Guidelines on the use of sildenafil (Revatio) in acute pulmonary hypertension for paediatric cardiac patients

Indications
Rebound pulmonary hypertension caused by withdrawal of Nitric Oxide in paediatric patients on PICU (unlicensed indication).

Treatment of acute pulmonary hypertension prior to corrective surgery or immediately post-op (unlicensed for children under 1 year old)

Cautions
- Severe hypotension
- Bleeding disorders (active and chronic)
- Patients with fluid depletion
- Severe left ventricular outflow obstruction
- Autonomic dysfunction
- Predisposition to prolonged erection (e.g. in sickle cell disease, multiple myeloma or leukaemia) or anatomical deformation of the penis
- Ocular disorders
- In children who are septic there may be high circulating levels of cGMP due to activation of the nitric oxide synthase pathway, and the introduction of sildenafil in this situation could cause significant hypotension. Hence, although not contraindicated, there should be close monitoring of blood pressure (preferable invasive arterial pressure) during administration in these circumstances. It is advisable to introduce sildenafil at the lower end of the dose range.
- Also initiate cautiously if child is also on epoprostenol, iloprost or bosentan.

Renal impairment
Initial dose adjustments are not required in patients with renal impairment; including severe renal impairment (creatinine clearance is less than 30ml/min/1.73m$^2$). A downward dose adjustment twice a day from three times a day should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Hepatic impairment
Initial dose adjustments are not required in patients with hepatic impairment. A downward dose adjustment twice a day from three times a day should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.

Contraindicated in severe hepatic impairment.

Interactions (see BNF for further guidance)
- CYP3A4 inhibitors i.e. Erythromycin, saquinavir, can increase sildenafil levels and a dose adjustment maybe necessary after a careful benefit-risk assessment.
- Antihypertensive i.e. alpha-blockers, nitrates, calcium channel blockers
- Antifungals i.e. itraconazole, can increase sildenafil levels
- Antibacterials - clarithromycin, can increase sildenafil levels
- Bosentan, can reduce sildenafil levels.
Contraindications
- Although children are rarely treated with oral or intravenous nitrates, the use of these medicines (GTN and sodium nitroprusside) is a contra-indication to the use of Sildenafil.
- Combination with potent CYP3A4 inhibitors (eg.itraconazole, ritonavir, erythromycin, saquinavir)
- Myocardial infarction, recent history of strokes and severe hypotension
- Contraindicated in children who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy.
- Patients with pulmonary hypertension secondary to sickle cell anaemia
- Patients with known hereditary degenerative retinal disorders.

Side-effects (for further information see SPC)
- Dyspepsia, diarrhoea, vomiting
- flushing, headaches, dizziness, visual disturbances, raised intraocular pressure
- cough
- pyrexia
- erection

Mode of action
Sildenafil belongs to a group of drugs called phosphodiesterase (PDE) inhibitors, which also includes milrinone. Milrinone acts on PDE3 within cardiac muscle, whereas sildenafil acts specifically on PDE5. PDE5 is found within the corpus cavernosum of the penis, but is also found within the pulmonary vasculature. It is therefore theorised that sildenafil might decrease pulmonary vascular resistance by promoting pulmonary vasodilatation.

Phosphodiesterase 5 acts to break apart cyclic GMP, an intracellular signalling protein. cGMP acts a second messenger in the nitric oxide mediated pathway which controls vascular reactivity. By inhibiting PDE5, the concentrations of cGMP are increased as breakdown is reduced. This potentiates the action of nitric oxide and causes pulmonary vasodilatation. Whilst nitric oxide itself (when used as an inhalation agent) increases cGMP, this effect is seen to cease very rapidly once the drug is removed. The half life of nitric oxide in tissue is at most a few minutes. However, as sildenafil has a much longer half life, the increase in cGMP levels is greatly prolonged.

Note; Sildenafil used in addition to nitric oxide therapy, produces higher blood levels of cGMP than could be achieved with one or other medication alone, as they act synergistically.

Dosing Regime

Rebound pulmonary hypertension caused by withdrawal of Nitric Oxide in paediatric patients on PICU.

