

Pulmonary hypertension in neonates: sildenafil

Evidence summary: unlicensed or off-label medicine

Published: 29 March 2016

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Key points from the evidence

Summary

There is evidence from small, short-term randomised controlled trials (RCTs) in resource-limited settings where nitric oxide is not available that oral sildenafil reduces mortality and improves physiological parameters of oxygenation compared with placebo in term or near-term neonates with persistent pulmonary hypertension of the newborn (PPHN). However, there is very little evidence of sildenafil use for PPHN in settings such as the UK where inhaled nitric oxide is available. In a small RCT in premature neonates at risk of bronchopulmonary dysplasia (BPD) sildenafil was not beneficial, and it remains unclear if sildenafil leads to improved outcomes in premature neonates with BPD-associated pulmonary hypertension. The long-term safety of sildenafil in neonates with pulmonary hypertension is not known.

Regulatory status: off-label. This topic was prioritised following a request for an evidence review from the Neonatal and Paediatric Pharmacists Group because the use of sildenafil for pulmonary hypertension in neonates varies across centres in the UK.

Effectiveness	Safety
<ul style="list-style-type: none"> • In neonates with PPHN not receiving nitric oxide: <ul style="list-style-type: none"> - A Cochrane review of 3 placebo-controlled RCTs (total n=77) found oral sildenafil statistically significantly reduced mortality (3 deaths in the sildenafil group [n=40] and 16 deaths in the placebo group [n=37]) and improved the oxygenation index and partial pressure of oxygen. - An RCT comparing oral sildenafil with intravenous magnesium sulphate (n=72) found no difference in mortality; there were statistically significant improvements in the time to an adequate clinical response, the duration of ventilation and the number of neonates requiring inotropic drugs with sildenafil. • In a dose-escalation study of intravenous sildenafil in 36 neonates with PPHN (29 also receiving nitric oxide), the oxygenation index improved after sildenafil treatment. One neonate died and 1 required extracorporeal membrane oxygenation. • In premature neonates at risk of BPD: <ul style="list-style-type: none"> - a placebo-controlled RCT (n=20) found oral sildenafil did not improve any short-term 	<ul style="list-style-type: none"> • Sildenafil is contraindicated in combination with nitrates, guanylate cyclase stimulators, potent CYP3A4 inhibitors, severe hepatic impairment, recent history of stroke or myocardial infarction, severe hypotension and non-arteritic anterior ischaemic optic neuropathy (Revatio 10 mg/ml powder for oral suspension summary of product characteristics). • The safety and efficacy of sildenafil in children below 1 year of age has not been established. Doses higher than the recommended doses should not be used in children with pulmonary hypertension (Revatio 10 mg/ml powder for oral suspension summary of product characteristics).

<p>respiratory outcomes and did not reduce the length of invasive or non-invasive ventilation. There were 3 deaths in the sildenafil group (n=10) and 1 death in the placebo group (n=10).</p>	
<p>Patient factors</p> <ul style="list-style-type: none"> • In most studies, sildenafil was given orally via an orogastric tube. • Data on tolerability from studies of sildenafil in neonates with pulmonary hypertension are limited and relate mainly to hypotension. 	<p>Resource implications</p> <ul style="list-style-type: none"> • The cost of sildenafil as Revatio 10 mg/ml powder for oral suspension is £186.75 for 112 ml. Revatio tablets cost £4.96 per 20 mg tablet and generic sildenafil tablets cost £0.24 per 25 mg tablet (MIMS and Drug Tariff February 2016, all costs excluding VAT). • Most studies of sildenafil in neonates with pulmonary hypertension have been carried out in resource-limited settings where inhaled nitric oxide was not available.

Introduction and current guidance

Pulmonary hypertension in neonates represents a heterogeneous group of diagnoses, including PPHN, which are associated with a 10% to 20% mortality rate ([Perez and Laughon 2015](#)). Pulmonary hypertension can also occur in premature neonates with BPD.

In term or near-term neonates with pulmonary hypertension, the pulmonary vasodilator, inhaled nitric oxide, is considered the mainstay of treatment. The role of inhaled nitric oxide in premature neonates is less clear ([Shah and Ohlsson 2011](#)). Other treatments that can be used include epoprostenol, sildenafil, magnesium sulfate, milrinone and bosentan. However, none of these are specifically licensed for treating pulmonary hypertension in neonates.

[Full text of introduction and current guidance.](#)

Product overview

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cGMP. PDE5 is

present in the pulmonary vasculature. Sildenafil therefore increases cGMP within pulmonary vascular smooth muscle cells, resulting in relaxation. This can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation the systemic circulation in people with pulmonary arterial hypertension ([Revatio 10 mg/ml powder for oral suspension summary of product characteristics](#)).

Sildenafil, as [Revatio 10 mg/ml powder for oral suspension](#) and [Revatio 20 mg tablets](#), is licensed for treating children aged 1 year and over with pulmonary arterial hypertension. These products are not licensed for use in children less than 1 year of age; therefore the use of sildenafil for pulmonary hypertension in neonates is an off-label use. Sildenafil is also available as [Revatio solution for injection](#), which is licensed for treating adults with pulmonary arterial hypertension, and generic 25 mg, 50 mg and 100 mg tablets, which are licensed for treating erectile dysfunction.

There is a [paediatric investigation plan for Revatio](#) in the treatment of pulmonary arterial hypertension. This covers neonates from birth to less than 1 month of age with PPHN and children from 1 month to less than 18 years of age with pulmonary arterial hypertension. The plan includes a 7-day open-label, multicentre pharmacokinetic study of intravenous sildenafil in neonates with PPHN ([Steinhorn et al. 2009](#)) and an ongoing, placebo-controlled RCT, which is investigating the efficacy and safety of intravenous sildenafil plus inhaled nitric oxide for the treatment of neonates with PPHN or hypoxic respiratory failure at risk for PPHN ([NCT01720524](#)).

[Full text of product overview.](#)

Evidence review

This evidence summary is based on a Cochrane review and a further systematic review of several small RCTs of sildenafil use in neonates with pulmonary hypertension. The largest [observational studies](#) of sildenafil use in this condition are also included. The majority of the evidence is for oral sildenafil use in term or near-term neonates with PPHN. There is also a small amount of evidence for oral sildenafil use in premature neonates with or at risk of BPD.

