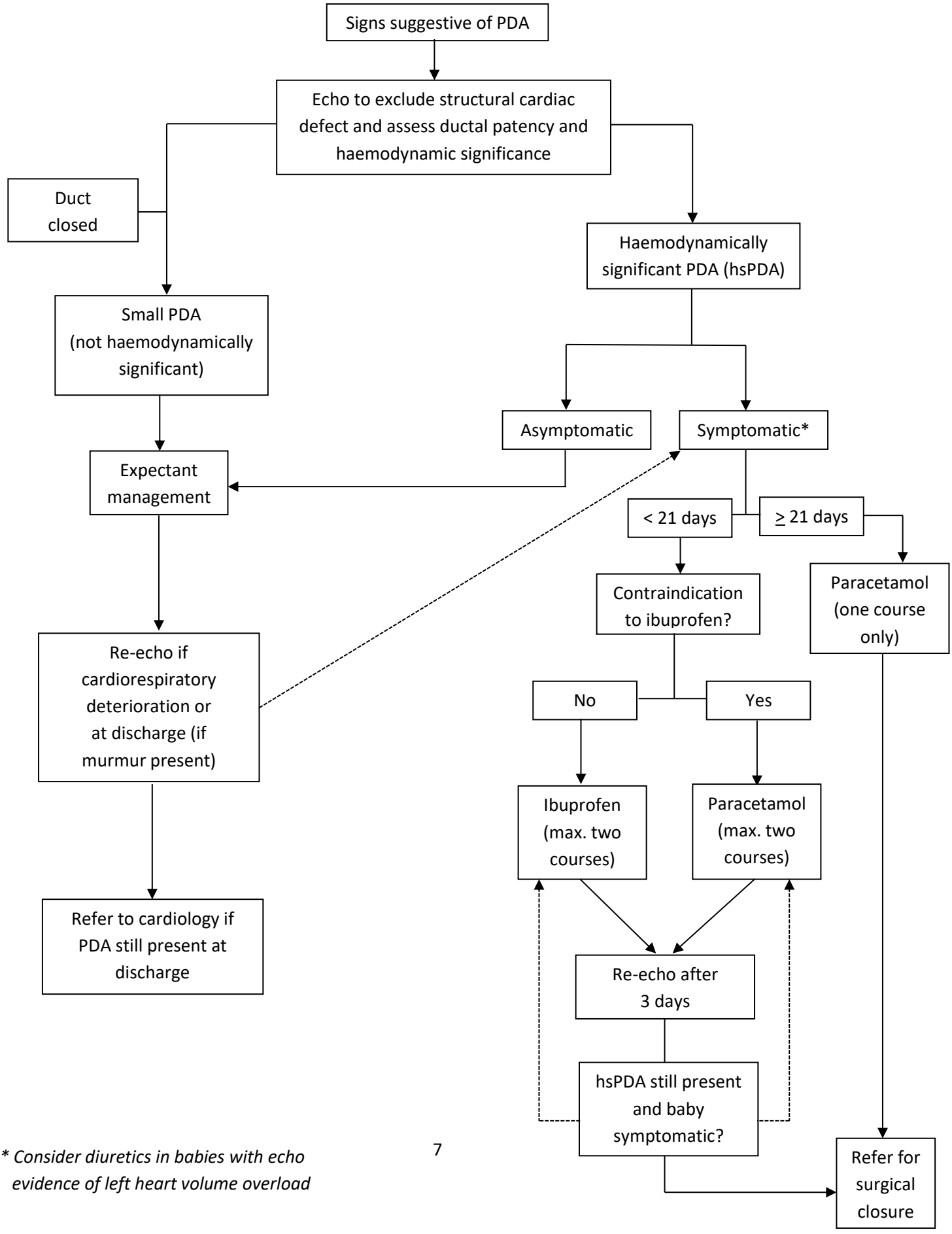
Surgical closure should be considered in babies with hsPDA despite pharmacological therapy (or in whom pharmacological therapy is contraindicated) who remain dependent on high levels of respiratory support (ventilation, CPAP or HFNC). Duct ligation carries significant risks associated with transfer, surgery and post-operative complications (such as post-ligation cardiac syndrome) [12]. Catheter closure might be appropriate in selected larger babies (> 6 kg) at the discretion of the cardiologists.

