Tadalafil
Newborn Use Only

2025

Alert	Sildenafil and tadalafil are Phosphodiesterase type-5 (PDE-5) inhibitors. Only one PDE-5 agent is to be prescribed if a PDE-5 inhibitor is indicated, not in combination. Tadalafil can be used in combination therapy with other agents.
Indication	Refractory pulmonary hypertension (PH).
Action	Phosphodiesterase type-5 (PDE-5) inhibitor. PDE-5 inhibitors block the action of cGMP-specific phosphodiesterase type 5 on cyclic GMP. This increases the amount of cyclic GMP in smooth muscle cells, which relaxes the blood vessels.
Drug Type	Phosphodiesterase type 5 inhibitor (PDE-5 inhibitor).
Trade Name	Multiple brands are available.
Presentation	5, 10, and 20 mg tablets, 5 mg/mL oral suspension (compounded in hospital pharmacy).[8]
Dosage	**ANMF consensus** • **To be prescribed only on the advice of a paediatric cardiologist.** • **Sildenafil and tadalafil are Phosphodiesterase type-5 (PDE-5) inhibitors. Only one PDE-5 inhibitor (either sildenafil or tadalafil) is to be prescribed at any one time, not in combination. Tadalafil can be used in combination with other agents.** **1 mg/kg/day as a single DAILY DOSE.** **Switching from sildenafil to tadalafil:** Cease sildenafil at the time of the next dose to be administered and replace at that time with tadalafil. Do not give sildenafil and tadalafil together. Example: If sildenafil is due at 8pm, do not give the sildenafil 8pm dose; give the first dose of tadalafil at 8pm instead. **Duration of therapy –** To be determined by the treating cardiology team – often for 6 months to 2 years. **Cessation of therapy –** Can be ceased without weaning.
Dose Adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Renal impairment – No information. Hepatic impairment – No information.
Maximum Dose	Dose >1 mg/kg/day is only on the advice and close monitoring of a paediatric cardiologist.
Route	Oral
Preparation	5 mg/mL oral suspension (Compounded in hospital pharmacy) – Recommended. Tablets are practically insoluble in water and not suitable for aliquots (part doses).
Administration	Oral. Can be given with or without feeds. Shake bottle well before measuring the dose.
Monitoring	Periodic clinical and echocardiographic review as per the advice of paediatric cardiologist. Consider NT-proBNP levels. Periodic assessment of full blood count (in particular platelets) and liver function tests. Auditory function and eye check.
Contraindications	Serious hypersensitivity to tadalafil or any component of the formulation. Concurrent use of organic nitrate. Concurrent use of sildenafil.
Precautions	Prolonged (defined as >4 hours) erection (priapism) – this is a medical emergency and requires active management. A cold or icy cloth is to be applied while waiting for further medical assistance. Monitor for nose bleeds and any unusual bruising.
Drug Interactions	Tadalafil is principally metabolised by CYP3A4. Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolised by CYP450 isoforms.[1]
Adverse Reactions	Gastrointestinal (vomiting), flushing, rashes, myalgia, respiratory tract infections, nasal congestion, peripheral oedema, hypotension, hearing impairment, visual disturbances. Priapism - Prolonged (defined as >4 hours) erection (priapism) is a medical emergency and requires active management. A cold or icy cloth is to be applied while waiting for further medical assistance. Nose bleeds, bruising.