- The Cochrane review ([Shah and Ohlsson 2011](#)) included 3 placebo-controlled RCTs (total n=77) of sildenafil use in neonates with PPHN. All 3 were single-centre trials in resource-limited settings where inhaled nitric oxide, high-frequency ventilation and extracorporeal membrane oxygenation (ECMO) were not available. Sildenafil was given orally via an orogastric tube in all 3 RCTs, at doses of: 1 mg/kg (which could be doubled to 2 mg/kg) every 6 hours to a maximum of 8 doses or until the oxygenation index improved to less than

20; 2 mg/kg every 6 hours for 72 hours; or 3 mg/kg every 6 hours until the oxygenation index was less than 10.

- Sildenafil statistically significantly reduced mortality compared with placebo, with 3 deaths in the sildenafil group (n=40) and 16 deaths in the placebo group (n=37). The typical relative risk (RR) was 0.20; 95% confidence interval (CI) 0.07 to 0.57; typical risk difference (RD) -0.38, 95% CI -0.60 to -0.16; and number needed to treat (NNT) 3, 95% CI 2 to 6.
- Physiological parameters of oxygenation suggested a steady improvement after the first dose of sildenafil. The mean oxygenation index after 24 hours of treatment was between 11 and 25 in the sildenafil group (n=39), and between 36 and 52 in the placebo group (n=30). After 24 hours of treatment, the mean partial pressure of oxygen (PaO₂) in the sildenafil group (n=32) was 70 to 85 mmHg and 56 to 62 mmHg in the placebo group (n=25).
- For sildenafil use in term or near-term neonates with PPHN, the systematic review ([Perez and Laughon 2015](#)) included the same 3 RCTs as the Cochrane review plus [Soliz et al. 2009](#) (a multicentre, placebo-controlled RCT of oral sildenafil 2 mg/kg every 6 hours in 3 centres where inhaled nitric oxide was not available; abstract only [n=49]).
 - Using mortality data from the same 3 trials as the Cochrane review (no mortality data were available from [Soliz et al. 2009](#)), the systematic review reported similar mortality rates. A statistically significant improvement in oxygenation index was reported for all 4 RCTs. The duration of mechanical ventilation was shorter with sildenafil compared with placebo in 2 RCTs, no difference in 1 RCT and not reported in 1 RCT.
- Oral sildenafil was compared with intravenous magnesium sulfate in an RCT in 72 term and near-term neonates with PPHN in a single centre without facilities for inhaled nitric oxide, high-frequency ventilation or ECMO ([Uslu et al. 2011](#)). The dose of sildenafil was 0.5 mg/kg (which could be doubled to a maximum of 2 mg/kg) via an orogastric tube every 6 hours. There was no difference in the mortality rate between the 2 groups (1 death in the sildenafil group [3.2%] and 2 deaths in the magnesium sulfate group [5.9%], p=0.96). However, the time to an adequate clinical response, the duration of ventilation and the number of neonates requiring inotropic drugs were all statistically significantly improved in the sildenafil group.
- A multicentre, open-label dose escalation study of intravenous sildenafil in 36 term and near-term neonates with PPHN was conducted in 6 centres in the US, France and the UK where nitric oxide was available ([Steinhorn et al. 2009](#)). For all 36 neonates (including 29 also receiving nitric oxide), the oxygenation index improved from a mean of 28 before sildenafil

treatment to a mean of 11 after 24 hours of sildenafil treatment ($p < 0.0001$). One neonate died and 1 required ECMO. For the 7 neonates not receiving inhaled nitric oxide, the oxygenation index improved from a mean of 25 before sildenafil treatment to a mean of 15 after 4 hours ($p = 0.0088$).

- A retrospective study of oral sildenafil and inhaled iloprost use in 47 neonates with PPHN in a single centre where inhaled nitric oxide and ECMO was not used has been published ([Kahveci et al. 2014](#)). The dose of sildenafil was 0.5 mg/kg (doubled to a maximum of 2 mg/kg) via an orogastric tube every 6 hours. In the sildenafil group, 4/27 neonates died compared with 3/20 in the iloprost group. The authors present a statistical analysis comparing the sildenafil and iloprost groups suggesting that iloprost was more effective than sildenafil in terms of inotropic agent use, magnesium sulfate use, mean time to an adequate response and mean duration of mechanical ventilation. However, this was an observational study and there are inherent limitations with the study and therefore the interpretation of the results.
- The systematic review ([Perez and Laughon 2015](#)) included a single-centre, placebo-controlled RCT of oral sildenafil use in 20 premature neonates at risk of BPD ([Konig et al. 2014](#)). Neonates receiving nitric oxide were excluded. Sildenafil, at a dose of 1 mg/kg every 8 hours via an orogastric tube for 4 weeks, did not improve any short-term respiratory outcomes, and did not reduce the length of invasive (median 29 days versus 9 days) or non-invasive (median 67 days versus 59 days) ventilation compared with placebo. There were 3 deaths in the sildenafil group and 1 death in the placebo group. More neonates in the sildenafil group required postnatal steroid treatment but this was not statistically significant ($p = 0.091$). No controlled trials evaluating the use of sildenafil in premature neonates with BPD-associated pulmonary hypertension were found.
- In a retrospective study of oral sildenafil use in 23 premature neonates with BPD-associated pulmonary hypertension, oral sildenafil resulted in echocardiographic improvement in 15/21 neonates (71%), but there was clinical improvement in only 8/23 neonates (35%), mostly in the first 48 hours ([Trottier-Boucher et al. 2015](#)). Sildenafil was started at a median chronological age of 106 days at an initial dose of 1 mg/kg/day (median dose 4.4 mg/kg/day) for a median of 71 days. Most neonates (21/23) also received inhaled nitric oxide.
- In a further retrospective investigation of 19 premature neonates with BPD-associated pulmonary hypertension, pulmonary hypertension resolved in 10/14 neonates (71%) treated with oral sildenafil and 2/5 neonates (40%) not treated with sildenafil ([Wardle et al. 2015](#)). Two babies (14%) treated with sildenafil died at a median of 845 days post diagnosis, and 2 babies (40%) not treated with sildenafil died at a median of 388 days post diagnosis. Sildenafil was given at a dose of 0.5 mg/kg 4 times daily, starting at a median chronological age of 69 days and continuing for a median of 78 days.

