

Vitamins in cholestasis

Newborn use only

2022

Alert	The dose recommendations for cholestasis are based on expert opinion. International units (IU) are labelled as units in this formulary. Bio-Logical Vitamin A oral solution and OsteVit D oral liquid contains sodium benzoate. Avoid exposure of >99mg/kg/day in neonates.					
Indication	Neonatal cholestasis					
Action	Vitamin A: Fat soluble vitamin required for vision, growth and bone development, immune function and maintenance of epithelial cells particularly in the retina and respiratory tract tissues. Vitamin D: Regulating levels of calcium and phosphorus and mineralisation of bone. Vitamin E: Antioxidant protecting cell membranes from oxidative stress. Active isomer is α-tocopherol. Vitamin K: Promotes the activation of blood coagulation Factors II, VII, IX and X in the liver.					
Drug type	Fat and water soluble vitamins					
Trade name	Pentavite Infant liquid 0-3 years Bio-Logical Vitamin A oral solution Ostelin Vitamin-D3 1000 IU liquid Pretorius Micel-E oral liquid Konakion MM Paediatric					
Presentation	Pentavite Infant – Each 0.45 mL contains 1287 units of vitamin A and 400 units of vitamin D. Bio-Logical Vitamin A oral solution – 0.1 mL contains 2500 units of vitamin A. Ostelin Vitamin -D (Vitamin D3) oral liquid – 0.5 mL contains 1000 units of vitamin D. Pretorius Micel-E oral liquid – 0.1 mL contains 15.6 units of vitamin E. Konakion MM Paediatric – 0.2 mL contains 2 mg vitamin K ₁ .					
Dose	Suggested starting regimen ⁽¹⁻⁴⁾					
		Vitamin A	Vitamin D	Vitamin E	Vitamin K ₁	
	Dose range per day (not per kg)	3000-5000 units	1000-2000 units (25-50 µg)	15-30 units	2 mg twice a week up to 2 mg daily	
	Medical officers to prescribe the following		Dose Range			
	Vitamins	Oral preparation	Vitamin A (units)	Vitamin D (units)	Vitamin E (units)	Vitamin K ₁ (mg)
		Dose (mL) and Frequency				
	Pentavite Infant	0.45 mL once or twice daily	1287-2574	400-800 (10-20 µg)	-	-
	Bio-Logical Vitamin A solution	0.1 mL daily*	2500	-	-	-
	Ostelin Vitamin-D oral liquid 1000 units/0.5 mL [#]	0.5 mL daily*	-	1000 (25 µg)	-	-
	Pretorius Micel-E liquid	0.1-0.2 mL daily*	-	-	15-30	-
Konakion MM Paediatric	0.2 mL twice a week to daily	-	-	-	2 mg twice a week to 2 mg daily	
		Total	3787-5074	1400-1800 (35-45 µg)	15-30	2 mg twice a week to 2 mg daily
*The daily dose may be administered in two divided doses. [#] Ostelin Vitamin-D is the preferred liquid because it doesn't contain sodium benzoate. Please check the strengths in each preparation before prescribing.						
Dose adjustment	Not applicable					
Maximum dose						

