

Enalapril

Newborn use only

2021

Alert	Avoid in preterm neonates until term corrected age for the treatment of hypertension due to concern of impaired kidney development, hyperkalaemia and acute kidney injury. (ANMF consensus) (1)
Indication	Hypertension - Calcium channel blockers (e.g. Amlodipine) or peripheral vasodilators (hydralazine) are better alternatives. Heart failure Congenital nephrotic syndrome - To reduce proteinuria. However, short acting angiotensin-converting enzyme inhibitor (ACEI) e.g. captopril is preferable (2)
Action	Angiotensin-converting enzyme inhibitor (ACEI). Hypertension: Several mechanisms of action: (1) inhibits formation of angiotensin II (2) decreases bradykinin degradation and (3) inhibits norepinephrine release from sympathetic nerve endings. All these effects produce significant vascular relaxation, reduction of after-load and improvement in cardiac output. Heart failure: Peripheral vasodilator - Reduces afterload by decreasing systemic vascular resistance (blood pressure (BP) and systemic vascular resistance) and preload (right atrial pressure and left ventricular filling pressure) and increases cardiac output. Proteinuria: The mechanism of the anti-proteinuric effect is not clearly understood. Reduction of systemic and intraglomerular pressures and improved size selectivity of glomerular basement membrane have been proposed.(3) Proteinuria reduction may also occur by a dose dependent hemodynamic effect on the efferent arteriole which can result additionally in reduction of glomerular filtration rate (GFR). (4)
Drug type	Angiotensin-converting enzyme inhibitor (ACEI).
Trade name	Renitec. Multiple other brands are available as tablets.
Presentation	Tablets: 5 mg, 10 mg and 20 mg. Oral suspension: 0.3 mg/mL or 1 mg/mL compounded by pharmacy in-house.
Dose	*Avoid in preterm neonates until term corrected age *Hypertension Starting dose: 0.04 mg/kg/day DAILY. Titrate the dose up to 0.1 mg/kg/day DAILY(5-7) *Heart failure Starting dose: 0.1 mg/kg/day in 1-2 divided doses. Increase as required over 2 weeks to 0.4 mg/kg/day in 1-2 divided doses.(8-10) *Proteinuria in steroid resistant nephrotic syndrome It is preferable to use short acting ACEI eg captopril. Discuss with nephrology first. Starting dose: 0.2 mg/kg/day in 2 divided doses. Increase the dose over 1-2 weeks to 0.5-0.6 mg/kg/day to achieve anti-proteinuric effect. Monitor potassium and creatinine levels closely. (3)
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment - If GFR > 50 mL/min/1.73m ² – No dose adjustment is needed. If GFR 10-50 mL/min/1.73m ² – 50% of recommended dose. (11) If GFR < 10 mL/min/1.73m ² – Avoid (ANMF consensus) Hepatic impairment – No studies to recommend dose adjustment but hepatic failure is known in adults.
Maximum dose	Hypertension: 0.1 mg/kg/day Heart failure: 0.4 mg/kg/day Proteinuria: 0.6 mg/kg/day
Total cumulative dose	Not applicable
Route	Oral
Preparation	Oral suspension: 0.3 mg/mL or 1 mg/mL compounded by pharmacy (15) Solution using 5 mg tablet: Disperse ONE tablet in 10 mL of water for injection to make 0.5 mg/mL. The tablet will disperse within 4 minutes. Mix well to obtain an even dispersion. Measure the desired dose and administer immediately. Prepare a fresh solution for each dose. (16)

