Cyclomydril
Newborn Use Only

2017

Alert	Unapproved medicine in Australia and New Zealand. Available only through Special Access Scheme Category C Pathway.
Indication	Mydriatic (dilates the pupil) and cycloplegic (prevents accommodation of the eye) for ophthalmic examinations and therapeutic procedures
Action	Contains cyclopentolate hydrochloride 0.2% and phenylephrine hydrochloride 1%. Cyclopentolate hydrochloride is an anticholinergic drug and phenylephrine hydrochloride is an adrenergic drug. This combination induces mydriasis that is greater than that of either drug alone at its respective concentration. The concentrations of cyclopentolate and phenylephrine have been selected to induce mydriasis with little accompanying cycloplegia.
Drug Type	Antimuscarinic (cyclopentolate) and sympathomimetic (phenylephrine).
Trade Name	Cyclomydril
Presentation	2 mL DROP-TAINER® dispenser. Each mL contains: Cyclopentolate hydrochloride 0.2%, phenylephrine hydrochloride 1%. Preservative: Benzalkonium chloride 0.01%. Inactives: Edetate disodium, boric acid, hydrochloric acid and/or sodium carbonate (to adjust pH), purified water.
Dosage/Interval	Instil one drop into each eye 30–60 minutes prior to procedure. Dark irises may require additional drops. Instillation of one drop into each eye, may be repeated up to three times (maximum of four drops), at least 5 minutes apart.
Maximum dose	Four drops into each eye.
Route	Topical instillation into the eyes.
Preparation/Dilution	N/A
Administration	Apply pressure to the lacrimal sac during and for 2 minutes after instillation of eye drop to minimise systemic absorption. Wipe away excess medication.
Monitoring	Observe infants for at least 30 minutes up to 120 minutes. Blood pressure, heart rate and oxygen saturation. Signs of ileus.
Contraindications	Concurrent use with beta-blockers. Acute stage of necrotising enterocolitis (NEC).
Precautions	To minimise systemic absorption, apply pressure over the nasolacrimal sac for 2 to 3 minutes following instillation. Bronchopulmonary dysplasia. Feeding intolerance. Severe neurological impairment.
Drug Interactions	Propranolol: An enhanced pressor response to phenylephrine has been shown in patients on propranolol (blocks the beta-adrenergic vasodilation that normally reduces the blood pressure effect).
Adverse Reactions	These usually only occur with excess dosing. Anticholinergic side effects include fever, tachycardia, vasodilation, dry mouth, restlessness, delayed gastric emptying and decreased gastrointestinal motility, and urinary retention. Alpha-adrenergic side effects include decreased pulmonary compliance, tidal volume and peak airflow in babies with bronchopulmonary dysplasia. Increased heart rate and blood pressure.
Compatibility	N/A
Incompatibility	N/A
Stability	Single use only. Discard after use.
Storage	Store at room temperature < 25°C.
Special Comments	Cyclomydril is an unapproved medicine in Australia and New Zealand.

Evidence summary	**Efficacy** ***Trials comparing mydriatics:*** Several controlled studies have reported the mydriatic effect of cyclopentolate 0.2% + phenylephrine 1% [Cyclomydril] in preterm infants screened for ROP. Isenberg et al [1], in 30 preterm infants, reported that the cyclopentolate 0.2% + phenylephrine 1% combination produced greater mydriasis and longer duration of mydriasis than cyclopentolate 0.5% + tropicamide 0.5% or cyclopentolate 0.5% alone [LOE III-2]. Chew et al[2], in 39 infants with dark irides randomly allocated to cyclopentolate 1% + phenylephrine 2.5% versus tropicamide 1% + phenylephrine 2.5% versus cyclopentolate 0.2% with phenylephrine 1%, reported all three mydriatic regimens provided adequate pupillary dilation at 45 minutes, with dilation sustained at 60 minutes. They concluded the combination cyclopentolate 0.2% + phenylephrine 1% provided adequate pupillary dilation with the least systemic side effects [LOE II]. ***Trials assessing dose:*** Punyawattanaporn et al[3], in 70 preterm infants with each eye randomly allocated, reported the pupil size was larger after three drops of cyclopentolate 0.2% + phenylephrine 1.0% than after a single drop. However, a dilated pupil diameter ≥ 6 mm, adequate for the peripheral retina examination, was not obtained at 60 minutes in 21.4% of eyes after 1 drop and only 1.4% after 3 drops [LOE II]. Vincente et al [4], in 64 eye examinations performed on 15 enrolled infants, with the left eye randomly allocated to receive to receive either 0, 1 or 2 drops of cyclopentolate 0.2% and phenylephrine 1%, reported that effective mydriasis was achieved in the test eye with 1 or 2 drops and sustained to 120 minutes. Retinal examinations could be completed by 90 minutes in most infants with the use of 1 drop [LOE II]. **Side effects** Isenberg et al [1] showed no clinically significant effect on systolic blood pressure or pulse rate [LOE III-2]. Chew et al [2], in 39 infants, reported a significant increase in mean blood pressure in infants allocated cyclopentolate 1% + phenylephrine 2.5% and the tropicamide 1% + phenylephrine 2.5% groups but not cyclopentolate 0.2% + phenylephrine 1%. They concluded the combination cyclopentolate 0.2% + phenylephrine 1% provided adequate pupillary dilation with the least systemic side effects [LOE II]. Mitchell et al [5], in infants given cyclopentolate 0.2% + phenylephrine 1% 3 drops at 0, 5 and 10 minutes, reported there was a significant association between cyclopentolate concentrations and gastric residuals in tube-fed infants not receiving oxygen (p = 0.01) [LOE IV]. There are several case reports of necrotising enterocolitis [6-8], seizures [9] and cyclopentolate toxicity [10] occurring after mydriatic instillation. Cyclopentolate toxicity occurred with cyclopentolate 1%, 1 drop x 6 instillations, and resolved with physostigmine infusion 0.02 mg/kg over 10 minutes. Nefendorf et al[11] reported a cohort of 138 infants with 1246 eyes screened during 623 examinations using phenylephrine 2.5% + cyclopentolate 0.5% instilled 3 times, 5 minutes apart. Five infants of 623 (0.8%) having eye examinations had adverse events recorded in the 24-hour period after ROP screening [apnea and/or respiratory deterioration with 4 requiring ventilation]. One case of NEC occurred 1 week post-examination [LOE III-2]. Strube et al [12] reported in a controlled study that feeding infants 1 hour before compared with withholding feeding 2 or more hours before ROP examinations may reduce percentage crying during the examination, with no increased incidence of vomiting or gastric aspirates [LOE III-2]. ***Conclusion:*** Cyclopentolate 0.2% + phenylephrine 1% eye drops are an effective mydriatic with 1 to 3 drops producing adequate dilatation within 60 minutes sustained to 120 minutes. It is generally well-tolerated with minimal physiological effects reported at this dose. [LOE II GOR B] **Pharmacokinetics:**

