South African National Essential Medicine List
Tertiary and Quaternary Medication Review Process
Component: Neonates

TITLE: Phosphodiesterase-5 (PDE5) inhibitors for persistent pulmonary hypertension in neonates (PPHN)

Date: June 2024

Executive Summary

Medicine (INN): PDE5-inhibitors (sildenafil/tadalafil/vardenafil)
Medicine (ATC): G04BE03/G04BE08/G04BE09
Indication (ICD10 code): P29.3
Patient population: Infants with persistent pulmonary hypertension of the newborn (PPHN).
Prevalence of condition: A retrospective study in Limpopo, South Africa found an incidence of 0.76%[1], and a retrospective Cape Town study reported an incidence of 1.1%.[2]
Level of Care: Tertiary
Prescriber Level: Specialist
Motivator/reviewer name(s): Tertiary ERC

Key findings

- We conducted a review of literature to explore the efficacy and safety of PDE5-inhibitor versus placebo in the management of persistent pulmonary hypertension of the newborn (PPHN) where nitric oxide is not available.
- Placebo was the selected comparator as this review was conducted to determine management of PPHN where nitric oxide and ventilation are not available.
- One study (a systematic review and meta-analysis) was selected for data extraction. This review explored sildenafil for PPHN and included 5 randomised / quasi-randomised trials (n = 166).
- **Comparison: Sildenafil vs Placebo:**
  - All-cause mortality
    A statistically significant reduction in mortality rate was observed for patients in the sildenafil group compared with patients in the placebo group (RR 0.20, 95% CI 0.07 to 0.56; NNTB 3, 95% CI 2 to 6; three studies, 77 participants; I^2 = 39% - GRADE: Low (downgraded for imprecision and unreported methodological features).
  - Oxygenation: PaO2 in mmHg
    Significant increases in PaO_2 were found in the sildenafil groups at baseline, after first dose, after 6-7 hours of treatment, after 24 to 25 hours, and after 72 hours or end of therapy.
    The mean difference (MD) in PaO_2 after 24 to 25 hours was 15.31mmHg higher in patients receiving placebo (6.49 higher to 24.13 higher); GRADE: Low (downgraded for imprecision and unreported methodological features).
  - Change in oxygenation index (after 24 hours of therapy)
    A statistically significant reduction in oxygen index after administration of five doses of sildenafil alone (at 24 hours after administration) compared with placebo (MD -38.79, 95% CI -56.97 to -20.61; one study, 12 participants; heterogeneity estimates - not applicable – GRADE: Low (downgraded for imprecision and unreported methodological features).
- Based on the Single Exit Prices (SEP) of the lowest priced generic formulation available in South Africa, the cost per patient per day is R 25.41 for sildenafil, R71.50 for tadalafil, and R21.04 for vardenafil. Future contracted pricing will likely be more favourable.

TERTIARY HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The Tertiary and Quaternary Expert Review Committee recommends the use of a PDE5-inhibitor for persistent pulmonary hypertension in neonates (PPHN) in situations where nitric oxide is not available, but neonates with PPHN are being managed.

Rationale: In settings where nitric oxide is not available, a PDE5-inhibitor is a suitable alternative showing a mortality benefit as compared to placebo. Although most of the evidence evaluates sildenafil, the beneficial effects are expected to be observed across the class of PDE5-inhibitors.

Level of Evidence: II Meta-analysis including trials with small numbers, and some methodological quality issues

Review indicator: safety changes

NEMLC RECOMMENDATION:

NEMLC recommended that PDE5-inhibitors be an essential medicine for use for PPHN in situations where nitric oxide is not available, but where neonates with PPHN are being managed.

Monitoring and evaluation considerations:

Research priorities:

1. **Name of author(s)**
   - Prakash Jeena (Head of Clinical department of Paediatrics at Inkosi Albert Luthuli Central Hospital).
   - Jane Riddin (Essential Drugs Programme, National Department of Health).
   - Derusha Frank (CHAI).
   - Tertiary and Quaternary Expert Review Committee.

2. **Author affiliation and conflict of interest details**
   - Prakash Jeena has no interests to declare.
   - Jane Riddin has no interests to declare.
   - Derusha Frank has no interests to declare.
   - Tertiary and Quaternary Expert Review Committee had no specific interests to declare.