- The [Revatio 10 mg/ml powder for oral suspension](#) summary of product characteristics states that the safety and efficacy of sildenafil in children below 1 year of age has not been established. In a long-term paediatric extension study of children aged 1–17 years with primary pulmonary hypertension or pulmonary arterial hypertension secondary to congenital heart disease ([STARTS-2](#)), an increase in deaths was observed in children given doses higher than the recommended dose, and the summary of product characteristics recommends that doses higher than the recommended doses should not be used in children with pulmonary hypertension.
- Data on adverse events from studies of sildenafil in neonates with pulmonary hypertension are limited. The Cochrane review ([Shah and Ohlsson 2011](#)) of sildenafil use in a total of 77 neonates with PPHN states that no clinically important adverse effects were identified. A review of the safety of sildenafil in infants was published in 2014 ([Samiee-Zafarghandy et al. 2014](#)). This included pharmacokinetic studies of sildenafil in neonates and infants, where higher volumes of distribution, longer serum half-lives and intra- and interpatient variability in plasma concentrations of sildenafil were seen. In the open-label dose escalation study of intravenous sildenafil in 36 term and near-term neonates with PPHN by [Steinhorn et al. 2009](#), 6 treatment-related adverse events were reported (1 patent ductus arteriosus and 5 reports of hypotension or blood pressure lability). In the placebo-controlled RCT of oral sildenafil use in 20 premature neonates with evolving BPD by [Konig et al. 2014](#), 1 neonate in the sildenafil group developed hypotension severe enough to require withdrawal from the study. In the retrospective study by [Trottier-Boucher et al. 2015](#), of 23 premature neonates with BPD-associated pulmonary hypertension who were treated with oral sildenafil, the main adverse event seen was transient hypotension in 10 neonates.
- The quality of the evidence for sildenafil use in neonates with pulmonary hypertension is limited. The controlled RCTs in neonates with PPHN are mainly single-centre, short-term trials, which enrolled small numbers of patients in resource-limited settings where inhaled nitric oxide was not available. They provide no information on long-term efficacy or safety and may not be applicable to UK practice, where standard treatments such as inhaled nitric oxide are routinely available. The other evidence presented in this evidence summary also has limitations being either from small, short-term controlled trials, an open-label study with no control group or small, retrospective studies with inherent risks of bias and confounding.

[Full text of evidence review.](#)

Context and estimated impact for the NHS

[Nitric oxide](#) is considered the mainstay of treatment for pulmonary hypertension in neonates. It is licensed for use in newborn infants of at least 34 weeks' gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for ECMO. Other treatments that can be used for pulmonary hypertension in neonates include [epoprostenol](#) (which is licensed for use in adults but not children with pulmonary hypertension), [sildenafil](#) (which is licensed for children aged 1 and over with pulmonary arterial hypertension, but not children under 1 year), [magnesium sulfate](#) (which is not licensed for use in adults or children with pulmonary hypertension), [milrinone](#) (which is not licensed for use in adults or children with pulmonary hypertension) and [bosentan](#) (which is licensed for children aged 1 year and over with pulmonary arterial hypertension; the summary of product characteristics states that in neonates with PPHN the benefit of bosentan has not been shown in the standard-of-care treatment and no recommendation on a posology can be made).

The use of sildenafil for pulmonary hypertension in neonates varies across centres in the UK. A survey of sildenafil use for the treatment of PPHN in tertiary neonatal intensive care units in England and Wales was carried out in December 2013 and January 2014 ([Murphy et al. 2014](#)). Sildenafil was used frequently (in more than 5 neonates per year) in 12% of units, infrequently (in between 1 and 5 neonates per year) in 23% of units and rarely (in less than 1 neonate per year) in 51% of units.

The cost of sildenafil as [Revatio 10 mg/ml powder for oral suspension](#) is £186.75 for 112 ml. Revatio tablets cost £4.96 per 20 mg tablet and generic sildenafil tablets cost £0.24 per 25 mg tablet ([MIMS](#) and [Drug Tariff](#) February 2016, all costs excluding VAT). The costs of some of the drugs used for pulmonary hypertension in neonates are given in the full text of this evidence summary.

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents or carers of neonates with pulmonary hypertension who are being treated with sildenafil.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Pulmonary hypertension in neonates (term and premature) represents a heterogeneous group of diagnoses associated with a 10% to 20% mortality rate ([Perez and Laughon 2015](#)). There are several causes of pulmonary hypertension in neonates including congenital heart disease, congenital diaphragmatic hernia and sepsis. Persistent pulmonary hypertension of the newborn (PPHN) is a specific type of pulmonary hypertension in neonates ([Shah and Ohlsson 2011](#)). It occurs when the high pulmonary vascular resistance characteristic of fetal circulation fails to decrease at birth, resulting in right-to-left shunting of blood through fetal channels, diminished pulmonary blood flow, and profound hypoxaemia. PPHN can be a primary condition or can be secondary to a variety of disorders causing hypoxic respiratory failure, including meconium aspiration syndrome, congenital infection and, in premature neonates, bronchopulmonary dysplasia (BPD).

The management of pulmonary hypertension in neonates includes maintaining normal temperature, biochemistry and fluid balance, and ventilation. The aim is to maintain adequate systemic blood pressure, decrease pulmonary vascular resistance, ensure oxygen release to tissues, and minimise ventilator- and oxygen-induced lung injury. Continuous monitoring of oxygenation, blood pressure, and perfusion is critical.

In term or near-term neonates with pulmonary hypertension, inhaled nitric oxide (a pulmonary vasodilator), is considered the mainstay of treatment. The role of inhaled nitric oxide in premature

neonates is less clear ([Shah and Ohlsson 2011](#)). [Nitric oxide](#) is licensed for use in newborn infants of at least 34 weeks' gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation (ECMO).

Other treatments that can be used in neonates with pulmonary hypertension include [epoprostenol](#) (which is licensed for use in adults but not children with pulmonary hypertension), [sildenafil](#) (which is licensed for children aged 1 year and over with pulmonary arterial hypertension, but not children under 1 year), [magnesium sulfate](#) (which is not licensed for use in adults or children with pulmonary hypertension), [milrinone](#) (which is not licensed for use in adults or children with pulmonary hypertension) and [bosentan](#) (which is licensed for children aged 1 year and over with pulmonary arterial hypertension; the summary of product characteristics states that in neonates with PPHN the benefit of bosentan has not been shown in the standard-of-care treatment and no recommendation on a posology can be made). See the [British national formulary for children](#) for more details.

Product overview

Drug action

Sildenafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cGMP. PDE5 is present in pulmonary vasculature. Sildenafil therefore increases cGMP within pulmonary vascular smooth muscle cells, resulting in relaxation. In people with pulmonary arterial hypertension this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation ([Revatio 10 mg/ml powder for oral suspension summary of product characteristics](#)).