If after the above sequential assessment the baby is felt to require consideration for surgical or interventional closure of a haemodynamically significant Persistent Ductus Arteriosus (hsPDA) please refer to the *Congenital Heart Network Guidance 'Referral for management of patent ductus arteriosus (PDA) in premature babies'.*

Action:

- Consider duct ligation in babies with hsPDA who are dependent on high levels of respiratory support (ventilation, CPAP or HFNC) .
- A consultant-to-consultant referral should be made to the cardiology team verbally and using the referral process outlined in the Congenital Cardiac *Congenital Heart Network Guidance 'Referral for management of patent ductus arteriosus (PDA) in premature babies'.* See Appendix 2 for flow chart of process.
- A pre-op echo should be performed within 3 days of transfer to confirm that a hsPDA is still present.

## Appendix 1




** Consider diuretics in babies with echo evidence of left heart volume overload*

## Appendix 2: Summary of PDA Referral Pathway

**hsPDA confirmed on assessment**
**Neonatal guidance suggests intervention**
Patient should be fully assessed and be free of inter-current infection

**Referring team to complete MDT Form**

**MDT Coordinators**
**Megan Johnson**
megan.johnson23@nhs.net
0151 282 4514
**Tracy Oakes**
tracy.oakes@nhs.net
0151 282 4515

**Neonatal team contacts Alder Hey Paediatric Cardiology ST or consultant of the week**

Via Switchboard on 0151 228 4811

Directly on Consultant of the week phone 0151 252 5220

Via SpR on Call 0151 228 4811 Bleep 369

Echo images/CXR to be sent via PACS where possible
MDT discussion form to be sent to cardiology ST on call Ahc-tr.cardreg@nhs.net for review and telephone discussion
**Referral accepted**
MDT coordinator will liaise with referrer to agree date for MDT discussion via MS Teams

**Patient discussed at regional cardiac MDT**
If suitable patient listed for surgery or intervention
On call team to feedback meeting outcome and plan to referring team

**Provisional date arranged (listing meeting)**
Cardiac surgery or interventional PCO to liaise with referring centre regarding date and enter on calendar

**Transport to be arranged for date**
**Please telephone ICU on 0151 252 5242/ 5241 on the morning of transfer and prior to departure to confirm bed available and provide clinical handover**

ICU to contact referring centre and transport team when patient ready for transport back to neonatal care

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Please note any **changes to clinical condition** following referral should be discussed with the cardiology on call team e.g

**Escalation of respiratory support*
**New vasoactive support*
**Infection concerns*

## Appendix 3: Sample Ibuprofen Drug Information Summary (LWH, May 2020)

### IBUPROFEN

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|---|---|
| **INDICATION:** | Treatment of haemodynamically significant patent ductus arteriosis (PDA) confirmed by ECG examination in neonates <34 weeks gestational age. |

**BACKGROUND**

Ibuprofen is a non-steroidal anti-inflammatory drug with anti-pyretic and analgesic effects. It interferes with prostaglandin synthesis through cyclo-oxygenase inhibition. Ibuprofen has less of an effect on organ perfusion as compared to indomethacin. Ibuprofen may inhibit platelet aggregation and increase bleeding time.

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|---|---|
| **PRESENTATION** | 2mL ampoule containing 10mg Ibuprofen Pedea® (5mg/mL)<br>pH 7.8 – 8.2 |

| | |
|---|---|
| **DOSE:** | Initial (loading) dose of **10 mg/Kg** by IV infusion over 15 minutes followed at 24 hourly intervals by two further (maintenance) doses of **5 mg/Kg** by IV infusion over 15 minutes.<br>A second course of high dose ibuprofen may be given if the PDA remains haemodynamically significant 48 hours after the end of the first course:<br>Initial (loading) dose of **20 mg/Kg** by IV infusion over 15 minutes followed at 24 hourly intervals by two further (maintenance) doses of 10 **mg/Kg** by IV infusion over 15 minutes. |
| **ADMINISTRATION:** | Preferably administer undiluted. However, may be diluted to a suitable volume with sodium chloride 0.9% or glucose 5% to adjust the volume to enable practical administration.<br>Select IBUFROFEN on GUARDRAILS system<br>**LOADING DOSE**: Infuse intravenously at a rate of 40mg/Kg/hour for 15mins to deliver a dose of 10mg/Kg **OR** 80mg/Kg/hour for 15mins to deliver a dose of 20mg/Kg<br>**MAINTENANCE DOSE**: Infuse intravenously at a rate of 20mg/Kg/hour for 15mins to deliver a dose of 5mg/Kg **OR** 40mg/Kg/hour for 15mins to deliver a dose of 10mg/Kg |

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| **DILUENTS** | Sodium chloride 0.9% or Glucose 5% |