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	<p>Solution using 10 mg tablet: Disperse ONE tablet in 20 mL of water for injection to make 0.5 mg/mL. The tablet will disperse within 4 minutes. Mix well to obtain an even dispersion. Measure the desired dose and administer immediately. Prepare a fresh solution for each dose. (16)</p> <p>20 mg tablet: Disperse ONE tablet in 40 mL of water for injection to make 0.5 mg/mL. The tablet will disperse within 4 minutes. Mix well to obtain an even dispersion. Measure the desired dose and administer immediately. Prepare a fresh solution for each dose.</p>
Administration	Administer orally without regard to feeds
Monitoring	<p>Close monitoring of blood pressure –</p> <p style="padding-left: 20px;">BP is measured at 10 minute intervals for 30-40 minutes following the first dose and 15 and 30 minutes following the first dose of any increase in dosage.</p> <p style="padding-left: 20px;">BP is monitored twice daily once a maintenance dose is achieved.</p> <p>Regular monitoring of serum potassium and creatinine(1)</p> <p>White cell count (neutropenia)</p> <p>Watch for angioedema</p> <p>In nephrotic syndrome: Weekly monitoring of urine albumin/creatinine ratio(3)</p>
Contraindications	<p>Severe renal impairment</p> <p>Hypersensitivity to enalapril or components of the formulation</p> <p>Angioedema</p> <p>Preterm neonates until term corrected age, because of impaired nephrogenesis risk (ANMF consensus) (1)</p>
Precautions	<p>Neutropenia</p> <p>Renal impairment</p>
Drug interactions	<p>ACE-inhibitors will increase the effect of diuretics.</p> <p>Combination of ACE inhibitor, diuretic and NSAID may precipitate acute renal failure</p> <p>Drugs which increase potassium level (e.g. spironolactone) – risk of hyperkalaemia</p> <p>Antihypertensive medications in combination with enalapril will increase risk of hypotension.</p>
Adverse reactions	<p>Hypotension</p> <p>Neutropenia, agranulocytosis</p> <p>Hyperkalaemia, raised serum creatinine and renal failure(2, 3)</p> <p>Angioedema and anaphylaxis</p> <p>Hepatic impairment</p> <p>Isolated dry cough in children(5)</p>
Compatibility	Not applicable
Incompatibility	Not applicable
Stability	<p>0.3 mg/mL oral suspension: 30 day expiry</p> <p>1 mg/mL oral suspension: 91 day expiry (15)</p> <p>Tablet dispersed in water: Prepare a fresh solution for each dose. Discard unused portion.</p>
Storage	<p>0.3 mg/mL and 1 mg/mL compounded oral suspension: Store 2-8°C</p> <p>Tablets: Store below 30°C</p>
Excipients	<p>Compounded oral suspension: Check with hospital pharmacy.</p> <p>Tablet – Renitec brand: Sodium bicarbonate, lactose monohydrate, maize starch, pregelatinised maize starch, magnesium stearate, iron oxide red (10 mg and 20 mg Renitec tablets only), iron oxide yellow (20 mg Renitec tablets only).</p>
Special comments	
Evidence	<p>Efficacy</p> <p>Hypertension</p> <p>There are no prospective trials on enalapril in term and preterm infants with hypertension. A retrospective case series reported on the adverse effects of enalapril in preterm and term neonates in the first 120 days of life in 348 neonatal intensive care units from 1997 to 2012. The median postnatal age at first exposure was 25 days, with a median duration of exposure of 3 days. Approximately 20% develop adverse effects. The most common adverse event was hyperkalaemia (13%), followed by elevated serum creatinine (5%), hypotension (4%), and death (0.5%). They did not report on the dosage administered in this cohort.(12) A double blind, randomised dose-response trial in hypertensive</p>

