

# Phenylephrine

## Newborn Use Only

2018

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| <b>Alert</b>                | Watch for apnoeas and abdominal distension following administration.<br>Lower concentration solutions and regimens minimising number of additional drops are recommended.  |
| <b>Indication</b>           | Mydriatic (dilates the pupil) for ophthalmic examinations and therapeutic procedures.  |
| <b>Action</b>               | Selective alpha-1-adrenoceptor agonist.<br>Contracts dilator muscle of pupil and constricts arterioles in conjunctiva.   |
| <b>Drug Type</b>            | Sympathomimetic.   |
| <b>Trade Name</b>           | Minims® Phenylephrine hydrochloride.   |
| <b>Presentation</b>         | Phenylephrine hydrochloride 2.5 % (25 mg/mL) single-use sterile eye drop, approximately 0.5 mL.  |
| <b>Dosage/Interval</b>      | Use in conjunction with cyclopentolate 0.5% and/or tropicamide 0.5% eye drops.<br><br><b>REGIMEN 1:</b><br>Phenylephrine 2.5% + cyclopentolate 0.5% + tropicamide 0.5% eye drops [1-4].<br>Instil one drop of each agent (5 minutes apart) into each eye 60 minutes prior to examination.<br>Repeat if pupillary dilatation inadequate.<br>Perform examination 60 to 120 minutes after instillation.<br><br><b>REGIMEN 2:</b><br>Phenylephrine 2.5% + cyclopentolate 0.5% eye drops [5].<br>Instil one drop of each agent (5 minutes apart) into each eye 60 minutes prior to examination.<br>Repeat if pupillary dilatation inadequate.<br>Perform examination 60 to 120 minutes after instillation.<br><br>Dark irides may require additional drops. |
| <b>Maximum daily dose</b>   | REGIMEN 1: 3 drops of each eye drop.<br>REGIMEN 2: 4 drops of each eye drop.   |
| <b>Route</b>                | Topical instillation into the eyes from the container or use a microdrop (5–7 microL) cannula.   |
| <b>Preparation/Dilution</b> |  |
| <b>Administration</b>       | Apply pressure to the lacrimal sac during and for 60 seconds after instillation of eye drop to minimise systemic absorption. Wipe away excess medication.<br>Consider withholding feeds for four hours from administration of the last drops to reduce incidence of feed intolerance.  |
| <b>Monitoring</b>           | Blood pressure, heart rate and oxygen saturation in infants with bronchopulmonary dysplasia.   |
| <b>Contraindications</b>    | Necrotising enterocolitis (NEC) at the time of eye examination.<br>Concurrent use with beta-adrenoceptor antagonists (beta-blockers).  |
| <b>Precautions</b>          | Infants with bronchopulmonary dysplasia.<br>Lower concentration solutions and regimens minimising number of additional drops are recommended to minimise toxicity.   |
| <b>Drug Interactions</b>    | Atropine, beta-adrenoceptor antagonists (beta-blockers).   |
| <b>Adverse Reactions</b>    | Decreased pulmonary compliance, tidal volume and peak air flow in babies with bronchopulmonary dysplasia.<br>Increased blood pressure.<br>Skin pallor around eyes.   |
| <b>Compatibility</b>        | Cyclopentolate, tropicamide, amethocaine   |
| <b>Incompatibility</b>      |  |
| <b>Stability</b>            | Discard immediately after use.   |
| <b>Storage</b>              | Store in refrigerator at 2°C to 8°C. Do not freeze. Protect from light.  |
| <b>Special Comments</b>     | Cross check correct strength of Minims® Phenylephrine hydrochloride is used.   |