GRADE Table: Sildenafil compared to placebo

Summary of findings for the main comparison. Sildenafil compared with placebo for pulmonary hypertension in neonates

Sildenafil compared with placebo for pulmonary hypertension in neonates

Patient or population: pulmonary hypertension in neonates
Setting: neonatal intensive care unit
Intervention: sildenafil
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sildenafil				
PaO_2 in mmHg (absolute values) After 24-25 hours	Mean PaO_2 in mmHg (absolute values) After 24 to 25 hours = 0	MD 15.31 higher (6.49 higher to 24.13 higher)	-	57 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Evidence was downgraded due to unreported methodological features and imprecision (small sample size)
Change in oxygenation index After 24 hours of treatment	Mean change in oxygenation index After 24 hours = 0	MD 38.79 lower (56.97 lower to 20.61 lower)	-	12 (1 RCT)	⊕⊕⊖⊖ LOW[a,b]	Evidence was downgraded due to unreported methodological features and imprecision (small sample size)
All-cause mortality	Study population		RR 0.20 (0.07 to 0.56)	77 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Evidence was downgraded due to unreported methodological features and imprecision (small sample size)
	432 per 1000	77 per 1000 (22 to 238)				

***The risk in the intervention group** (and its 95% confidence interval) is based on assumed risk in the comparison group and **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3. Introduction/ Background

Persistent pulmonary hypertension of the newborn (PPHN) is a condition which is characterized by severe respiratory failure and hypoxaemia, usually affecting term or near-term newborns (although preterm neonates can also be affected). Although there have been advancements in treatment, it remains a potentially fatal condition, particularly in resource constrained settings. Mortality ranges from 4-33% in developed countries, and from 25-44% in developing countries.[3] South African studies have found mortality rates of 31% at Tygerberg Children's Hospital[2], 48% at Chris Hani Baragwanath Academic hospital[4] and 34.7% at Charlotte Maxeke Johannesburg Academic Hospital.[3]

Survival rates has been improved by use of high-frequency oscillatory ventilation, selective pulmonary vasodilators (e.g. inhaled nitric oxide and phosphodiesterase inhibitors, surfactant, and extracorporeal membrane oxygenation).

Nitric oxide is an expensive gas (pulmonary vasodilator) that requires administration via ventilation with a specialised machine at a certain dose to obtain efficacy without developing adverse effects. There are inadequate ventilator facilities for neonates in South Africa and therefore this mode of therapy is not routinely possible. PDE5-inhibitors thus offer a potential advantage in this indication as they are less costly, and more practical in terms of method of administration.

RESEARCH QUESTION: For patients with PPHN in settings where nitric oxide is unavailable, would the use of a PDE5-inhibitor be a safe and effective?

4. Purpose/Objective i.e. PICO question:

Population:	Neonatal period for PPHN where nitric oxide not available
Intervention:	PDE5-inhibitors
Comparators:	Placebo
Outcomes:	1. Mortality; 2. Haemodynamic parameters: ○ Mean pulmonary arterial pressure (mPAP); ○ Systolic pulmonary arterial pressure (sPAP); ○ mean aortic pressure (mAOP); ○ pulmonary artery and aortic ratio (PA/AO); 3. Mechanical ventilation in hours length; 4. Intensive care unit (ICU) stays in hours, 5. Hospital stays in hours; 6. Ability to wean off ventilator.
Study designs:	Systematic reviews and Meta-analyses

5. Methods:

a. Data sources: A search was run on 6 May 2024, using Pubmed and Cochrane Library.

b. Search strategy *See appendix 2 for full search strategy. The table below outlines the search findings.*

Pubmed	13 citations
Cochrane	4 citations
Overlap	1 citation
Excluded	12 citations
Total for consideration	**4 citations**

