

# Vitamins in cholestasis

## Newborn use only

2022

<b>Alert</b>	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.																																																																			
<b>Indication</b>	Correcting vitamin deficiencies in neonatal cholestasis																																																																			
<b>Action</b>	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 $\alpha$ -tocopherol. Vitamin K: Promotes the activation of blood coagulation Factors II, VII, IX and X in the liver.																																																																			
<b>Drug type</b>	Fat and water soluble vitamins																																																																			
<b>Trade name</b>	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																																																																			
<b>Presentation</b>	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 <sub>1</sub> .																																																																			
<b>Dose</b>	<p><b>Suggested starting regimen<sup>(1-4)</sup></b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">Vitamin A</th> <th style="text-align: center;">Vitamin D</th> <th style="text-align: center;">Vitamin E</th> <th style="text-align: center;">Vitamin K<sub>1</sub></th> </tr> </thead> <tbody> <tr> <td><b>Dose range per day (not per kg)</b></td> <td style="text-align: center;">3000-5000 units</td> <td style="text-align: center;">1000-2000 units (25-50 <math>\mu</math>g)</td> <td style="text-align: center;">15-30 units</td> <td style="text-align: center;">2 mg twice a week up to 2 mg daily</td> </tr> </tbody> </table> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2" style="text-align: left;">Medical officers to prescribe the following</th> <th colspan="4" style="text-align: center;">Dose Range</th> </tr> <tr> <th style="text-align: center;">Vitamins</th> <th style="text-align: center;">Oral preparation</th> <th style="text-align: center;">Vitamin A (units)</th> <th style="text-align: center;">Vitamin D (units)</th> <th style="text-align: center;">Vitamin E (units)</th> <th style="text-align: center;">Vitamin K<sub>1</sub> (mg)</th> </tr> <tr> <th colspan="2"></th> <th colspan="4" style="text-align: center;">Dose (mL) and Frequency</th> </tr> </thead> <tbody> <tr> <td>Pentavite Infant</td> <td>0.45 mL once or twice daily</td> <td style="text-align: center;">1287-2574</td> <td style="text-align: center;">400-800 (10-20 <math>\mu</math>g)</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Bio-Logical Vitamin A solution</td> <td>0.1 mL daily*</td> <td style="text-align: center;">2500</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Ostelin Vitamin-D oral liquid 1000 units/0.5 mL<sup>#</sup></td> <td>0.5 mL daily*</td> <td style="text-align: center;">-</td> <td style="text-align: center;">1000 (25 <math>\mu</math>g)</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Pretorius Micel-E liquid</td> <td>0.1-0.2 mL daily*</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">15-30</td> <td style="text-align: center;">-</td> </tr> <tr> <td>Konakion MM Paediatric</td> <td>0.2 mL twice a week to daily</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">-</td> <td style="text-align: center;">2 mg twice a week to 2 mg daily</td> </tr> <tr> <td colspan="2" style="text-align: right;">Total</td> <td style="text-align: center;">3787-5074</td> <td style="text-align: center;">1400-1800 (35-45 <math>\mu</math>g)</td> <td style="text-align: center;">15-30</td> <td style="text-align: center;">2 mg twice a week to 2 mg daily</td> </tr> </tbody> </table> <p>*The daily dose may be administered in two divided doses.  <sup>#</sup>Ostelin Vitamin-D is the preferred liquid because it doesn't contain sodium benzoate. Please check the strengths in each preparation before prescribing.</p>					Vitamin A	Vitamin D	Vitamin E	Vitamin K <sub>1</sub>	<b>Dose range per day (not per kg)</b>	3000-5000 units	1000-2000 units (25-50 $\mu$ g)	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 <sub>1</sub> (mg)			Dose (mL) and Frequency				Pentavite Infant	0.45 mL once or twice daily	1287-2574	400-800 (10-20 $\mu$ g)	-	-	Bio-Logical Vitamin A solution	0.1 mL daily*	2500	-	-	-	Ostelin Vitamin-D oral liquid 1000 units/0.5 mL <sup>#</sup>	0.5 mL daily*	-	1000 (25 $\mu$ g)	-	-	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 $\mu$ g)	15-30	2 mg twice a week to 2 mg daily
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<b>Route</b>	Oral																									