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|                         | Do NOT use 10 % in neonates.  |
| <b>Evidence summary</b> | <p><b><u>Efficacy</u></b></p> <p><b>Phenylephrine (<math>\alpha</math>1-adrenoceptor agonist) alone:</b> Ogut et al, in a RCT in 80 preterm infants screened for ROP, found two drops phenylephrine 2.5% resulted in a mean pupillary diameter 5.7 mm at 60 minutes and 4.7 mm with light. Maximum side effects (increased heart rate and BP) were seen with 2.5% phenylephrine.[2] Caputo et al, in a controlled study, reported three drops phenylephrine 10% or 2.5% produced inadequate mydriasis for peripheral retinal examination. Phenylephrine 10% caused skin blanching and elevation of heart rate and BP.[4]</p> <p><b>Conclusion:</b> Phenylephrine alone is insufficient for adequate mydriasis. Phenylephrine 10% and 2.5% are associated with significant systemic physiological effects. [LOE II GOR A]</p> <p><b>Phenylephrine added to combination eye drops:</b> Ogut et al, in a RCT in 80 preterm infants screened for ROP, found maximum mydriasis was achieved with cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine. Adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide.[2]</p> <p>Several RCTs have reported increased mydriatic effect of added phenylephrine. Merritt et al reported phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5% 1 drop each produced maximal mydriasis at 75–90 minutes with adequate funduscopy at 120 minutes.[1]</p> <p>Fleck et al reported the mydriatic effect of phenylephrine 2.5% + tropicamide 0.5% 1 drop each was superior to tropicamide 0.5% alone (mean 6 mm versus 2.7 mm; <math>p &lt; 0.001</math>), and adequate mydriasis in phenylephrine 2.5% + tropicamide 0.5% group only.[6]</p> <p>Lux et al reported phenylephrine 5% 1 drop + tropicamide 0.5% 2 drops produced pupil surface area 1.9 times greater than tropicamide 0.5% 3 drops alone. Visualisation of the retinal periphery was possible for 30 of 30 eyes dilated with the PTT regimen and for 16 of 30 eyes dilated with the TTT regimen.[9]</p> <p><b>Conclusion:</b> Maximum mydriasis is achieved with addition of phenylephrine 2.5% in the combination (cyclopentolate 0.5% + tropicamide 0.5% + 2.5% phenylephrine). However, adequate mydriasis without side effects was achieved with 1% cyclopentolate + 1% tropicamide. [LOE II GOR B]</p> <p><b>Phenylephrine combinations:</b> Several RCTs have assessed various phenylephrine combinations. Chew et al compared cyclopentolate 1% + phenylephrine 2.5% versus tropicamide 1% + phenylephrine 2.5% versus cyclopentolate 0.2% + phenylephrine 1% (all 3 drop regimens). Cyclopentolate 0.2% + phenylephrine 1% 3 drops provided adequate pupillary dilation with the least systemic side effects. Combination cyclopentolate 1% + phenylephrine 2.5% and tropicamide 1% + phenylephrine 2.5% are associated with increased BP and cyclopentolate 1% + phenylephrine 2.5% may be associated with feed intolerance.[10]</p> <p>Khoo et al reported cyclopentolate 0.2% + phenylephrine 1% is as effective a mydriatic as tropicamide 0.5% + phenylephrine 2.5%. No significant differences in blood pressure over baseline values. Cyclopentolate 0.2% + phenylephrine 1% was as safe as tropicamide 0.5% + phenylephrine 2.5%.[7]</p> <p>Bolt et al reported the mydriatic effect of the phenylephrine 2.5% (1 drop) + tropicamide 0.5% (2 drops) combination was superior to that of cyclopentolate 0.5% + tropicamide 0.5% (2 drops) combination.[8]</p> <p>Sindel et al reported that, on exposure to bright light, the pupillary size with phenylephrine 1.0% + tropicamide 1.0% was significantly smaller than phenylephrine 2.5% + tropicamide 1.0% or phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5%. Dialatation was sufficient to allow appropriate examination in all infants (pupillary diameter <math>&gt; 6.0</math> mm). Pulse and heart rate increased transiently in all groups receiving mydriatic but returned to baseline values in 25 minutes. This increase was significant in infants with 2.5% phenylephrine.[3]</p> |