The search and screening of studies was undertaken by one reviewer (JR) and presented to the ERC for discussion and final selection. Four systematic reviews were identified for full text review. Of these four, one was excluded as it was only available in Spanish. The three remaining studies were He et.al. 2021, Kelly et. al. 2017 and Perez 2015. The included studies were mapped against each other, and quality assessment undertaken with AMSTAR II independently by two reviewers (JR and DF) . On analysis, only one systematic review was included (Kelly et.al. 2017) which was evaluated to be of high quality and included only RCTs. See excluded list and reasons below:

c. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
Sildenafil for pulmonary hypertension in neonates: An updated systematic review and meta-analysis. He Z, Zhu S, Zhou K, Jin Y, He L, Xu W, Lao C, Liu G, Han S.Pediatr Pulmonol. 2021 Aug;56(8):2399-2412.	Systematic Review and meta-analysis	AMSTAR: Critically low quality. Included observation studies.
Sildenafil in Term and Premature Infants: A Systematic Review. Perez KM, Laughon M.Clin Ther. 2015 Nov 1;37(11):2598-2607.e1.	Systematic Review	AMSTAR: Critically low quality. Included conference proceedings, and a study where patient diagnosis was unclear.
Use of sildenafil for pulmonary hypertension in neonates. Márquez-González H, Ríos DI, Jean Tron MG, Barajas-Nava LA.Bol Med Hosp Infant Mex. 2020;77(4):202-206.	Systematic Review	Article in Spanish

d. Evidence synthesis

Data was extracted by one reviewer (JR), checked by another reviewer (KM) and presented to the TQ ERC for final consensus.

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**	**Effect sizes**
Kelly et.al. 2017[5]	Meta-analysis and systematic review	5 randomised/ quasi-randomised trials (n = 166)	Infants with pulmonary hypertension in neonates	Placebo and active comparators (pulmonary vasodilators)	• All-cause mortality within first 28 days of life • Haemodynamic parameters (PAP, PaO2 or FiO2 requirement, Cardiac output, MPAP.	<u>All-cause mortality vs placebo:</u> Statistically significant ($p < 0.0001$) reduction in mortality rate for the sildenafil group compared with the placebo group (RR 0.20, 95% CI 0.07 to 0.56; NNTB 3, 95% CI 2 to 6; three studies, 77 participants; $I^2 = 39\%$ - GRADE low). <u>PaO2 in mmHg after 24-25 hours</u> Mean difference with sildenafil 15.31 higher (6.49 to 24.14 higher); 2 studies, 57 participants – GRADE low <u>Change in oxygenation index after 24 hours.</u> Mean difference with sildenafil 38.79 lower (56.97 to 20.61)

*NNTB: number needed to treat for additional beneficial outcome

e. Evidence quality:

AMSTAR II assessment was undertaken in duplicate by two reviewers (JR and DF) on the included SR (Kelly 2017) and deemed to be of high quality (see appendix 3).

The risk of bias (RoB) assessment from Kelly 2017 conducted on the selected studies was extracted directly. The RoB was generally considered to be unclear to low, however attrition bias was identified in 3 studies as being at high risk of bias. See Figure 1 below.