	May cause pulmonary over-circulation in the setting of a patent ductus arteriosus.[2]
Overdose	AUSTRALIA Contact the Poisons Information Centre on **13 11 26** for information on the management of overdose. NEW ZEALAND Contact the National Poisons Centre on **0800 764 766** for information on the management of overdose.
Compatibility	Not Applicable
Incompatibility	Not Applicable
Stability	5 mg/mL oral suspension: 28 days at room temperature (Australian Pharmaceutical Formulary). Refer to evidence section on further information on stability.[8]
Storage	Tablets: Store below 25°C. Store in the original package. [API] oral suspension: Store below 25°C
Excipients	Adcirca brand contains: croscarmellose sodium, hyprolose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, purified talc, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red.
Special Comments	
Evidence	**Background** Pulmonary hypertension (PH) in infants and children can result in right heart failure and has a high mortality among severe cases. Tadalafil is a selective phosphodiesterase type 5 (PDE-5) inhibitor with a long half-life (16 hours), stable pharmacokinetics and pharmacodynamics, and minimal adverse effects.[3] Tadalafil was approved for treating adult patients with PH in 2009 after an RCT showed that treatment with tadalafil improved exercise ability and quality of life and delayed time to clinical worsening.[4] **Efficacy** **<u>PH in neonates and infants with bronchopulmonary dysplasia (BPD)</u>** Kiskaddon et al, conducted a single-centre retrospective review at John Hopkins All Children's Hospital involving 42 infants (4 neonates and 38 infants) who were under 1 year of age at the initiation of tadalafil.[2] Most patients were receiving oxygen support (95.2%), inhaled nitric oxide (iNO) (76.2%), or invasive ventilation (64.3%) when tadalafil was started. After tadalafil initiation, 30 patients (71.4%) did not require additional concomitant PH medications. Tadalafil was associated with improvements in pulmonary artery pressures. Tadalafil was well tolerated, with only 1 patient experiencing pulmonary over-circulation due to patent ductus arteriosus (PDA), which led to the discontinuation of tadalafil.[2] **<u>PH in paediatric population</u>** Youssef et al, reported North American experience on safety and efficacy of tadalafil, either alone, or in combination with another vasodilator, for the management of PH due to various aetiologies.[3] Tadalafil was administered in a suspension. 154 children with a median age of 1.0 (range 0.0 – 6.9) years were treated with tadalafil. The median initial dose of tadalafil was 1 mg/kg once daily. They found tadalafil was safe with tolerable adverse effect profile. Following 6 months of therapy, there were improvements in clinical parameters, echocardiographic measurements, and laboratory results. There was a statistically significant increase in tricuspid annular plane systolic excursion as well as significant decreases in right-ventricular systolic pressure and NT-proBNP. Patient compliance was good and adverse effects were rare, minor, and manageable with nonpharmacological means.[3] Shiva et al, conducted an open-label, prospective interventional study involving 25 patients aged 2 months to 5 years across 3 medical centres in Iran.[5] The diagnoses included persistent pulmonary hypertension (12%), while 78% had associated congenital heart disease, including ventricular septal defect, atrioventricular septal defect, PDA, and double outlet right ventricle. All patients received tadalafil suspension at a dose of 1 mg/kg orally once per day. Of the 25 patients, 6 (24%) had been on sildenafil for longer than 6 months. At the time of transition, all of them were receiving oral sildenafil 1 mg/kg 3 times a day. All patients were successfully transitioned to tadalafil, and 19 patients received tadalafil as initial therapy. Side effects observed included nausea, flushing, headache, diarrhoea, and nasal congestion. There was an improvement in mean pulmonary artery pressure (MPAP).[5] Ivy et al, conducted a phase 3, randomized, double-blind, placebo-controlled study involving 35 paediatric patients aged 6 months to less than 18 years with PAH (pulmonary artery hypertension).[6] The study demonstrated a positive trend in improvement in non-invasive measurements with tadalafil dosages of 40 mg for patients weighing 40 kg or more, and 20 mg for patients weighing 25 kg to 40 kg, compared to the placebo group.[6] **<u>Persistent Pulmonary Hypertension of Newborn (PPHN)</u>**

Alipour et al, compared tadalafil and sildenafil for the management of PPHN.[7] A total of 32 neonates were studied, but there was no specification of weight, gestational age, or the age at which tadalafil or sildenafil was started. The aetiology of PPHN was meconium aspiration in 19 (59.3%), diaphragmatic hernia in 3 (9.3%), and asphyxia in 10 (31.2%) neonates. These neonates were randomly assigned to two groups of 16 cases: one group received oral tadalafil 1 mg/kg as a single dose, and the other received oral sildenafil 1 mg/kg 3 times a day. The results showed that both groups similarly reduced MPAP (mean pulmonary artery pressure), Tricuspid regurgitation severity, RVEDD (right ventricular end-diastolic dimension), and MPA (Main pulmonary artery) diameter, with no statistically significant difference between the groups. No side effects were observed in either group.[7]

Tadalafil suspension

Tadalafil is commercially available as tablets and not suitable for infants and young children. Compounded suspension provides flexibility in dosing and administration. Pettit et al studied the stability of an extemporaneously prepared suspension of tadalafil 5 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet.[8] The suspension was prepared by thoroughly grinding 15 20 mg tadalafil tablets in a glass mortar. Thirty millilitres of Ora-Plus and 30 mL of Ora-Sweet were mixed and added to the powder to make a final volume of 60 mL. Three identical samples of the formulation were prepared and placed in 2 oz amber plastic bottles with child-resistant caps and stored at room temperature (23 – 25°C). At least 99% of the initial tadalafil concentration remained throughout the 91-day study period. There were no detectable changes in colour, odour, taste, and pH, and no visible microbial growth was observed in any sample. This suspension was used in studies by Kiskaddon et al[2] and Youssef et al.[3]

Safety

Tadalafil is generally well tolerated and usually has only mild adverse effects such as gastrointestinal (1.3%), and flushing and rashes (0.6%).[3] One infant was reported to develop pulmonary over-circulation in the setting of a PDA.[2]