Regulatory status

Sildenafil, as [Revatio 10 mg/ml powder for oral suspension](#) and [Revatio 20 mg tablets](#), is licensed for treating children aged 1 year and over with pulmonary arterial hypertension. These products are not licensed for use in children aged less than 1 year; therefore the use of sildenafil for pulmonary hypertension in neonates is an off-label use. Sildenafil is also available as [Revatio solution for injection](#), which is licensed for treating adults with pulmonary arterial hypertension, and as generic 25 mg, 50 mg and 100 mg tablets, which are licensed for treating erectile dysfunction.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using sildenafil outside its authorised indications.

The summary of product characteristics for [Revatio](#) states that its safety and efficacy in children below 1 year of age has not been established. The licence for use in children aged 1 year and over was based on a placebo-controlled [randomised controlled trial \(RCT\)](#) in 234 children aged 1 to 17 years with primary pulmonary hypertension or pulmonary arterial hypertension secondary to congenital heart disease ([STARTS-1](#)).

There is a [paediatric investigation plan for Revatio](#) in the treatment of pulmonary arterial hypertension. This covers neonates from birth to less than 1 month of age with PPHN and children from 1 month to less than 18 years of age with pulmonary arterial hypertension. It includes the [STARTS-1](#) and [STARTS-2](#) RCTs of oral sildenafil in children aged 1 to 17 years with primary pulmonary hypertension or pulmonary arterial hypertension secondary to congenital heart disease plus a 7-day open-label, multicentre pharmacokinetic study of intravenous sildenafil in neonates with PPHN ([Steinhorn et al. 2009](#)).

The paediatric investigation plan also includes a multicentre, placebo-controlled RCT which is investigating the efficacy and safety of intravenous sildenafil plus inhaled nitric oxide for the treatment of neonates with PPHN or hypoxic respiratory failure at risk for PPHN. This RCT is currently ongoing in North America and Europe sponsored by Pfizer ([NCT01720524](#)). It is enrolling neonates aged 4 days or less with a gestational age of at least 34 weeks who have an oxygenation index of more than 15 and less than 60 and are receiving concurrent treatment with inhaled nitric oxide and at least 50% oxygen. Intravenous sildenafil is being given at a loading dose of 0.1 mg/kg over 30 minutes followed by maintenance dose of 0.03 mg/kg/hour for a minimum of 48 hours and maximum of 14 days. The trial started in August 2013 and is due to complete fully in December 2019, with an estimated primary completion date of October 2017.

Cost

[Revatio 10 mg/ml powder for oral suspension](#) is £186.75 for 112 ml. Revatio tablets cost £4.96 per 20 mg tablet and generic sildenafil tablets cost £0.24 per 25 mg tablet ([MIMS](#) and [Drug Tariff](#) February 2016; all costs excluding VAT).

Evidence review

This evidence summary is based on a Cochrane review and a further systematic review of several small RCTs of sildenafil use in neonates with pulmonary hypertension. The largest [observational studies](#) of sildenafil use in this condition are also included. The majority of the evidence is for oral sildenafil use in term or near-term neonates with PPHN. There is also a small amount of evidence for oral sildenafil use in premature neonates with BPD.

Clinical effectiveness

PPHN: Cochrane review of RCTs ([Shah and Ohlsson 2011](#))

The Cochrane review ([Shah and Ohlsson 2011](#)) included 3 RCTs ([Baquero et al. 2006](#), [Herrera Torres 2006](#) and [Vargas-Origel et al. 2010](#)) of sildenafil use in neonates with PPHN.

- [Baquero et al. 2006](#) was a single-centre RCT in a Columbian neonatal intensive care unit where inhaled nitric oxide, high-frequency ventilation and ECMO were not available. It included 13 term and near-term neonates with PPHN and an oxygenation index of at least 40 despite mechanical ventilation who received either oral sildenafil (n=7) or placebo (n=6) via an orogastric tube. The first dose of sildenafil was 1 mg/kg (0.5 ml/kg), with subsequent doses every 6 hours up to a maximum of 8 doses or until the oxygenation index improved to less than 20. The dose of sildenafil could be doubled to 2 mg/kg (1 ml/kg) if the oxygenation index did not improve and blood pressure remained stable.
- [Herrera Torres et al. 2006](#) was a single-centre RCT in a Mexican unit where inhaled nitric oxide was not available. It included 24 term neonates with PPHN and an oxygenation index of more than 25 who received either oral sildenafil (n=13) or placebo (n=11) via an orogastric tube. Sildenafil was given at a dose of 2 mg/kg every 6 hours for 72 hours. No criteria for discontinuing treatment were given.
- [Vargas-Origel et al. 2010](#) was also a single-centre, placebo-controlled RCT in Mexico, which included 51 term neonates with PPHN and an oxygenation index of more than 20. At the start of the trial inhaled nitric oxide was not available, but became available after 40 neonates had been randomised (n=20 in the sildenafil group and n=20 in the placebo group). The remaining 11 neonates received sildenafil plus inhaled nitric oxide, as it was considered unethical to use placebo once nitric oxide was available. The dose of sildenafil was 3 mg/kg every 6 hours via orogastric tube until the oxygenation index was less than 10.

The primary outcomes of the Cochrane review were neonatal mortality (all-cause mortality within the first 28 days of life) and haemodynamic parameters including pulmonary arterial pressure,

oxygenation (partial pressure of oxygen in blood [PaO₂]) or fraction of inspired oxygen [FiO₂] requirement, cardiac output and mean arterial blood pressure. Weighted treatment effects were calculated, which estimated typical relative risk (RR), typical risk difference (RD), number needed to treat (NNT) and number needed to harm (NNH) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes.

There was a statistically significant reduction in the mortality rate with sildenafil compared with placebo, with 3 deaths in the sildenafil group (n=40) and 16 deaths in the placebo group (n=37). The typical RR was 0.20, 95% confidence interval (CI) 0.07 to 0.57; typical RD -0.38, 95% CI -0.60 to -0.16; and NNT 3, 95% CI 2 to 6 (total 3 RCTs, n=77).

Physiological parameters of oxygenation suggested a steady improvement after the first dose of sildenafil. The mean oxygenation index after 24 hours of treatment was between 11 and 25 in the sildenafil group (n=39), and between 36 and 52 in the placebo group (n=30). After 24 hours of treatment, the mean PaO₂ in the sildenafil group (n=32) was 70 to 85 mmHg and 56 to 62 mmHg in the placebo group (n=25).

PPHN: systematic review of controlled trials (Perez and Laughon 2015)

For sildenafil use in term or near-term neonates with PPHN, the systematic review (Perez and Laughon 2015) included the same 3 RCTs as the Cochrane review plus Soliz et al. 2009. This RCT was excluded from the Cochrane review because it is only available as an abstract and the Cochrane authors felt there was inadequate information to distinguish it as a separate study.