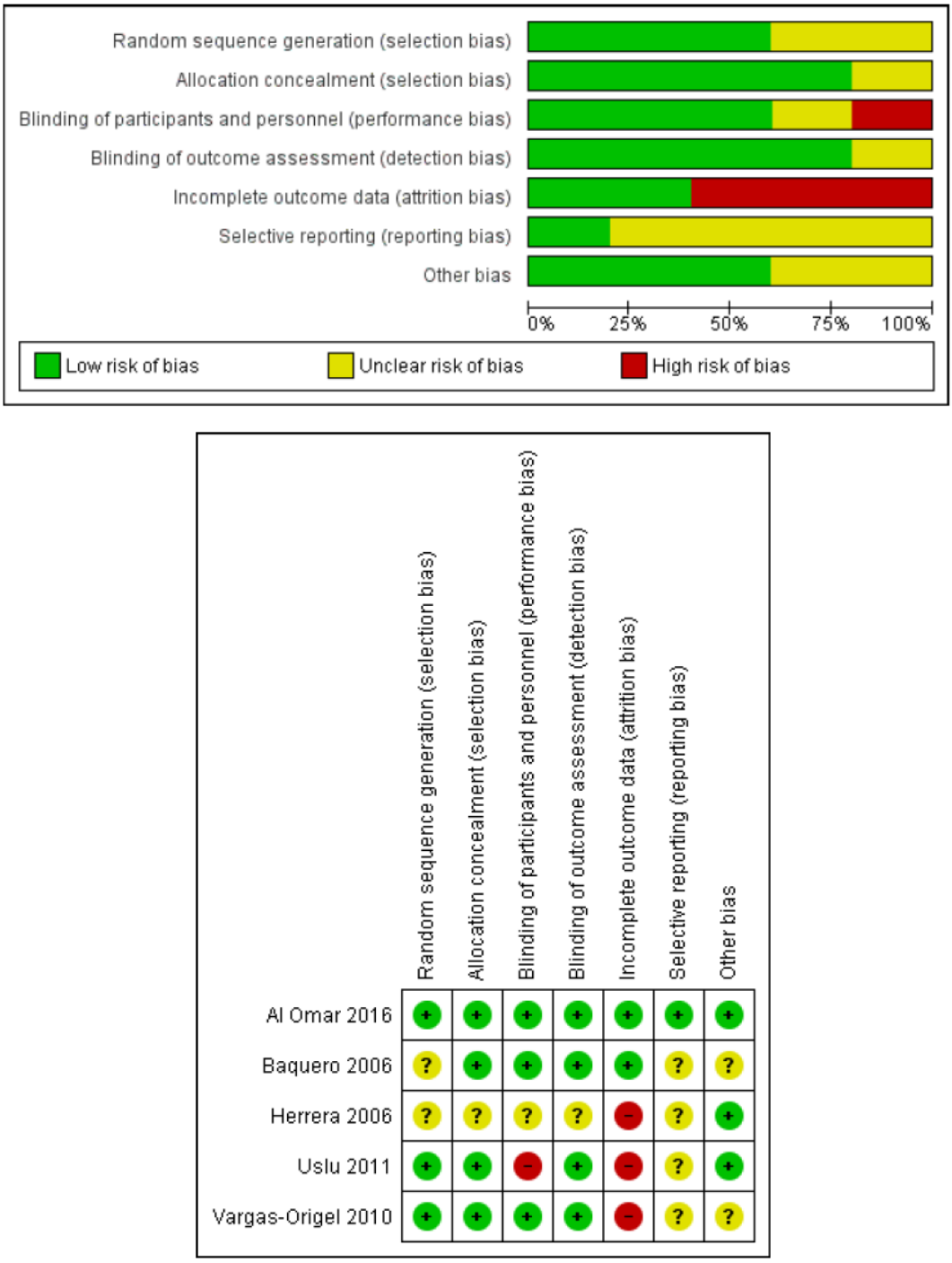

Figure 1: Risk of Bias Assessment extracted from Kelly 2017

Quality of evidence for outcomes extracted directly from Kelly 2017 (see Summary of Findings Tables) was considered to be of low quality. Quality was downgraded due to imprecision due to small sample size and concerns with risk of bias on account of unclear randomisation allocation and lack of clinical trial registration.

Effects of interventions

Comparison 1: Sildenafil compared to placebo

Outcome 1.1: Mortality

Three studies were included in the Kelly 2017 SR for this outcome (n=77). Sildenafil showed a statistically significant reduction in all-cause mortality rate within first 28 days of life compared to placebo (RR 0.20, 95% CI 0.07 to 0.56; RD -0.36, 95% CI -0.53 to -0.18. Number needed to treat for an additional benefit, NNTB = 3 (95% CI 2 to 6). Heterogeneity: i^2 = 39%, GRADED as low quality of evidence by Kelly 2017 SR – evidence downgraded due to imprecision (small studies) and unreported methodological features. See Figure 2.