Children under 1 years old
Initial starting dose;
0.25mg/kg/dose given 4 to 8 hourly (maximum total daily dose is 30mg)

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose every 24hrs.
- dose should be doubled at each increment (i.e. 0.25mg/kg to 0.5mg/kg to
1mg/kg then 2mg/kg) (maximum total daily dose is 30mg)

**Children aged 1 year to 18 years**

**Body weight under 20Kg**

**Initial starting dose;**
2.5mg three times a day (or 1mg 4 hourly)

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose every 24hrs.
- dose should be increased to 5mg three times a day (or 2.5mg 4 hourly) then to a maximum dose of 10mg three times a day (or 5mg 4 hourly).

**Body weight over 20Kg**

**Initial starting dose;**
5mg three times a day (or 2.5mg 4 hourly)

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose after 24hrs.
- dose should be increased to 10mg three times a day (or 5mg 4 hourly) then to a maximum dose of 20mg three times a day (or 10mg 4 hourly).

In acute use, wean the dose of sildenafil by staging increments every 2 days.

**Treatment of acute pulmonary hypertension prior to corrective surgery or immediately post-op.**
(If the child has been started on Sildenafil post-op and is going to remain on Sildenafil for up to 3 months then once the child is stable the dose regime should be reviewed in view of the long term treatment dose)

**Long term treatment dose:**

**Children under 1 years old**

**Initial starting dose;**
0.25mg/kg/dose three times a day (maximum dose; 10mg three times a day)

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose every 24hrs.
- dose should be doubled at each increment, i.e. 0.25mg/kg to 0.5mg/kg to 1mg/kg three times a day (maximum dose; 10mg three times a day)

**Children aged 1 year to 18 years**

**Body weight under 20Kg**

**Initial starting dose;**
2.5mg three times a day

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose every 24hrs.
- dose should be increased to 5mg three times a day, then to a maximum dose of 10mg three times a day.
**Body weight over 20Kg**

Initial starting dose;
5mg three times a day

Incremental increases;
- if systematic BP stable but ongoing evidence of pulmonary hypertension, increase dose after 24hrs.
- dose should be increased to 10mg three times a day, then to a maximum dose of 20mg three times a day.

**NOTE;**  
Sildenafil should be stopped before discharge from hospital unless there is evidence of ongoing pulmonary hypertension. If there is evidence that the child would benefit from short-term treatment (post-operation remodelling or waiting further surgery) then sildenafil can be continued for 3 months only. If a longer course of sildenafil is needed then liaison with Great Ormond Street Pulmonary Hypertension team needs to be done and funding sorted.

**Administration**

**Preparations available;**
Sildenafil (Revatio) tablets 20mg
Sildenafil (Revatio) compounded suspension 10mg in 1mL - before withdrawing the required dose from the bottle, shake the suspension for at least 10 seconds.

Sildenafil (Revatio) tablets may be dissolved in water. The stability of the solution has not been established and any of this solution remaining should be discarded after the dose has been administered. The 20mg tablets may be halved and the unused half discarded. This oral preparation is very bitter and the taste may be disguised using blackcurrant juice drink to aid patient compliance

**Parameters to Monitor**
- Continuous blood pressure whilst on PICU
- On the Paediatric Cardiology Ward, for the first dose and any increase of dose monitor blood pressure every 30mins for the first 2 hours for and then monitor blood pressure 12 hourly.
- Baseline U&E’s and LFT’s to check renal and hepatic function.

**Pharmacokinetics**
- Sildenafil is rapidly absorbed, with maximum plasma concentrations reached between 30 to 120 minutes
- Sildenafil is metabolised by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major metabolite has a similar phosphodiesterase selectivity profile to sildenafil, contributing to 36% of sildenafil’s pharmacological effects.
- The total body clearance is 41 hours with a resultant terminal phase half-life of 3 to 5 hours. Sildenafil is excreted as metabolites in the faeces (80%) and urine (13%).

**References and Provenance**
1. BNF for children 2012-13, page 98
2. emc.medicines.org.uk, Pfizer Limited, Revatio
6. Verbal correspondence form the paediatric pulmonary hypertension team at Great Ormond Street Hospital, February 2013