<b>Preparation</b>	No preparation is required																									
<b>Administration</b>	Administer undiluted or with a feed																									
<b>Monitoring</b>	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.																									
<b>Contraindications</b>	Hypersensitivity to vitamin A, D, E, K or any component of the formulations. Hypervitaminosis of A, E and/or D.																									
<b>Precautions</b>																										
<b>Drug interactions</b>	May increase effects of anticoagulant and antiplatelet agents																									
<b>Adverse reactions</b>	Hypervitaminosis A: Irritability, lethargy, vomiting, bulging fontanelle. Hypervitaminosis D: Hypercalcaemia, nephrocalcinosis. Vitamin E: Potentiation of coagulopathy, sepsis, necrotising enterocolitis.																									
<b>Compatibility</b>	Not applicable																									
<b>Incompatibility</b>	Not applicable																									
<b>Stability</b>	Pentavite Infant liquid: Use within 9 weeks after opening. Other vitamins: Refer to individual product information.																									
<b>Storage</b>	All products: Store below 25°C. Protect from light. Pentavite Infant liquid: Refrigerate after opening.																									
<b>Excipients</b>	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.																									
<b>Special comments</b>	Vitamin E 1 unit = 0.67 mg $\alpha$ -tocopherol. 1 mg of retinyl palmitate = 1818 units of vitamin A.																									
<b>Evidence</b>	<p><b>Background</b></p> <p>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%).<sup>(3)</sup> 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).<sup>(5)</sup></p> <p><b>Efficacy</b></p> <p>Dosing recommendations for vitamins in neonatal cholestasis vary and are based on expert opinions.<sup>(1-4)</sup> Many infants will require individual supplementation of vitamins D, A, E, or K, along with the preferred multivitamin formulation.<sup>(5)</sup></p> <p>Dosing recommendations for fat soluble vitamins are as follows:</p> <table border="1" style="width: 100%; border-collapse: collapse; margin: 10px 0;"> <thead> <tr> <th style="width: 15%;">Author</th> <th style="width: 20%;">Vitamin A</th> <th style="width: 20%;">Vitamin D</th> <th style="width: 20%;">Vitamin E</th> <th style="width: 25%;">Vitamin K</th> </tr> </thead> <tbody> <tr> <td>Feldman<sup>(4)</sup></td> <td>3000-10000 U/day</td> <td>800-5000 IU/day OR 1,25 OH<sub>2</sub> D<sub>3</sub>: 0.05-0.2 <math>\mu</math>g/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<sup>(1)</sup></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<sup>(3)</sup></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.<sup>(2)</sup></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> </tbody> </table> <p>Optimal approach would be to adjust the doses based on target serum levels. Refer to practice points.</p> <p><b>Safety</b></p> <p>Excessive doses of vitamins can lead to adverse effects listed in adverse reactions.<sup>(1)</sup></p>	Author	Vitamin A	Vitamin D	Vitamin E	Vitamin K	Feldman <sup>(4)</sup>	3000-10000 U/day	800-5000 IU/day OR 1,25 OH <sub>2</sub> D <sub>3</sub> : 0.05-0.2 $\mu$ g/kg/day	Maintain serum targets. No dose recommendations.	2.5- 5 mg twice a week to every day	Italian society <sup>(1)</sup>	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 <sup>(3)</sup>	1333-5000 IU/day	1000-3000 IU/day	15-150 U/kg/day	1 mg/day	Lane et al. <sup>(2)</sup>	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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<b>Practice points</b>	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 $\leq 1.2$ 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.
<b>References</b>	<ol style="list-style-type: none"> <li>1. Dani C, Pratesi S, Raimondi F, Romagnoli C. Italian guidelines for the management and treatment of neonatal cholestasis. <i>Italian Journal of Pediatrics</i>. 2015;41:1-12.</li> <li>2. Lane E, Murray KF. Neonatal cholestasis. <i>Pediatric Clinics</i>. 2017;64:621-39.</li> <li>3. Mancell S, Islam M, Dhawan A, Whelan K. Fat-soluble vitamin assessment, deficiency and supplementation in infants with cholestasis. <i>Journal of Human Nutrition and Dietetics</i>. 2022;35:273-9.</li> <li>4. Feldman AG, Sokol RJ. Neonatal cholestasis. <i>Neoreviews</i>. 2013;14(2):e63-e73.</li> <li>5. Feldman AG, Sokol RJ. Neonatal Cholestasis: Updates on Diagnostics, Therapeutics, and Prevention. <i>NeoReviews</i>. 2021;22:e819-e36.</li> </ol>

VERSION/NUMBER	DATE
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