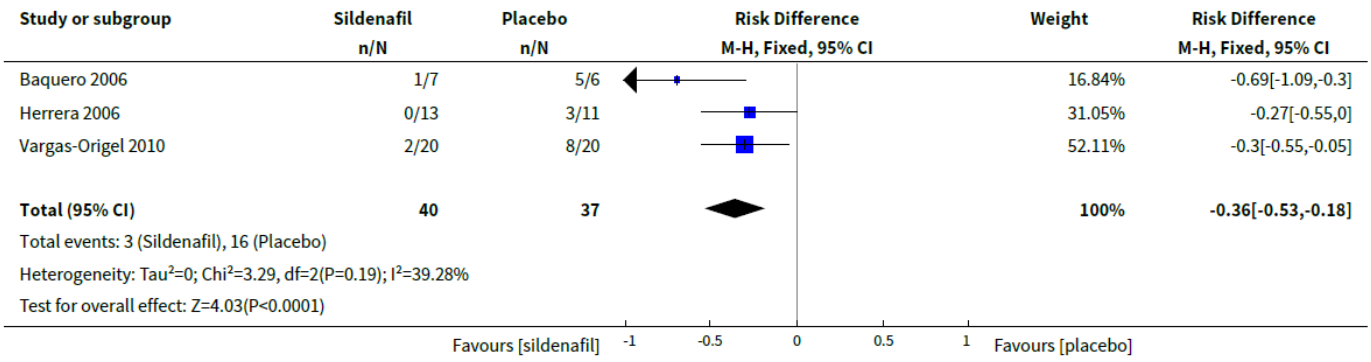

Figure 2: Comparison sildenafil vs placebo, outcome all-cause mortality – extracted from Kelly 2017.

Outcome 1.2 Haemodynamic parameters

Oxygenation: PaO_2 in mmHg

The SR (Kelly 2017) reported a significant difference found between sildenafil and placebo in PaO_2 in mmHg after 24 to 25 hours (MD 15.31 higher in favour of sildenafil, 95% CI (6.49 to 24.13), P=0, i^2=0; GRADE extracted from Kelly 2017: Low (downgraded for imprecision and unreported methodological features). Significant increases in PaO_2 were also found for sildenafil compared to placebo after first dose, after 6-7 hours of treatment, after 24 to 25 hours, and after 72 hours or end of therapy. See Figure 3 below.