	<p>children 6-16 years of age suggests a mean dose of 0.08 mg/kg once daily effectively lowered blood pressure within 2 weeks in most children. No neonates or infants were included in this trial.(7) A dose of 0.1 mg/kg daily led to acute renal failure in a neonate.(5)</p> <p>Heart failure</p> <p>Leversha et al 1994 reported the efficacy and safety of 63 paediatric patients with congestive heart failure. Median age was 5.4 months. Haemodynamic groups were left-to-right shunt (n = 15), impaired ventricular function (n = 14), after cardiac surgery (n = 23), valvar regurgitation (n = 12), and hypertension (n = 3). The mean (SD) maximal dose was 0.30 (0.21) mg/kg/day. Thirty nine (58%) patients improved, 20 (30%) showed no improvement, and eight (12%) had side effects requiring discontinuation of enalapril. Renal failure was a problem in young infants with left-to-right shunts. The dose that was found to be effective in the study was 0.36 mg/kg/day.(10) The Pediatric Heart Network conducted a double-blind trial involving 230 infants with single-ventricle physiology. Infants were randomised to receive enalapril (target dose 0.4 mg/kg/day) or placebo who were followed up until 14 months of age. The primary end point was weight-for-age z score at 14 months. Weight-for-age z score was not different between the enalapril and placebo groups. There were no significant group differences in height-for-age z score, Ross heart failure class, brain natriuretic peptide concentration, Bayley scores of infant development, or ventricular ejection fraction. The incidence of death or transplantation was 13% and did not differ between groups. Serious adverse events occurred in 88 patients in the enalapril group and 87 in the placebo group. In this trial, administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function, or heart failure severity. (8) Jovanovich et al 2018 reviewed the studies on use of ACEI in children with heart failure and found the dose of enalapril among the studies ranged from 0.02 mg/kg/day to 1.8 mg/kg/day and for up to 3 years. This review found that ACEIs were tolerated by children but common side effects were renal impairment, hypotension and hyperkalaemia.(9) In 2014, the International Society of Heart and Lung Transplantation made recommendation on the management of paediatric heart failure: (a) ACEIs are recommended in paediatric patients with heart failure with left ventricular systolic dysfunction; (b) ACEIs should not be routinely instituted for all patients with single-ventricle, but could be considered in specific cases such as in situations of valve regurgitation or ventricular dysfunction; (c) ACEI therapy should be started at low doses with a subsequent up-titration to the target dose with careful monitoring of blood pressure, renal function, and serum potassium.(13)</p> <p>Steroid resistant nephrotic syndrome (SRNS)</p> <p>A meta-analysis in adult population found that therapy with ACE inhibitors resulted in a 40% reduction in proteinuria.(14) Bagga et al, in a prospective study in children (1-16 years of age), examined the antiproteinuric efficacy of low- and high-dose enalapril in children with SRNS. Low dose regimen consisted of 0.2 mg/kg/day for 8 weeks, then 2-week wash out period followed by high dose 0.6 mg/kg/day for another 8 weeks. High dose regimen consisted of 0.6 mg/kg/day for 8 weeks, then 2-week wash out period followed by low dose 0.2 mg/kg/day for another 8 weeks. Treatment 0.6 mg/kg per day resulted in an almost two-fold higher Ua/Uc percentage reduction compared with 0.2 mg/kg per day.(3)</p> <p>Pharmacokinetics</p> <p>Enalapril is an inactive form and gets converted to the active form, enalaprilat in liver. Wells and colleagues (2) also investigated the pharmacokinetic effects of enalapril in infants and children. Forty children with hypertension between the age of 2 months and 15 years were studied. In infants younger than 6 months of age, an oral dose of 0.15 mg/kg in a single daily dose was used. Enalapril seems to be safe and effective in neonates with a normal renal function (2).</p>
Practice points	
References	<ol style="list-style-type: none"> 1. Flynn JT, editor The hypertensive neonate. Seminars in Fetal and Neonatal Medicine; 2020: Elsevier. 2. Boyer O, Schaefer F, Haffner D, Bockenbauer D, Hölltä T, Bérody S, et al. Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group. Nature Reviews Nephrology. 2021;17(4):277-89. 3. Bagga A, Mudigoudar BD, Hari P, Vasudev V. Enalapril dosage in steroid-resistant nephrotic syndrome. Pediatric Nephrology. 2004;19(1):45-50.

	<ol style="list-style-type: none"> 4. Heeg JE de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. <i>Kidney international</i>. 1987;32(1):78-83. 5. Dutta S, Narang A. Enalapril-induced acute renal failure in a newborn infant. <i>Pediatric Nephrology</i>. 2003;18(6):570-2. 6. Schilder JL, Van den Anker JN. Use of enalapril in neonatal hypertension. <i>Acta Paediatrica</i>. 1995;84(12):1426-8. 7. Wells T, Frame V, Soffer B, Shaw W, Zhang Z, Herrera P, et al. A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of enalapril for children with hypertension. <i>The Journal of Clinical Pharmacology</i>. 2002;42(8):870-80. 8. Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. <i>Circulation</i>. 2010;122(4):333-40. 9. Jovanovic I, Lagler F, Kingmann I, Laer S, de Wildt S. How safe are ACE inhibitors for heart failure in children? <i>Children with Dilated Cardiomyopathy</i>. 2018;103(1):97. 10. Leversha AM, Wilson NJ, Clarkson PM, Calder AL, Ramage MC, Neutze JM. Efficacy and dosage of enalapril in congenital and acquired heart disease. <i>Archives of Disease in Childhood</i>. 1994;70(1):35-9. 11. Paediatric Renal Dosing. Dosing guidance for pediatric renal patients. US Kidney disease website. Accessed on 14 October 2021. 12. Ku LC, Zimmerman K, Benjamin DK, Clark RH, Hornik CP, Smith PB. Safety of Enalapril in infants admitted to the neonatal intensive care unit. <i>Pediatric cardiology</i>. 2017;38(1):155-61. 13. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. <i>The Journal of Heart and Lung Transplantation</i>. 2014;33(9):888-909. 14. Gansevoort R, Sluiter W, Hemmelder M, De Zeeuw D, De Jong P. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. <i>Nephrology Dialysis Transplantation</i>. 1995;10(11):1963-74. 15. Nahata MC and Pai VB. <i>Pediatric Drug Formulations 7th Edition</i> 2018. 16. Australian Don't Rush to Crush Handbook. Third Edition. Published by The Society of Hospital Pharmacists of Australia. Accessed on 17 November 2021.
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