- Soliz et al. 2009 was a multicentre RCT in 3 centres in Miami, Mexico and El Salvador where inhaled nitric oxide was not available. It included 49 term neonates with PPHN and an oxygenation index of more than 25 who received either oral sildenafil 2 mg/kg every 6 hours (n=29) or placebo (n=20) via an orogastric tube before 72 hours of age. No criteria for discontinuing treatment were given.

No controlled trials comparing sildenafil with inhaled nitric oxide for neonates with PPHN in settings where inhaled nitric oxide was routinely available were found.

The systematic review reported similar mortality rates to the Cochrane review from the 3 fully published RCTs (Baquero et al. 2006, Herrera Torres 2006 and Vargas-Origel et al. 2010). There were 3 deaths in the sildenafil group (5.9%; n=51, because the 11 neonates receiving sildenafil plus inhaled nitric oxide were included) and 16 deaths in the placebo group (44%; n=37). The number of deaths was not reported in the fourth trial (Soliz et al. 2009). The authors of the systematic review report that there was a statistically significant improvement in oxygenation index for all 4 RCTs,

with an improvement in nearly all studies by 6 to 8 hours after the initial sildenafil dose and minimal or no improvement after placebo. In 3 trials, the duration of mechanical ventilation was reported; this was shorter with sildenafil compared with placebo in 2 RCTs ([Herrera Torres et al. 2006](#) and [Soliz et al. 2009](#)) but no different in 1 RCT ([Vargas-Origel et al. 2010](#)).

PPHN: other evidence

Oral sildenafil was compared with intravenous magnesium sulfate in an RCT by [Uslu et al. 2011](#) in term and near-term neonates.

- [Uslu et al. 2011](#) was a single-centre RCT conducted in a regional neonatal intensive care unit in Turkey without facilities for inhaled nitric oxide, high-frequency ventilation or ECMO. It included term and near-term neonates with PPHN and an oxygenation index of at least 30 (and pulmonary artery pressure of at least 40 mmHg) on mechanical ventilation who were randomised to oral sildenafil (n=36) or intravenous magnesium sulfate (n=36). The dose of sildenafil was 0.5 mg/kg via an orogastric tube every 6 hours, which could be doubled to a maximum of 2 mg/kg if the oxygenation index did not improve. Magnesium sulfate was given as a loading dose of 200 mg/kg intravenously over 30 minutes, followed by a maintenance dose of 20 mg/kg/hour. If the oxygenation index did not improve the infusion rate was increased slowly to a maximum of 100 mg/kg/hour. Both treatments were gradually tapered and stopped over 1 day when the oxygenation index was less than 15 and the pulmonary artery pressure was less than 20.

A total of 31 neonates in the sildenafil group and 34 neonates in the magnesium sulfate group completed the trial and had available results. There was no difference in the mortality rate between the 2 groups (1 death in the sildenafil group [3.2%] and 2 deaths in the magnesium sulfate group [5.9%], p=0.96). However, the time to an adequate clinical response, the duration of ventilation and the number of neonates requiring inotropic drugs were all statistically significantly improved in the sildenafil group.

- Time to adequate clinical response (pulmonary artery pressure of less than 20 and oxygenation index of less than 15): median 2 (1 to 11) days with sildenafil compared with median 3 (1 to 12) days with magnesium sulfate; p=0.002.
- Duration of ventilation: median 4 (3 to 11) days with sildenafil compared with median 6 (3 to 13) days with magnesium sulfate; p=0.001.
- Number of neonates requiring inotropic drugs: 14 (45%) with sildenafil compared with 28 (82%) with magnesium sulfate; p=0.002.

An open-label dose escalation study of intravenous sildenafil in term and near-term neonates with PPHN was conducted by [Steinhorn et al. 2009](#). The objective of this pilot trial was to determine the pharmacokinetics of intravenous sildenafil and assess its tolerability and safety.

- [Steinhorn et al. 2009](#) was a multicentre, open-label trial conducted in 6 centres in the United States, France and the UK. It included 36 neonates who were less than 3 days old and more than 34 weeks' gestational age with PPHN and an oxygenation index of at least 15. Inhaled nitric oxide was allowed at any time before or during the study, and 29 neonates were already receiving this when they started sildenafil. Open-label sildenafil was given by continuous intravenous infusion for at least 48 hours and up to 7 days at 8 different loading and maintenance dose regimens.

For all 36 neonates, the oxygenation index improved from a mean of 28 before sildenafil treatment to a mean of 11 after 24 hours of sildenafil treatment (based on observations of 34 neonates at 24 hours, $p < 0.0001$). One neonate died and 1 required ECMO. For the 7 neonates not receiving inhaled nitric oxide when sildenafil was started, the oxygenation index improved from a mean of 25 before sildenafil treatment to a mean of 15 after 4 hours ($p = 0.0088$).

An observational study of oral sildenafil and inhaled iloprost has been carried out by [Kahveci et al. 2014](#).

- [Kahveci et al. 2014](#) was a retrospective study carried out in a Turkish neonatal intensive care unit where inhaled nitric oxide and ECMO were not used because of costs and lack of experienced staff. Treatment with oral sildenafil ($n = 27$) or inhaled iloprost ($n = 20$) was given to full term neonates (at least 37 weeks' gestational age) with PPHN and an oxygenation index of at least 25. When iloprost was available, iloprost only was given; when there was no iloprost, oral sildenafil was given. The dose of sildenafil was 0.5 mg/kg via an orogastric tube every 6 hours, which could be doubled to a maximum of 2 mg/kg if the oxygenation index did not improve. The sildenafil dose was tapered by 50% after reaching an oxygenation index of 15 and systolic pulmonary artery pressure less than 30 mmHg, and then stopped. Inhaled iloprost was given at doses of 1 to 2.5 micrograms/kg with an interval of 2 to 4 hours between doses. Stopping iloprost was considered when the systolic pulmonary artery pressure decreased below half of the systolic blood pressure.

There were statistically significant reductions from day 0 to day 8 in mean airway pressure, systolic pulmonary artery pressure and oxygenation index in neonates in both the sildenafil and iloprost groups (all $p \leq 0.01$). Intravenous magnesium sulfate was given as a second vasodilator to 8/27 neonates who did not respond to sildenafil, and to 3/20 who did not respond to iloprost. Extra inotropic agents were used in 7/27 neonates in the sildenafil group and none in the iloprost group.