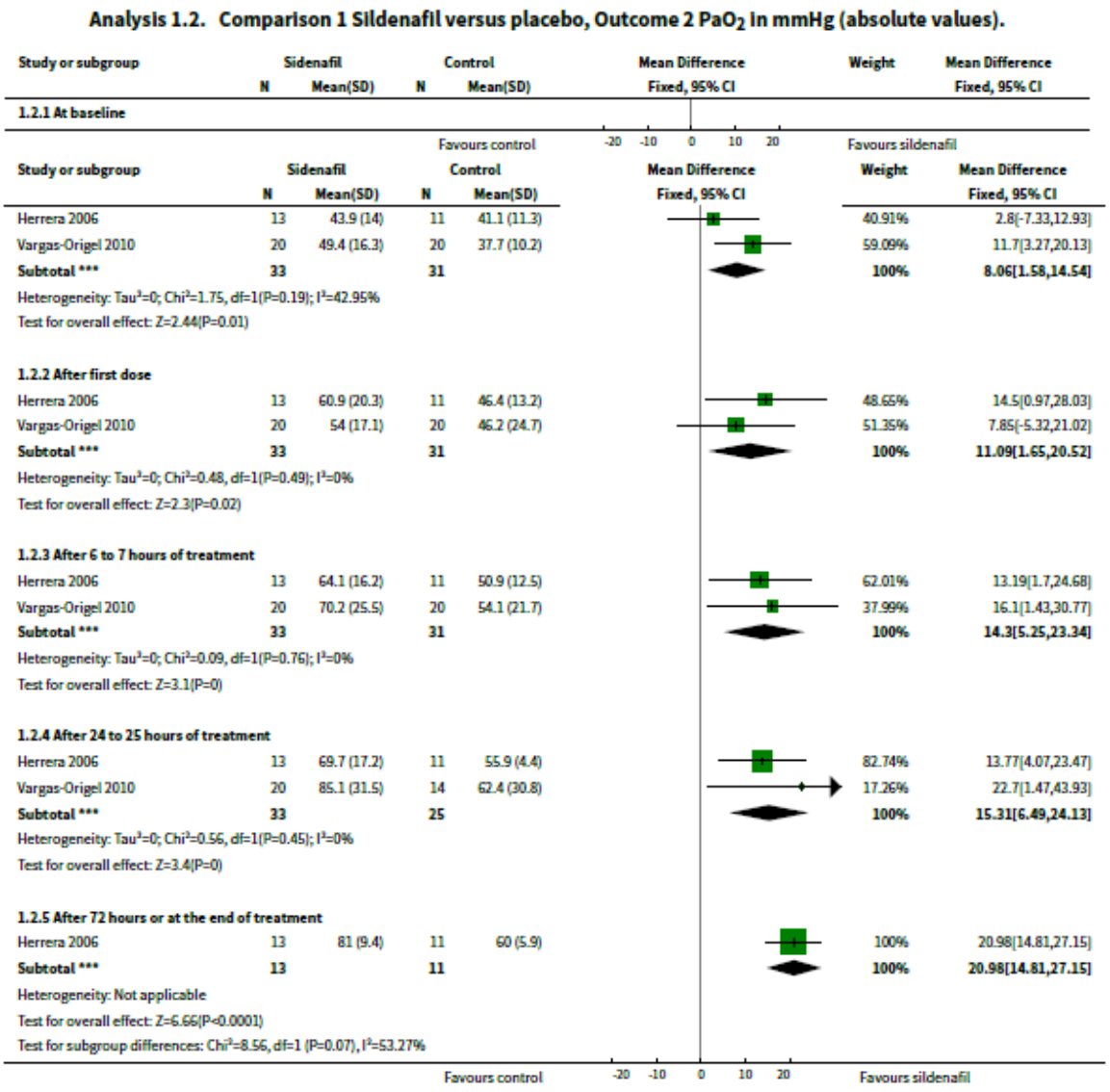

Figure 3: Comparison sildenafil vs placebo, change in PaO2 – extracted from Kelly 2017.

Change in oxygenation index (after 24 hours of therapy)

Statistically significant (p <0.0001) reduction in oxygen index after administration of five doses of sildenafil alone (at 24 hours after administration) compared with placebo (MD -38.79, 95% CI -56.97 to -20.61; one study, 12 participants; heterogeneity estimates - not applicable – GRADE: Low (downgraded for imprecision and unreported methodological features).

Outcome 1.3 Duration of mechanical ventilation

Not reported.

Outcome 1.4 Hospitalisation/ICU stay duration

Not reported.

Outcome 1.5 Ability to wean off ventilator.

Not reported.

Comparison 2 and 3: tadalafil compared to placebo, vardenafil compared to placebo.
No eligible studies were found for these comparisons.

Safety

- Intraventricular haemorrhage: no reported grade 3 or 4 intraventricular haemorrhages in either group.
- Neurodevelopmental disability at 18 to 24 months: 4 out of 6 survivors in sildenafil group in one study were assessed. All had normal neurological examinations and growth parameters were within normal limits.

6. Cost considerations

Table: Costs per patient based on most affordable generic product

		Dose	Tablet strength (mg)	Price per tablet	Cost per dose	Cost per day	Cost per week	Cost per month
SEP*	**Sildenafil**	25mg 8 hourly	50	R16.94	R8.47	R25.41	R177.84	R711.36
	Tadalafil	40 mg daily	20	R35.75	R71.50	R71.50	R500.50	R2,002.00
	Vardenafil	5mg 12 hourly	10	R21.04	R10.52	R21.04	R147.30	R589.21

SEP: Single Exit Price – April 2024

Duration of treatment depends on response and reduction of PAP as determined by echocardiography.

		Dose	Tablet strength (mg)	Price per tablet	Cost per dose	Cost per day	Cost per week	Cost per month
Contract price*	**Sildenafil**	25mg 8 hourly	20	R32.47	R32.47	R97.41	R681.87	R2,727.50

Contract price: HP09-2023SD (Note: high contracted price versus available generic product pricing raised with Contracting at NDoH

Utilisation

Current expenditure on the sildenafil product on contract (sildenafil 20mg 90s) is approximately R8 million, however this reflects general use and not specific to PPHN.