	Mitchell et al[5], in infants given cyclopentolate 0.2% + phenylephrine 1% 3 drops at 0, 5 and 10 minutes, reported a cyclopentolate concentration range of 6–53 nanogram/mL in 15 of 18 infants, while phenylephrine was not detected. Concentrations of cyclopentolate were significantly higher in infants who were on oxygen (p = 0.01) [LOE IV]. Systemic absorption of the ophthalmic eye drops via conjunctival sac or nasolacrimal mucosa remains a potential cause of systemic effects of topical agents as the majority (up to 99%) of every drop is considered to be absorbed systemically. Several approaches have been advocated for reducing systemic absorption and the associated side effects. These include eyelid closure, digital occlusion of nasolacrimal duct for several minutes, wiping away excess drops during and after drug instillation and proper dilution or reduced volume of eye drops for use in children. [13]
References	1. Isenberg S, Everett S, Parelhoff E. A comparison of mydriatic eyedrops in low-weight infants. Ophthalmology. 1984;91:278-9. 2. Chew C, Rahman RA, Shafie SM, Mohamad Z. Comparison of mydriatic regimens used in screening for retinopathy of prematurity in preterm infants with dark irides. Journal of Pediatric Ophthalmology and Strabismus. 2005;42:166-73. 3. Punyawattanaporn A, Tengtrisorn S, Sangsupawanich P. Pupil dilatation after single and triple doses of mydriatic agent in preterm infants. Journal of the Medical Association of Thailand. 2009;92:1458-62. 4. Vicente GV, Bahri M, Palafoutas JJ, Wang H, Mehta N. A randomized controlled trial to determine the lowest effective dose for adequate mydriasis in premature infants. Journal of AAPOS. 2012;16:365-9. 5. Mitchell A, Hall RW, Erickson SW, Yates C, Hendrickson H. Systemic Absorption of Cyclopentolate and Adverse Events After Retinopathy of Prematurity Exams. Current Eye Research. 2016;41:1601-7. 6. Bauer CR, Trottier MCT, Stern L. Systemic cyclopentolate (Cyclogyl) toxicity in the newborn infant. Journal of Pediatrics. 1973;82:501-5. 7. Nair AK, Pai MG, Da Costa DE, Al Khusaiby SM. Necrotising enterocolitis following ophthalmological examination in preterm neonates. Indian Pediatrics. 2000;37:417-21. 8. Ozgun U, Demet T, Ozge KA, Zafer D, Murat S, Mehmet Y, Nilgun K. Fatal necrotising enterocolitis due to mydriatic eye drops. Journal of the College of Physicians and Surgeons Pakistan. 2014;24:S147-S9. 9. Hu L, Dow K. Focal seizures after instillation of cyclomydril to a neonate with congenital CMV infection. Journal of Neonatal-Perinatal Medicine. 2014;7:147-9. 10. Derinoz O, Emeksiz HC. Use of physostigmine for cyclopentolate overdose in an infant. Pediatrics. 2012;130:e703-e5. 11. Nefendorf JE, Michael Mota P, Xue K, Darius Hildebrand G. Efficacy and safety of phenylephrine 2.5% with cyclopentolate 0.5% for retinopathy of prematurity screening in 1246 eye examinations. European Journal of Ophthalmology. 2015;25:249-53. 12. Strube YNJ, Bakal JA, Arthur BW. Relationship between feeding schedules and gastric distress during retinopathy of prematurity screening eye examinations. Journal of AAPOS. 2010;14:334-9. 13. Gunaydin B, Cok OY. Hazards of topical ophthalmic drug administration. Trends in Anaesthesia and Critical Care. 2011;1:31-4. 14. Micromedex solutions. Phenylephrine hydrochloride. Accessed on 23 August 2017.

Original version Date: 24/08/2017	**Author: NMF Consensus Group**
Current Version number: 1.0	**Current Version Date: 24/08/2017**
Risk Rating: Medium	**Due for Review:** 24/08/2020
Approval by: As per Local policy	**Approval Date:**