The mean duration of ventilation was 10 days with sildenafil and 6 days with iloprost. Sildenafil was continued for a mean duration of 8 days and iloprost for 5 days. In the sildenafil group, 4/27 neonates died compared with 3/20 in the iloprost group. The authors present a statistical analysis comparing the sildenafil and iloprost groups suggesting that iloprost was more effective than sildenafil in terms of inotropic agent use, magnesium sulfate use, mean time to an adequate response and mean duration of mechanical ventilation. However, this was an observational study, not an RCT, and there are inherent limitations with the study and therefore the interpretation of the results.

Premature neonates with BPD

The systematic review ([Perez and Laughon 2015](#)) included 1 RCT in premature neonates at risk of BPD ([Konig et al. 2014](#)). No controlled trials evaluating the use of sildenafil in premature neonates with BPD-associated pulmonary hypertension were found.

- [Konig et al. 2014](#) was a single-centre RCT in Australia, which included 20 extremely premature neonates (less than 28 weeks' gestational age) who were receiving mechanical ventilation on postnatal day 7 for evolving BPD. Neonates were randomised to oral sildenafil 1 mg/kg (n=10) or placebo (n=10) every 8 hours via an orogastric or nasogastric tube for 4 weeks. Exclusion criteria included congenital heart or lung defects or neonates receiving inhaled nitric oxide.

In this trial, sildenafil treatment did not improve any short-term respiratory outcomes in extremely preterm neonates. Sildenafil did not reduce the length of invasive (median 29 days versus 9 days, p=0.054) or non-invasive (median 67 days versus 59 days, p=0.460) ventilation compared with placebo. There were 3 deaths in the sildenafil group and 1 death in the placebo group. More neonates in the sildenafil group required postnatal steroid treatment but this was not statistically significant (p=0.091).

The most recent observational studies of oral sildenafil use in premature neonates with BPD-associated pulmonary hypertension are [Trottier-Boucher et al. 2015](#) and [Wardle et al 2015](#).

- [Trottier-Boucher et al. 2015](#) conducted a retrospective case review of 23 premature neonates (median gestational age 26 weeks) with BPD-associated pulmonary hypertension who were treated with oral sildenafil in a neonatal intensive care unit in Canada. Sildenafil was started at a median chronological age of 106 days at an initial dose of 1 mg/kg/day (median dose 4.4 mg/kg/day) for a median of 71 days. Neonates were on mechanical ventilation for a median of 54 days and oxygen for a median of 228 days (in hospital and at home). Most neonates (21/23) also received inhaled nitric oxide.

The primary outcomes of the study were clinical improvement (defined as a 20% decrease in respiratory severity scores or an absolute 20% decrease in FiO₂) and echocardiographic improvement. Treatment with sildenafil resulted in echocardiographic improvement in 15/21 neonates (71%), but there was clinical improvement in only 8/23 neonates (35%); mostly in the first 48 hours.

- [Wardle et al. 2015](#) conducted a retrospective investigation of 19 premature neonates (median gestational age 26 weeks) with BPD-associated pulmonary hypertension who were treated in a neonatal intensive care unit in the UK between 2008 and 2014. In 14 neonates, oral sildenafil 0.5 mg/kg 4 times daily was started at a median chronological age of 69 days for a median of 78 days. Five neonates were managed without sildenafil treatment, with the decision to treat based on individual clinician preference. Neonates received concomitant therapy including oxygen. One neonate receiving sildenafil also received epoprostenol, and 1 neonate receiving sildenafil also received nitric oxide.

The study results have only been published in a letter and details are limited. However, the authors reported that pulmonary hypertension resolved in 10 neonates (71%) treated with sildenafil and 2 neonates (40%) not treated with sildenafil. Two babies (14%) who were treated with sildenafil died at a median of 845 days post diagnosis, and 2 babies (40%) who were not treated with sildenafil died at a median of 388 days post diagnosis.

Safety and tolerability

Sildenafil is contraindicated in combination with nitrates in any form due to the hypotensive effects of nitrates, and in combination with guanylate cyclase stimulators, such as riociguat, because it may lead to symptomatic hypotension ([Revatio 10 mg/ml powder for oral suspension](#) summary of product characteristics). It is also contraindicated in combination with the most potent of the CYP3A4 inhibitors (such as ketoconazole, itraconazole, and ritonavir). The summary of product characteristics states that a downward dose adjustment should be considered when sildenafil is given to people already receiving CYP3A4 inhibitors such as erythromycin or clarithromycin. The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated in severe hepatic impairment, recent history of stroke or myocardial infarction, and severe hypotension (blood pressure <90/50 mmHg) at initiation. It is also contraindicated in people with non-arteritic anterior ischaemic optic neuropathy.

The [Revatio 10 mg/ml powder for oral suspension](#) summary of product characteristics states that the safety and efficacy of sildenafil in children below 1 year of age has not been established. In a long-term paediatric extension study of children aged 1 to 17 years with primary pulmonary hypertension or pulmonary arterial hypertension secondary to congenital heart disease

([STARTS-2](#)), an increase in deaths was observed in children given sildenafil at doses higher than the recommended dose. Of the 234 children included in the original study ([STARTS-1](#)), 220 entered a long-term extension ([STARTS-2](#)). Survival estimates at 3 years in children weighing more than 20 kg were 94%, 93% and 85% in the low, medium and high dose groups respectively; for children weighing 20 kg or less the survival estimates were 94% and 93% in the medium and high dose groups respectively. The study's data monitoring committee decided to down titrate children to a lower dosage, based on an observed mortality imbalance with increasing sildenafil doses, and the summary of product characteristics recommends that doses higher than the recommended doses should not be used in children with pulmonary arterial hypertension.

The summary of product characteristics states that the most common adverse reactions with sildenafil in [STARTS-1](#) and [STARTS-2](#) were upper respiratory infection, headache, vomiting, bronchitis, pharyngitis, pyrexia, diarrhoea influenza and epistaxis. All of these were very common (affected more than 1 in 10 people), and most were mild to moderate in severity. The most common serious adverse events (which affected up to 1 in 10 people) were pneumonia, cardiac failure, pulmonary hypertension, upper respiratory tract infection, right ventricular failure, gastroenteritis, syncope, bronchitis, bronchopneumonia, pulmonary arterial hypertension, chest pain, dental caries, cardiogenic shock, gastroenteritis viral and urinary tract infection. However, many of these would be impossible to determine or measure in neonates.