7. Alternative agents: Nitric oxide (only available in specialist Tertiary settings).

8. Conclusion

Evidence was found in favour of sildenafil compared to placebo for reduced mortality, reduced oxygen index and improved haemodynamics. Quality of evidence was low due to sample size and lack of standardized methodology. In the setting where access to nitric oxide is limited due to resource constraints and feasibility, a potential gap exists in the management of PPHN; thus, while the evidence for sildenafil was considered to be of low quality, the potential benefit and safety in this context is evident. As a result, the Tertiary and Quaternary Expert Review Committee recommends the inclusion of a PDE5-inhibitor on Essential Medicines List for the management of PPHN where nitric oxide services are not available.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*GRADED as Low – downgraded for imprecision and unreported methodological features.*
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ Moderate ☐ Small ☐ None ☐	*Statistically significant reduction in mortality rate compared to placebo, RR 0.20, 95% CI 0.07 to 0.56; RD -0.36, 95% CI -0.53 to -0.18. Number needed to treat for an additional benefit, NNTB = 3 (95% CI 2 to 6).*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*Not prespecified in the outcomes.*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒ List the members of the group. List specific exclusion from the group:	*Evaluating settings where nitric oxide (the alternative) not available.*
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [X]	**See cost heading**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [X] Major: [ ] Uncertain: [ ] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [X]	

Appendix 2: Search strategy

PubMed – SEARCH RUN 6 May 2024

Search	Query	Search Details	Results
#3	Neonatal population	((((Persistent pulmonary hypertension in neonates[MeSH Terms]) AND (Phosphodiesterase-5 (PDE5) inhibitors[MeSH Terms])) OR (sildenafil[MeSH Terms])) OR (tadalafil[MeSH Terms])) AND ((meta-analysis[Filter] OR systematicreview[Filter]) AND (newborn[Filter]))	13
#2	Meta-analyses and systematic review	((((Persistent pulmonary hypertension in neonates[MeSH Terms]) AND (Phosphodiesterase-5 (PDE5) inhibitors[MeSH Terms])) OR (sildenafil[MeSH Terms])) OR (tadalafil[MeSH Terms])) AND (meta-analysis[Filter] OR systematicreview[Filter])	147
#1	PPHN and PDE5-inhibitors	(((Persistent pulmonary hypertension in neonates[MeSH Terms]) AND (Phosphodiesterase-5 (PDE5) inhibitors[MeSH Terms])) OR (sildenafil[MeSH Terms])) OR (tadalafil[MeSH Terms])	7245

Table 2: COCHRANE LIBRARY– SEARCH RUN 6 May 2024

search	Query	Results
#1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1690
#2	MeSH descriptor: [Infant, Newborn] explode all trees	24025
#3	MeSH descriptor: [Phosphodiesterase 5 inhibitors] explode all trees	533
#4	MeSH descriptor: [Sildenafil Citrate] explode all trees	1185
#5	#1 AND #2 AND #3	4
#6	#5 in Cochrane Reviews	0
#7	#1 AND (#3 OR #4)	257
#8	#7 in Cochrane Reviews	**4**

Search summary

Pubmed	13 citations
Cochrane	4 citations
Overlap	1 citation
Excluded	12 citations
Total for consideration	**4 citations**

Studies identified through search but excluded prior to full text review.

