Alert	Data in neonates are limited. Use in neonates should be restricted and considered experimental. Further studies are needed.
Indication	Persistent Pulmonary Hypertension of the Neonate (PPHN): - refractory to inhaled nitric oxide (iNO) and other conventional therapies or - those who are persistently unable to be weaned off inhaled nitric oxide or - in situations where inhaled nitric oxide and high frequency ventilation are not available Chronic pulmonary hypertension secondary to respiratory, cardiac or chest wall disease.
Action	Selective phosphodiesterase type 5 (PDE5) inhibitor. PDE5 is found in the smooth muscle of the pulmonary vasculature, where it is responsible for the degradation of cyclic guanosine monophosphate (cGMP). cGMP produces smooth muscle relaxation. Sildenafil increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary hypertension, this can lead to selective vasodilatation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation.
Drug Type	Phosphodiesterase type 5 (PDE5) inhibitor.
Trade Name	IV: Revatio Oral: Pharmacy prepared
Presentation	IV: Vial for injection containing **10 mg/12.5 mL** = 0.8 mg/mL of sildenafil Oral: Pharmacy-prepared oral suspension
Dosage/Interval	**IV:** **Loading:** 0.4 mg/kg administered **over THREE hours** followed by: **Maintenance:** 1.6 mg/kg/day (0.067 mg/kg/hour) as a continuous infusion for up to 7 days. **PO:** Start at 0.5 to 1 mg/kg/dose given 6 to 8 hourly and titrate up to 2 mg/kg/dose according to response. May increase up to maximum of 3 mg/kg/dose given 6 hourly. To avoid the possible occurrence of sudden clinical deterioration during withdrawal of sildenafil, a gradual dose reduction should be considered when stopping sildenafil.
Route	IV, oral
Preparation/Dilution	See below
Administration	**IV infusion:** **Low concentration IV infusion (weight > 2.5 kg)** Draw up 2.5mL/kg (2 mg/kg of sildenafil) solution and make up to 15 mL using glucose 5% (preferred) or sodium chloride 0.9%. Infuse 1 mL/h **for 3 hours** (loading dose of 0.4 mg/kg) **followed by** 0.5 mL/h (0.067 mg/kg/h) **High concentration IV Infusion (weight ≤ 2.5 kg)** Draw up 4.2mL/kg (3.36 mg /kg of sildenafil) solution and make up to 15 mL using glucose 5% (preferred) or sodium chloride 0.9%. Infuse 0.6 mL/h for **3 hours**(loading dose of 0.4 mg/kg) **followed by** 0.3 mL/h (0.067 mg/kg/h) **Oral:** Shake well before drawing up the dose. Give via intragastric tube, preferably with feed to minimise risk of gastrointestinal irritation. If baby is not on enteral feeds or breast milk is not available, give dose via intragastric tube and flush with 0.5 mL water for injection.
Monitoring	Heart rate, blood pressure and oxygenation. Renal and hepatic function. Consider monitoring with echocardiogram.
Contraindications	Hypersensitivity to sildenafil

	Not to be used in patients taking organic nitrates of any form e.g. glyceryl trinitrate, isosorbide mononitrate, sodium nitroprusside
Precautions	Use with caution in neonates with sepsis or uncontrolled hypotension. Sildenafil clearance (in adults) is reduced in hepatic and severe renal impairment.
Drug Interactions	Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance. Thus, erythromycin and fluconazole may increase concentrations of sildenafil by reducing hepatic clearance and rifampicin may decrease concentrations by inducing its hepatic metabolism. Avoid concomitant use of sildenafil with: Alprostadil (prostaglandin E1), other antihypertensives and vasodilators, as they may have their effects potentiated by sildenafil.
Adverse Reactions	Most concerning short-term adverse effects: Worsening oxygenation and systemic hypotension. Epistaxis, respiratory symptoms (cough and nasal congestion), diarrhoea and vomiting, gastroesophageal reflux and abdominal pain, headaches, tremors, erections, facial flushing, dizziness, irritability and (rarely) fever, skin disorders, pain in limbs and oedema have been reported in children on sildenafil. The Sildenafil in Treatment-Naïve Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension long-term extension (STARTS-2) trial showed worse survival in children receiving high doses of sildenafil as monotherapy.[2] A recent study conducted by Roldan and colleagues, found there was a statistically significant increase in adverse drug reaction (ADR) frequency in children receiving higher-than-recommended doses. However, it was not associated with a lower survival rate.[14] Sildenafil has the potential to adversely affect vision.[13] Impaired liver function tests. May increase the risk of severe retinopathy of prematurity if used in extremely preterm neonates.
Compatibility	Glucose 5%, sodium chloride 0.9%.
Incompatibility	No data – where possible administer via dedicated line.
Stability	IV – infusion should be changed every 24 hours. Oral suspension – as per pharmacy advice.
Storage	IV – unopened vials at room temperature (20–25°C). Oral suspension – refrigerate, do not freeze
Special Comments	In paediatric patients with pulmonary arterial hypertension, an increased mortality risk was associated with long-term (> 2 year) use. The mortality risk of long-term use in neonates is unknown.
Evidence summary	Refer to Full version
References	Refer to Full version

Original version Date: 06/10/2016	**Author: Neonatal Medicines Formulary Consensus Group**
Current Version number: 1.1	**Current Version Date:** 20/02/2017
Risk Rating: Medium	**Due for Review:** 22/11/2019
Approval by: JHCH CQ&PCC	**Approval Date: 22/11/2016**