Data on adverse events from studies of sildenafil in neonates with pulmonary hypertension are limited. The Cochrane review ([Shah and Ohlsson 2011](#)) which included 3 RCTs ([Baquero 2006](#), [Herrera Torres 2006](#) and [Vargas-Origel 2010](#)) of sildenafil use in a total of 77 neonates with PPHN states that no clinically important adverse effects were identified. The systematic review ([Perez and Laughon 2015](#)) which included the same 3 RCTs as the Cochrane review plus [Soliz et al. 2009](#) (abstract only) states that no adverse events were reported in the 3 full-text articles available for review. This review also included an RCT in 20 premature neonates at risk of BPD ([Konig et al. 2014](#)). In this trial, 1 neonate stopped sildenafil after experiencing recurrent hypotension; no other adverse events were reported.

A review of the safety of sildenafil in infants was published in 2014 ([Samiee-Zafarghandy et al. 2014](#)). This included pharmacokinetic studies of sildenafil in neonates and infants, in which a higher volume of distribution and longer serum half-life were seen compared with adults. High intra- and interpatient variability in plasma concentrations of sildenafil were also seen. The authors of this review identified about 40 case reports and prospective or retrospective studies where sildenafil was used in neonates or young infants with pulmonary hypertension of various aetiologies. Of these, only the open-label dose escalation study of intravenous sildenafil in 36 term and near-term neonates with PPHN by [Steinhorn et al. 2009](#) was designed to record adverse events. In this study,

6 treatment-related adverse events were reported in 5 neonates. One neonate developed a patent ductus arteriosus, and there were 5 reports related to hypotension or blood pressure lability.

In the single-centre RCT by [Uslu et al. 2011](#), which compared oral sildenafil with intravenous magnesium sulfate in 72 term and near-term neonates with PPHN, gastrointestinal bleeding developed in 3/36 neonates in the sildenafil group and 2/36 in the magnesium sulfate group. In the retrospective study of oral sildenafil and inhaled iloprost in 47 full term neonates with PPHN by [Kahveci et al. 2014](#), systemic hypotension developed in 9/27 neonates in the sildenafil group and 0/20 in the iloprost group. Abdominal distension developed in 8/27 neonates in the sildenafil group and 0/20 in the iloprost group. In both studies, all the neonates had normal auditory screening test and ophthalmological examinations at discharge.

In the single-centre RCT by [Konig et al. 2014](#), which included 20 premature neonates with evolving BPD randomised to oral sildenafil or placebo, 1 neonate in the sildenafil group developed hypotension severe enough to require withdrawal from the study. No unexpected pathology was seen on routine ophthalmology screening, although all neonates developed some degree of retinopathy of prematurity. In the retrospective study by [Trottier-Boucher et al. 2015](#) of 23 premature neonates with BPD-associated pulmonary hypertension who were treated with oral sildenafil, the main adverse event seen was transient hypotension in 10 neonates. The degree of retinopathy of prematurity did not differ before and during treatment. In the retrospective investigation by [Wardle et al. 2015](#), no significant adverse effects were recorded in the 14 premature neonates with BPD-associated pulmonary hypertension treated with oral sildenafil.

Evidence strengths and limitations

Most of the studies included in this evidence summary were completed in resource-limited settings where standard treatments for pulmonary hypertension in neonates such as inhaled nitric oxide were not available. This limits the applicability of the evidence to UK practice where such treatments are routinely available. Care is also needed in interpreting the results of these studies because the differences between resource-limited settings and resourceful settings extend beyond the availability of medications. The physiological effects of sildenafil, for example on oxygenation index, are likely to be the same in resource-limited and resourceful settings. However, other effects, such as effects on mortality, may be less easy to extrapolate because of confounding factors, including differences in baseline mortality rates.

The Cochrane review ([Shah and Ohlsson 2011](#)) included 3 RCTs of sildenafil use in neonates with PPHN. All 3 RCTs were short-term, single-centre trials which enrolled small numbers of patients (n=13, n=24 and n=51) and did not provide information on long-term effects. All 3 trials were

blinded, but random sequence generation and allocation concealment were unclear, increasing the risk of bias. All 3 trials were conducted in resource-limited settings where inhaled nitric oxide, high-frequency ventilation and ECMO were not available.

The dose of oral sildenafil given in the trials, duration of treatment and stopping criteria varied. In [Baquero et al. 2006](#), the dose was 1 mg/kg (which could be doubled to 2 mg/kg) every 6 hours until a maximum of 8 doses or the oxygenation index improved to less than 20. In [Herrera Torres et al. 2006](#), it was 2 mg/kg every 6 hours for 72 hours, and in [Vargas-Origel et al. 2010](#) it was 3 mg/kg every 6 hours until the oxygenation index was less than 10.

The Cochrane review concluded that sildenafil has a potential for improvement in physiological parameters in neonates with pulmonary hypertension. However, the safety and effectiveness of sildenafil for PPHN has not yet been established in a large RCT and its use should be restricted within the context of RCTs. The authors concluded that further multicentre studies with neurodevelopmental follow-up are needed in both resource limited and resourceful settings where stand alone and adjunctive treatment could be evaluated.

The systematic review by [Perez and Laughon 2015](#), which included the same 3 RCTs of sildenafil use in PPHN as the Cochrane review (plus [Soliz et al. 2009](#)) concluded that, in resource-limited settings, sildenafil may offer a less expensive and life-saving alternative for neonates with PPHN. However, there is no evidence to support sildenafil use for term neonates with PPHN in areas where inhaled nitric oxide or high-frequency ventilation are available.

This review also concluded that there is very little evidence to support the use of sildenafil for the prevention of BPD and it remains unclear if sildenafil leads to improved outcomes in premature neonates with BPD-associated pulmonary hypertension. The review included 1 small, single-centre RCT ([Konig et al. 2014](#)) in 20 premature neonates with evolving BPD. This RCT was blinded, but again random sequence generation and allocation concealment were unclear, increasing the risk of bias.

Because sildenafil is given orally, premature neonates who develop pulmonary hypertension secondary to lung disease are sometimes discharged on sildenafil and then slowly weaned off over time. However, the evidence to support use in these premature neonates is limited to small, retrospective studies, such as [Trottier-Boucher et al. 2015](#) and [Wardle et al. 2015](#), which have inherent risks of [bias](#) and [confounding](#).