	Study Citation	**Reason for exclusion**
1	Phosphodiesterase 5 inhibitors for pulmonary hypertension Parthipan Kanthapillai, E Haydn Walters 18 October 2004	Did not include neonatal population
2	Endothelin receptor antagonists for pulmonary arterial hypertension Chao Liu, Junmin Chen, Yanqiu Gao, Bao Deng, Kunshen Liu 25 March 2021	Wrong drug
3	Phosphodiesterase 5 inhibitors for pulmonary hypertension Hayley Barnes, Zoe Brown, Andrew Burns, Trevor Williams 31 January 2019	Did not include neonatal population
4	Phosphodiesterase-5 inhibitors in pregnancy: Systematic review and meta-analysis of maternal and perinatal safety and clinical outcomes. Turner JM, Russo F, Deprest J, Mol BW, Kumar S.BJOG. 2022 Oct;129(11):1817-1831. doi: 10.1111/1471-0528.17163. Epub 2022 Apr 15.PMID: 35352868 Review.	Wrong population
5	Sildenafil for pulmonary hypertension in neonates. Shah PS, Ohlsson A.Cochrane Database Syst Rev. 2011 Aug 10;(8):CD005494. doi: 10.1002/14651858.CD005494.pub3.PMID: 21833954 Updated. Review.	Updated Cochrane included
6	Sildenafil in Pregnancy: A Systematic Review of Maternal Tolerance and Obstetric and Perinatal Outcomes. Dunn L, Greer R, Flenady V, Kumar S.Fetal Diagn Ther. 2017;41(2):81-88. doi: 10.1159/000453062. Epub 2016 Dec 8.PMID: 27926905 Free article. Review.	Wrong population
7	Sildenafil for pulmonary hypertension in neonates. Shah PS, Ohlsson A.Cochrane Database Syst Rev. 2007 Jul 18;(3):CD005494. doi: 10.1002/14651858.CD005494.pub2.PMID: 17636802 Updated. Review.	Updated Cochrane included
8	The effects of sildenafil citrate on intrauterine growth restriction: a systematic review and meta-analysis. Rakhanova Y, Almawi WY, Aimagambetova G, Riethmacher D.BMC Pregnancy Childbirth. 2023 Jun 2;23(1):409. doi: 10.1186/s12884-023-05747-7.PMID: 37268873	Wrong outcome
9	Effect of L-arginine and sildenafil citrate on intrauterine growth restriction fetuses: a meta-analysis. Chen J, Gong X, Chen P, Luo K, Zhang X.BMC Pregnancy Childbirth. 2016 Aug 16;16:225. doi: 10.1186/s12884-016-1009-6.PMID: 27528012 Free PMC article. Review.	Wrong outcome
10	Interventions affecting the nitric oxide pathway versus placebo or no therapy for fetal growth restriction in pregnancy. Pels A, Ganzevoort W, Kenny LC, Baker PN, von Dadelszen P, Gluud C, Kariya CT, Leemhuis AG, Groom KM, Sharp AN, Magee LA, Jakobsen JC, Mol BWJ, Papageorghiou AT.Cochrane Database Syst Rev. 2023 Jul 10;7(7):CD014498. doi: 10.1002/14651858.CD014498.PMID: 37428872 Review.	Wrong drug
11	Perioperative Sildenafil Therapy in Pediatric Congenital Cardiac Disease Patients. Jiang L, Sun W, Zhang K, Zhou B, Kong X.Int Heart J. 2018 Nov 28;59(6):1333-1339. doi: 10.1536/ihj.17-548. Epub 2018 Sep 25.PMID: 30249921	Wrong population
12	Efficient administration of a combination of nifedipine and sildenafil citrate versus only nifedipine on clinical outcomes in women with threatened preterm labor: a systematic review and meta-analysis. Manouchehri E, Makvandi S, Razi M, Sahebari M, Larki M.BMC Pediatr. 2024 Feb 10;24(1):106. doi: 10.1186/s12887-024-04588-3.PMID: 38341578	Wrong population

Appendix 3. Summary of AMSTAR 2 assessments

AMSTAR-2 item	INCLUDED Kelly 2017 High quality Also includes GRADE assessment	NOT INCLUDED He 2021 Critically Low quality	NOT INCLUDED Perez 2015 Critically Low quality
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Partial yes	Partial yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Partial yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	No	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	No
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes

References:

[1] Nchabeleng MJ, Hamese MHK, Ntuli TS. Prevalence and outcomes of persistent pulmonary hypertension of the newborn in a neonatal unit, Mankweng Hospital, Limpopo Province, South Africa. South African Journal of Child Health. 2021, 15(2): 103-106.

[2] Smith J, Kirsten GF. Persistent pulmonary hypertension of the neonate in a developing country – does extracorporeal membrane oxygenation have a role to play? South African Medical Journal. 1993, 83.

[3] Harerimana I, Cooper PA. Retrospective review of neonates with persistent pulmonary hypertension of the newborn at Charlotte Maxeke Johannesburg Academic Hospital. S Afr J Child Health. 2018; 12(1): 29-33.

[4] Velaphi S, van Kwawegen AV. Meconium aspiration syndrome requiring assisted ventilation: Perspective in a setting with limited resources. J Perinato 2008;28(Suppl 3):S36-S42. https://doi.org/10.1038/jp.2008.155

[5] Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates (review). Cochrane Database of Systematic Reviews. 2017, issue 8: CD005494.