In the study by Ivy et al, the most common adverse events in non-neonatal age group were headache (29.4% in the tadalafil group; 11.1% in the placebo group), upper respiratory tract infection (17.6% in the tadalafil group; 5.6% in the placebo group), influenza (17.6% in the tadalafil group; 0.0% in the placebo group), arthralgia (11.8% in the tadalafil group; 5.6% in the placebo group), and epistaxis (11.8% in the tadalafil group; 5.6% in the placebo group). Two adverse events of special interest in tadalafil-treated subjects included one case of spontaneous intermittent penile erection and one case of uterine bleeding.[6]
A Japanese post-marketing surveillance study, which included data on safety for 1,676 adult and paediatric patients with a mean age of 43.5 ± 26.55 years (23.3% of patients were <18 years old, and 28.7% were ≥65 years), demonstrated that the incidence rate of adverse drug reactions (ADRs) was 31.2%, and the incidence rate of serious ADRs (SADRs) was 7.1%. The most reported ADRs (>1.0%) were headache, diarrhoea, thrombocytopenia (1.8%), anaemia, epistaxis, nausea (1.6% each), flushing (1.3%), hepatic function abnormalities (1.1%), hot flush, and myalgia (1.0% each). The most reported SADRs (≥0.3%, 5 cases) included cardiac failure (0.7%), thrombocytopenia, PAH (aggravation of primary disease), and interstitial lung disease (0.3% each). Adverse events leading to the discontinuation of tadalafil included headache, cardiac failure, PH (aggravation of primary disease), PAH (aggravation of primary disease), nausea, diarrhoea, and interstitial lung disease. From the safety analysis population, a total of 964 patients were administered tadalafil for more than 1 year. The incidence rate of ADRs in these patients was 8.0%, and the rate of SADRs was 2.4%.[9]

Pharmacokinetics

Tadalafil is primarily metabolized by CYP3A4. It is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by CYP450 isoforms.[1]
A 3-way crossover pharmacokinetic study in healthy adult subjects demonstrated linear pharmacokinetic behaviour and time under the conditions of the study. Food had negligible effects on the rate and extent of absorption. Therefore, tadalafil may be taken without regard to meal timing or the fat content of the meal. Tadalafil was rapidly absorbed, with a mean Cmax of 378 microgram/L for the 20 mg dose observed at 2 hours. Thereafter, concentrations declined nearly monoexponentially, with a mean (5th, 95th percentiles) t1/2 of 17.5 (11.5, 29.6) hours. The mean oral clearance was 2.48 (1.35, 4.35) L/h, and the apparent volume of distribution was 62.6 (39.5, 92.1) L.[10]

References

1. Australian Product Information. Adcirca (Tadalafil) tablets. 14 July 2023.

	2. Kiskaddon A, Dang T, Mauriello D. Tadalafil in Neonates and Infants with Pulmonary Hypertension Secondary to Bronchopulmonary Dysplasia. The Journal of Pediatric Pharmacology and Therapeutics. 2024;29(2):140-3. 3. Youssef DE, Handler SS, Richards SM, Sheppard CA, Smith J, Tillman K, et al. Multicenter review of a tadalafil suspension formulation for infants and children with pulmonary hypertension: A North American experience. Frontiers in Pediatrics. 2023;11:1055131. 4. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119(22):2894-903. 5. Shiva A, Shiran M, Rafati M, Zamani H, Babazadeh K, Saeedi M, et al. Oral tadalafil in children with pulmonary arterial hypertension. Drug research. 2016;66(01):7-10. 6. Ivy D, Bonnet D, Berger RM, Meyer GM, Baygani S, Li B, et al. Efficacy and safety of tadalafil in a pediatric population with pulmonary arterial hypertension: phase 3 randomized, double-blind placebo-controlled study. Pulmonary circulation. 2021;11(3):20458940211024955. 7. Alipour MR, Lookzadeh MH, Namayandeh SM, Pezeshkpour Z, Sarebanhassanabadi M. Comparison of tadalafil and sildenafil in controlling neonatal persistent pulmonary hypertension. Iranian Journal of Pediatrics. 2017;27(1). 8. Pettit RS, Johnson CE, Caruthers RL. Stability of an extemporaneously prepared tadalafil suspension. American Journal of Health-System Pharmacy. 2012;69(7):592-4. 9. Yamazaki H, Kobayashi N, Taketsuna M, Tajima K, Suzuki N, Murakami M. Safety and effectiveness of tadalafil in pediatric patients with pulmonary arterial hypertension: a sub-group analysis based on Japan post-marketing surveillance. Current Medical Research and Opinion. 2017;33(12):2241-9. 10. Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE, et al. Tadalafil pharmacokinetics in healthy subjects. British journal of clinical pharmacology. 2006;61(3):280-8.

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