The other evidence presented in this evidence summary also has limitations. The RCT by [Uslu et al. 2011](#) was a small, short-term, single-centre RCT comparing oral sildenafil with intravenous

magnesium sulfate in 72 neonates with PPHN in a resource limited setting. [Steinhorn et al. 2009](#) was a multicentre trial of sildenafil use in PPHN carried out in the United States, France and the UK where nitric oxide was available. However, it was an open-label dose escalation study of intravenous sildenafil in 36 neonates, with no control group. [Kahveci et al. 2014](#) was a small, retrospective study of oral sildenafil and inhaled iloprost carried out in a Turkish neonatal intensive care unit where inhaled nitric oxide was not used.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies of sildenafil for pulmonary hypertension in neonates were identified.

The cost of sildenafil as [Revatio 10 mg/ml powder for oral suspension](#) is £186.75 for 112 ml. Revatio tablets cost £4.96 per 20 mg tablet and generic sildenafil tablets cost £0.24 per 25 mg tablet ([MIMS](#) and [Drug Tariff](#) February 2016, all costs excluding VAT).

The table below gives costs for some of the drugs used for pulmonary hypertension in neonates. [Nitric oxide](#), which is considered the mainstay of treatment, is licensed for use in newborn infants of at least 34 weeks' gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for ECMO. Other treatments that can be used include [epoprostenol](#) (which is licensed for use in adults but not children with pulmonary hypertension), [sildenafil](#) (which is licensed for children aged 1 year and over with pulmonary arterial hypertension, but not children under 1 year), [magnesium sulfate](#) (which is not licensed for use in adults or children with pulmonary hypertension), [milrinone](#) (which is not licensed for use in adults or children with pulmonary hypertension) and [bosentan](#) (which is licensed for children aged 1 year and over with pulmonary arterial hypertension; the summary of product characteristics states that in neonates with PPHN the benefit of bosentan has not been shown in the standard-of-care treatment and no recommendation on a posology can be made).

Table 1 Costs of drugs used for pulmonary hypertension in neonates

	Example dose in neonate ^a	Estimated cost excluding VAT
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Nitric oxide (inhaled)	In newborns >34 weeks' gestation, the maximum recommended dose of nitric oxide is 20 ppm and this dose should not be exceeded. Starting as soon as possible, and in the first 4 to 24 hours of therapy, the dosage must be reduced gradually to 5 ppm or less, titrating it to the needs of the individual patient. Treatment can be continued until the oxygen desaturation is resolved and the patient is ready for gradual withdrawal. The required duration varies but should be as brief as possible, and is typically less than 4 days. ^b	£29 to £40 per hour. ^c
Epoprostenol (intravenous)	Initially 2 nanograms/kg/minute adjusted according to response; usual maximum dose 20 nanograms/kg/minute (rarely up to 40 nanograms/kg/minute) by continuous intravenous infusion. ^d	1×500 microgram vial=£22.22 to £24.44. ^e
Magnesium sulfate (intravenous)	Initially 200 mg/kg (0.8 mmol/kg Mg ²⁺) magnesium sulfate heptahydrate over 20–30 minutes; if response occurs, then 20–75 mg/kg/hour (0.08–0.3 mmol/kg/hour Mg ²⁺) by continuous intravenous infusion for up to 5 days. ^d	1×2 ml vial of magnesium sulfate 50% (magnesium 2 mmol/ml)=£1.19. ^f
Milrinone (intravenous)	0.25 to 0.75 micrograms/kg/min by continuous intravenous infusion for up to 35 hours. ^g	1×10 mg/10 ml vial=£19.91. ^e
Bosentan (oral)	2 mg/kg twice daily. ^h	1×62.5 mg bosentan tablet (Tracleer)=£26.97. ^e
Sildenafil (oral)	Initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; max. 30 mg daily; start with lower dose and frequency especially if used with other vasodilators. ^d	1×112 ml of sildenafil 10 mg/ml powder for oral suspension. (Revatio)=£186.75. ^e 1×20 mg sildenafil tablet (Revatio)=£4.96. ^e 1×25 mg generic sildenafil tablets=£0.24. ^f

Sildenafil (intravenous)	A trial (NCT01720524) is ongoing using intravenous sildenafil at a loading dose of 0.1 mg/kg over 30 minutes followed by a maintenance dose of 0.03 mg/kg/hour for a minimum of 48 hours and maximum of 14 days. ⁱ	1×20 ml vial of sildenafil 800 microgram/ml solution for injection (Revatio)=£45.28. ^e Each 20 ml vial contains 12.5 ml of solution (10 mg of sildenafil).
<p>^a See text above for licensed indications.</p> <p>^b Dose taken from summary of product characteristics for nitric oxide.</p> <p>^c These are example costs provided by specialists involved in the production of this evidence summary. Local costs may vary.</p> <p>^d Doses taken from BNF for Children. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence. See text above for licence status of these medicines.</p> <p>^e Costs taken from MIMS, February 2016. Costs are excluding VAT.</p> <p>^f Costs taken from the Drug Tariff, February 2016. Costs are excluding VAT.</p> <p>^g Dose taken from summary of product characteristics for milrinone which is licensed in children for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy and for the short-term treatment (up to 35 hours) of acute heart failure, including low output states following cardiac surgery.</p> <p>^h Dose taken from summary of product characteristics for bosentan which is licensed for use in children aged 1 year and older with pulmonary arterial hypertension; the summary of product characteristics states that in neonates with PPHN the benefit of bosentan has not been shown in the standard-of-care treatment and no recommendation on a posology can be made.</p> <p>ⁱ Sildenafil solution for injection (Revatio) is licensed for the treatment of adults with pulmonary arterial hypertension. The summary of product characteristics states it is not recommended for use in children due to insufficient data on safety and efficacy.</p>		

Current drug usage

The use of sildenafil for pulmonary hypertension in neonates varies across centres in the UK. A survey of sildenafil use for the treatment of PPHN in tertiary neonatal intensive care units in England and Wales was carried out in December 2013 and January 2014 ([Murphy et al. 2014](#)).

Responses were received from 43 of 48 units contacted. Sildenafil was used frequently (in more than 5 neonates per year) in 12% of units, infrequently (in between 1 and 5 neonates per year) in 23% of units and rarely (in less than 1 neonate per year) in 51% of units. No units had fixed indications for starting sildenafil. Amongst the 6 units with a guideline, the initial dose of sildenafil varied between 250 to 300 micrograms/kg every 4 to 12 hours. No guidelines stipulated weaning or stopping practice.

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents or carers of neonates with pulmonary hypertension who are being treated with sildenafil.

Relevance to NICE guidance programmes

This use of sildenafil is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme. There is currently no NICE guidance on managing pulmonary hypertension in neonates.

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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ISBN: 978-1-4731-1783-9