Total cumulative dose																										
Route	Oral																									
Preparation	No preparation is required																									
Administration	Administer undiluted or with a feed																									
Monitoring	Check serum levels of vitamins A, D, E and PT/INR in 1-3 monthly. May need more frequent monitoring in the initial weeks of therapy.																									
Contraindications	Hypersensitivity to vitamin A, D, E, K or any component of the formulations. Hypervitaminosis of A, E and/or D.																									
Precautions																										
Drug interactions	May increase effects of anticoagulant and antiplatelet agents																									
Adverse reactions	Hypervitaminosis A: Irritability, lethargy, vomiting, bulging fontanelle. Hypervitaminosis D: Hypercalcaemia, nephrocalcinosis. Vitamin E: Potentiation of coagulopathy, sepsis, necrotising enterocolitis.																									
Compatibility	Not applicable																									
Incompatibility	Not applicable																									
Stability	Pentavite Infant liquid: Use within 9 weeks after opening. Other vitamins: Refer to individual product information.																									
Storage	All products: Store below 25°C. Protect from light. Pentavite Infant liquid: Refrigerate after opening.																									
Excipients	Pentavite Infant liquid: sodium saccharin, pineapple flavour. Bio-Logical Vitamin A oral solution: sodium benzoate. OsteVit-D oral liquid: sodium benzoate, caramel flavour. Pretorius Micel-E oral liquid: Potassium sorbate and soy bean products. Konakion MM Paediatric: Glycocholic acid, lecithin, sodium hydroxide, hydrochloric acid.																									
Special comments	Vitamin E 1 unit = 0.67 mg α-tocopherol. 1 mg of retinyl palmitate = 1818 units of vitamin A.																									
Evidence	Background There is a high prevalence of vitamin deficiency in neonatal cholestasis, with one study reporting rates of deficiency for vitamin E (71%), vitamin D (61%), vitamin A (29%) and vitamin K (13%).⁽³⁾ Fat-soluble vitamin serum levels should be monitored frequently in all cholestatic infants to avoid life threatening bleeding (vitamin K deficiency), bone fractures and rickets (vitamin D deficiency), corneal/retinal defects and blindness (vitamin A deficiency), and neurologic and muscular abnormalities (vitamin E deficiency).⁽⁵⁾ Efficacy Dosing recommendations for vitamins in neonatal cholestasis vary and are based on expert opinions.⁽¹⁻⁴⁾ Many infants will require individual supplementation of vitamins D, A, E, or K, along with the preferred multivitamin formulation.⁽⁵⁾ Dosing recommendations for fat soluble vitamins are as follows: <table><tr><th>Author</th><th>Vitamin A</th><th>Vitamin D</th><th>Vitamin E</th><th>Vitamin K</th></tr><tr><td>Feldman⁽⁴⁾</td><td>3000-10000 U/day</td><td>800-5000 IU/day OR 1,25 OH₂ D3: 0.05-0.2 µg/kg/day</td><td>Maintain serum targets. No dose recommendations.</td><td>2.5- 5 mg twice a week to every day</td></tr><tr><td>Italian society⁽¹⁾</td><td>5000-25000 IU/day</td><td>800-5000 U/day</td><td>15-25 U/kg/day</td><td>2.5-5 mg twice a week to every day</td></tr><tr><td>King’s college, London⁽³⁾</td><td>1333-5000 IU/day</td><td>1000-3000 IU/day</td><td>15-150 U/kg/day</td><td>1 mg/day</td></tr><tr><td>Lane et al.⁽²⁾</td><td>5000-50000 IU/day</td><td>1000-8000 IU/day</td><td>1 unit/kg/day</td><td>ORAL:2.5-5 mg IM/SQ/IV: 1-10 mg/dose</td></tr></table> Optimal approach would be to adjust the doses based on target serum levels. Refer to practice points. Safety Excessive doses of vitamins can lead to adverse effects listed in adverse reactions.⁽¹⁾	Author	Vitamin A	Vitamin D	Vitamin E	Vitamin K	Feldman ⁽⁴⁾	3000-10000 U/day	800-5000 IU/day OR 1,25 OH ₂ D3: 0.05-0.2 µg/kg/day	Maintain serum targets. No dose recommendations.	2.5- 5 mg twice a week to every day	Italian society ⁽¹⁾	5000-25000 IU/day	800-5000 U/day	15-25 U/kg/day	2.5-5 mg twice a week to every day	King’s college, London ⁽³⁾	1333-5000 IU/day	1000-3000 IU/day	15-150 U/kg/day	1 mg/day	Lane et al. ⁽²⁾	5000-50000 IU/day	1000-8000 IU/day	1 unit/kg/day	ORAL:2.5-5 mg IM/SQ/IV: 1-10 mg/dose
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Practice points	Aim to maintain the normal range of serum vitamin A, E and D levels. Reference values may vary. Check with your local laboratory. Published recommendations of INR ≤ 1.2 is often not possible in practice despite high doses of vitamin K. Higher INR values are often accepted as long as there is no clinical evidence of coagulation dysfunction.
References	1. Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. Italian Journal of Pediatrics. 2015; 41:1-12. 2. Lane E, Murray KF. Neonatal cholestasis. Pediatric Clinics. 2017;64:621-39. 3. Mancell S, Islam M, Dhawan A, Whelan K. Fat-soluble vitamin assessment, deficiency and supplementation in infants with cholestasis. Journal of Human Nutrition and Dietetics. 2022; 35:273-9. 4. Feldman AG, Sokol RJ. Neonatal cholestasis. Neoreviews. 2013;14(2):e63-e73. 5. Feldman AG, Sokol RJ. Neonatal Cholestasis: Updates on Diagnostics, Therapeutics, and Prevention. NeoReviews. 2021;22:e819-e36.

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