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| **ROUTE OF ADMINISTRATION** | Administer by INTRAVENOUS INFUSION over 15 minutes.<br><br>In order to avoid ibuprofen being in contact with any acidic solution, the infusion line should be rinsed over 15 minutes before and after administration, with 1.5-2mL sodium chloride 0.9% or glucose 5% |
| **FLUSH** | Sodium chloride 0.9% or Glucose 5% |
| **CAUTION** | Monitor for bleeding problems including upper gastrointestinal bleeding. May mask signs of infection. Avoid in severe liver disease. Avoid in moderate/severe renal impairment. If anuria or oliguria occurs after the first or second dose, the next dose should be withheld until urine output returns to normal levels. |
| **COMPATIBILITY** | Do not infuse with any other medicines. |
| **KNOWN INCOMPATABILITIES** | Do not use chlorhexidine to disinfect ampoules as it is incompatible with ibuprofen (Pedea®) solution. For asepsis use ethanol 60% or isopropyl alcohol 70%. Ensure external surface of ampoules is dry before opening. |
| **SIDE EFFECTS** | Thrombocytopenia, neutropenia, intraventricular haemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, hypoxemia, necrotising enterocolitis, intestinal perforation, gastrointestinal haemorrhage, oliguria, acute renal failure, fluid retention, haematuria |
| **MONITORING** | Weight, urine output, urea, electrolytes, platelet function and severe hyperbilirubinaemia. Blood creatinine increase and blood sodium decrease may occur. |
| **INTERACTIONS** | Ibuprofen may decrease the clearance of aminoglycosides such as gentamicin and strict surveillance of antibiotic levels is important during co-administration with ibuprofen. Ibuprofen may reduce the effect of diuretics. It may increase the risk of gastrointestinal haemorrhage when used in combination with corticosteroids. |
| **STORAGE** | Store at room temperature in original packaging to protect from light. After first opening of an ampoule, any unused portions must be discarded. |

## OTHER INFORMATION

1. Licensed for closure of ductus arteriosis (premature neonate <34 weeks)
2. Excipients include: trometamol.
3. Not used for analgesia in this neonatal unit.
4. Contraindicated with duct-dependent congenital heart disease; life-threatening infections; active bleeding especially intracranial or gastrointestinal; thrombocytopaenia or coagulopathy; marked unconjugated hyperbilirubinaemia; known or suspected NEC, pulmonary hypertension.

## REFERENCES

BNF for Children (ONLINE), Neonatal Formulary 7th Edition, Medusa injectable medicines guide (ONLINE), Trissel Handbook on Injectable Drugs (ONLINE), SPC: Pedea 5mg/ml solution for injection (ONLINE). Online resources accessed 03/03/2019.

High dose Ibuprofen: Dani et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. Clin Pharmacol Ther. 2012 Apr;91(4):590-6

## Appendix 4: Sample Paracetamol Drug Information Summary (LWH, 2019)

# PARACETAMOL

**INDICATION:**

- For analgesia and pyrexia in babies ≥ 28 weeks post-menstrual age (PMA) (See pain and sedation guideline)
- Treatment of Patent Ductus Arteriosus (PDA) (See Management of Patent Ductus Arteriosus guideline)

**BACKGROUND**

Paracetamol is a non-opioid analgesic with antipyretic properties. It does not cause respiratory depression and causes less irritation to the stomach than NSAIDs such as ibuprofen. Paracetamol causes ductal constriction and is used as an alternative to Ibuprofen in the management of babies with a PDA. Paracetamol can cause severe life-threatening hepatic damage in overdosage. It can be given orally, rectally and intravenously. There are limited safety data on the use of paracetamol in preterm infants. Optimum pain relief occurs approximately one hour after peak serum concentration has been reached. Peak concentrations are reached almost immediately after IV administration and in 30-60 minutes following oral administration (longer with rectal administration). The reported elimination half-life varies from a median of 4 hours in term infants to 8 hours in infants <32 weeks.

**PRESENTATION**

100mL vial containing 1000mg Paracetamol (10mg/mL)
Already in solution

Paracetamol oral suspension 120mg/5mL

pH 5 – 7

**FOR ANALGESIA AND PYREXIA**

- Can be prescribed regularly or when required (PRN)
- Review prescription regularly and stop if no longer required.

| | | |
|---|---|---|
| **INTRAVENOUS Dose** | ≥ 28 weeks PMA | **20mg/Kg** Loading Dose followed 6 hours later by Maintenance Dose of **10mg/Kg** every **SIX** hours |
| **ORAL/ENTERAL Dose** | 28 – 32 weeks PMA | **20mg/Kg** Loading Dose followed 12 hours later by Maintenance Dose of **10mg/Kg** every **TWELVE** hours |
| | > 32 weeks PMA | **20mg/Kg** Loading Dose followed 6 hours later by Maintenance Dose of **10mg/Kg** every **SIX** hours |