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|  | <p>Nefendorf et al, in a cohort of 1246 eyes screened during 623 examinations of 138 infants, reported phenylephrine 2.5% + cyclopentolate 0.5% eye drops (3 times 5 minutes apart) was efficacious with 98.8% successful dilatation and well-tolerated although 0.8% had significant clinical deterioration in the following 24 hours.[5]</p> <p>Wheatcroft et al, in a controlled study comparing effects in each eye in 26 preterm infants, reported no difference in mydriasis from 5 microL versus 26 microL drops of cyclopentolate 0.5% and phenylephrine 2.5% (mean pupil diameter 6.05 mm [range 4.5 to 7.1 mm] in the eyes dilated with standard drops and 6.1 mm [range 5. 0 to 7.5 mm] in microdrop eyes).[11]</p> <p><b>Conclusions:</b> Phenylephrine 2.5% + cyclopentolate 0.5% (3 drops) produces adequate mydriasis in 98.8% of infants without side effects resulting in the need to discontinue examination. It is unclear if a reported 0.8% subsequent clinical deterioration in the next 24 hours is related to the use of mydriatics and examination.[5] [LOE IV GOR C] However, cyclopentolate 0.2% + phenylephrine 1% 3 drops provided adequate pupillary dilation with the least systemic side effects. [LOE II GOR B]</p> <p><b>Safety</b></p> <p>Caputo et al reported phenylephrine 10% causes skin blanching and elevation of heart rate and BP.[4] Ogut et al reported maximum side effects (increased heart rate and BP) were seen with 2.5% phenylephrine.[2] Chew et al reported combination cyclopentolate 1% + phenylephrine 2.5% and tropicamide 1% + phenylephrine 2.5% were associated with increased BP and cyclopentolate 1% + phenylephrine 2.5% may be associated with feed intolerance.[10] Nefendorf et al, in a cohort of 1246 eyes screened during 623 examinations of 138 infants, reported phenylephrine 2.5% + cyclopentolate 0.5% eye drops (3 times 5 minutes apart) was well-tolerated although 0.8% had significant clinical deterioration in the following 24 hours.[5]</p> <p>Feed intolerance [10], delayed gastric emptying [12], transient ileus [13], and necrotising enterocolitis [14, 15] have been reported in infants after administration of mydriatics, including phenylephrine. [LOE IV] Low quality evidence reported the incidence of feed intolerance may be reduced by withholding feeds for four hours after eye examination.[16] [LOE IV GOR C]</p> <p>Phenylephrine 2.5% (every 15 minutes for three drops) caused decreased pulmonary compliance, tidal volume and peak airflow values in infants with bronchopulmonary dysplasia but not in infants without pulmonary disease.[17] Bronchoconstriction after phenylephrine 2.5% + tropicamide 1% instillation was reported in premature infants with BDP.[18]</p> <p><b>Conclusion:</b> Combination eye drops containing phenylephrine 2.5% produce maximal mydriasis but produce acute physiological effects [2, 10]. [LOE II GOR B] Combination eye drops containing phenylephrine 1% produce adequate mydriasis with least physiological effect [7, 10]. [LOE II GOR B] Three drop regimens of combination eye drops were associated with more acute physiological effects and feed intolerance [7, 10]. [LOE II GOR B]</p> <p><b>Pharmacokinetics/pharmacodynamics</b></p> <p>In preterm infants receiving phenylephrine 2.5%, mean phenylephrine concentration at 10 minutes was 0.9 ng/mL after 8 microlitre drops and 1.9 ng/mL after 30 microlitre drops.[19] In contrast, in preterm infants receiving phenylephrine 1%, phenylephrine blood concentrations were below the lower limit of detection.[20]</p> <p>Combined 0.75% tropicamide + 2.5% phenylephrine resulted in a mean time to pupillary diameter 7 mm of 46 minutes.[21] Cyclopentolate 0.2% and phenylephrine 1% produced a response by 45 minutes, maximal mydriasis at 90 minutes with effect sustained for at least 120 minutes.[22]</p> <p>Approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by nasal mucosa without lacrimal sac</p> |
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|                   | occlusion.[23] In adults, duration of mydriasis is 3 to 8 hours. [24]   |
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**Authors Contribution**

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