**FOR PDA CLOSURE**

- Use IV route if available
- Use for 3 days initially then review clinically and by ECHO. A further 3-day course may be prescribed, if indicated (Consultant decision)

| | | |
|---|---|---|
| **INTRAVENOUS Dose** | All babies | **20mg/Kg** Loading Dose followed 6 hours later by Maintenance Dose of **10mg/Kg** every **SIX** hours |
| **ORAL/ENTERAL Dose** | All babies | **15mg/Kg** every **SIX** hours (no loading dose required) |

**ADMINISTRATION**

**INTRAVENOUS:**

1. Calculate volume needed for required dose.
2. Withdraw the required volume from the vial into a syringe (plus extra volume to prime the administration line). Can be administered without further dilution.
3. Administer dose by INTRAVENOUS INFUSION over **15 minutes** using GUARDRAILS.

| | |
|---|---|
| **Loading dose** (select **Paracetamol LOADING**) | 20 mg/kg over 15 minutes is equivalent to 80 mg/kg/hour |
| **Maintenance dose** (select **Paracetamol MAINT**) | 10 mg/kg over 15 minutes is equivalent to 40 mg/kg/hour |

***** In smaller infants an excess will have to be drawn up and VTBI set on the pump to allow administration of small volumes or IV preparation may be diluted to a suitable volume to enable practical administration. (Diluted solution has an expiry of one hour including infusion time)

**ORAL/ENTERAL:** Shake bottle before use. Measure required dose and administer orally or via enteral feeding tube.

**DILUENTS** Sodium Chloride 0.9%, Glucose 5%

**ROUTE OF ADMINISTRATION** Administer by IV infusion over 15 minutes via peripheral or central access using GUARDRIALS.

**FLUSH** Sodium Chloride 0.9% or Glucose 5%

**CAUTION** Reduce intravenous dose by 50% in patients with hepatic impairment or neonates with unconjugated hyperbilirubinaemia. Drug clearance is slower in jaundiced babies. Risk of liver toxicity with overdosage. Clinical signs and symptoms of liver damage are not usually seen until 2-6 days after administration.

**COMPATIBILITY** Glucose 5%, glucose 10%, sodium chloride 0.9%

**KNOWN** Do infuse with other medicines or infusions.

**INCOMPATABILITIES**

**SIDE EFFECTS** Hypotension, hypersensitivity reactions, flushing, tachycardia, injection site reactions. Rarely thrombocytopaenia, leucopaenia, neutropaenia.

**MONITORING** Monitor pain score (NPASS), temperature, oxygenation, hepatic function, renal function and ECHO (if treating PDA)

**INTERACTIONS** Increased risk of hepatotoxicity with carbamazepine, clavulanic acid, flucloxacillin, fluconazole, valproate. Decreased efficacy with phenobarbitone, phenytoin and rifampicin

**STORAGE** Vials: Store at room temperature and protect from light. Each vial is single use, discard any remaining solution after use.

Oral Suspension: Store at room temperature.

Do NOT refrigerate or freeze paracetamol.

**OTHER INFORMATION**

1. Paracetamol is not licensed for use in children under 2 months of age.
2. Paracetamol solution for injection is isotonic.
3. Paracetamol suppositories for rectal administration are not stocked at LWH. Rectal absorption in the neonate is unpredictable and this route is rarely used.
4. Paracetamol toxicity is treated with acetylcysteine as it reduces the hepatotoxic effects of paracetamol overdose by replenishing glutathione stores, thereby enhancing production of the non-toxic metabolites.
   **Acetylcysteine dose and administration instructions** (as per BNFc)
   - 150 mg/Kg IV during the first hour and then 50 mg/Kg over the next 4 hours followed by 100 mg/Kg over 16 hours as described below:
   - Initial infusion: Take one 10mL vial of acetylcysteine and dilute with 30mL of Glucose 5% to give a 50mg/mL solution. Infuse at a rate of 3mL/Kg/hour for one hour only.
   - Subsequent infusion: Take one 10mL vial of acetylcysteine and dilute with 310mL of Glucose 5% to give a 6.25mg/mL solution. When the initial infusion has finished, infuse this solution at a rate of 2mL/Kg/hour for 4 hours and then at a rate of 1mL/Kg/hour for 16 hours.

**REFERENCES**

BNF for Children (ONLINE), Neonatal Formulary 7th Edition, Medusa injectable medicines guide (ONLINE), Trissel Handbook on Injectable Drugs (ONLINE), SPC: Paracetamol 10mg/ml solution for infusion; Paracetamol 120mg/5ml oral suspension (ONLINE). Online resources accessed 28/05/2019.

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