

# Lactulose

## Newborn use only

2022

<b>Alert</b>	Lactulose is not the first line therapy to treat constipation in neonates. Do not use lactulose in infants with body weight <2000 g without the consent of the neonatologist/paediatrician in-charge. Quality of evidence of lactulose in neonates is very low. Dose in this formulary is extrapolated from infants and children. <sup>(1, 2)</sup> Laxative use at an early age has been associated with allergic disease development in later life. <sup>(3)</sup>
<b>Indication</b>	Functional constipation
<b>Action</b>	Osmotic laxative. Lactulose is a semisynthetic disaccharide made from lactose. It is used for constipation and hepatic encephalopathy in adults and children. It also has prebiotic properties and the addition of low doses to infant formula changes the composition of the colonic microflora similar to breastfed infants ("the bifidus factor"). <sup>(4)</sup>
<b>Drug type</b>	Laxative
<b>Trade name</b>	Actilax, Duphalac, Dulose, GenRx Lactulose
<b>Presentation</b>	Actilax solution 3.3 g/5 mL Duphalac solution 10 g/15 mL Dulose oral liquid 3.3 g/5 mL GenRx Lactulose syrup 3.3 g/5 mL
<b>Dose</b>	1 mL/kg to a maximum of 5 mL once daily* (ANMF consensus). <sup>(1, 2)</sup> Large daily dose may be given in 2 divided doses. <b>*Do not use in infants with body weight &lt;2000 g without the consent of the neonatologist/paediatrician in-charge.</b>
<b>Dose adjustment</b>	No information
<b>Maximum dose</b>	5 mL daily
<b>Total cumulative dose</b>	
<b>Route</b>	Oral
<b>Preparation</b>	No preparation is required
<b>Administration</b>	Administer undiluted, preferably mixed with feeds
<b>Monitoring</b>	Loose stools, abdominal cramps, serum electrolytes
<b>Contraindications</b>	Gastrointestinal obstruction. Hirschsprung's disease. Galactosaemia. Disaccharide deficiency. Infants on galactose or lactose free diet.
<b>Precautions</b>	Use with caution in patients with diabetes mellitus. Concomitant use with antibiotics (may lead to diarrhoea).
<b>Drug interactions</b>	Lactulose increases effect of warfarin
<b>Adverse reactions</b>	Gaseous distension Flatulence Intestinal cramps Loose stools, dehydration and hyponatraemia Chronic misuse of laxatives may result in electrolyte imbalance, in particular serum potassium levels may be decreased. Loss of effectiveness with prolonged usage.
<b>Compatibility</b>	Not applicable
<b>Incompatibility</b>	Not applicable
<b>Stability</b>	Discard solution if dark or cloudy
<b>Storage</b>	Store below 25°C. Protect from light.
<b>Excipients</b>	No excipients, but lactulose contains lactulose and other sugars including lactose, galactose, tagatose and epilactose. Also contains sulfites <sup>(2)</sup>

<b>Special comments</b>	
<b>Evidence</b>	<p><b>Background</b> Osmotic laxatives draw water into the stool, resulting in softer stools and more frequent, easier to pass bowel movements. Some commonly used laxatives in children are polyethylene glycol (PEG), lactulose and milk of magnesia.<sup>(5)</sup> Administration of low doses of lactulose to infants fed with cow's milk produces a predominance of lactobacilli in the stools, thus simulating the intestinal flora following maternal milk feeding. Lactulose also appears to increase the production of lysosome in infants receiving cow's milk.<sup>(4)</sup></p> <p><b>Efficacy</b> There are no controlled trials evaluating the efficacy of lactulose for constipation in neonates. However, there was a pilot randomised controlled trial evaluating a low dose (1% lactulose) to assess the prebiotic effect of lactulose in 28 preterm infants. Preterm infants on lactulose had more Lactobacilli-positive stool cultures. The lactulose group tended to have less intolerance to enteral feedings, to reach full oral feeds earlier, and to be discharged home earlier. They also tended to have fewer episodes of late-onset sepsis, lower Bell stage necrotizing enterocolitis, and their nutritional laboratory indices were better, especially calcium and total protein.<sup>(4)</sup> A Cochrane review by Gordon et al. evaluated the efficacy and safety of osmotic and stimulant laxatives in childhood constipation. Study population in this review was mostly beyond the neonatal age group. Out of 25 RCTs included in this review, 13 trials used lactulose as one of the interventions. Studies were extremely heterogenous with different study agents and a variety of treatment regimens making it difficult to draw strong conclusions for any of the agents. There was no trial comparing lactulose with placebo. Trials comparing lactulose with other agents including polyethylene glycol (e.g. macrogol in Movicol), milk of magnesia, liquid paraffin, dietary fibre mix did not find lactulose statistically superior to any of these agents.<sup>(5)</sup></p> <p><b>Dose:</b> European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) performed systematic literature search and made recommendations on the management of functional constipation children. The committee recommended a dose of 1-2 g/kg, once or twice a day and this dose was NOT neonate specific.<sup>(1)</sup> Commercially available preparations in Australia contain 0.66 g/1 mL. ANMF consensus was to recommend a pragmatic dose of 1 mL/kg to a maximum of 5 mL daily.</p> <p><b>Safety</b> Lactulose seems well tolerated in preterm neonates with no major adverse effects.<sup>(4)</sup> A nationwide matched cohort study of Taiwanese children found an association between early life laxative exposure within the first 6 months of life and subsequent allergic disease development in all subgroups of children, including those born to mothers without allergic diseases or prenatal laxative use.<sup>(3)</sup></p> <p><b>Pharmacokinetics</b> Lactulose is not absorbed by the small intestine. Lactulose reaches the colon virtually unchanged. It is metabolised by colonic bacteria to low molecular weight acids i.e. lactic acid and other short chain carboxylic acids.<sup>(2)</sup></p>
<b>Practice points</b>	
<b>References</b>	<ol style="list-style-type: none"> <li>1. Tabbers M, DiLorenzo C, Berger M, Faure C, Langendam M, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. <i>Journal of Pediatric Gastroenterology and Nutrition.</i> 2014;58(2):258-74.</li> <li>2. Actilax. MIMS online. Accessed on 30 May 2022.</li> <li>3. Lin TL, Wu CY, Fan YH, Chang YL, Ho HJ, Chen YJ. Association between early life laxative exposure and risk of allergic diseases. A nationwide matched cohort study. <i>Ann Allergy Asthma Immunol.</i> 2022;128(3):291-8.e3.</li> <li>4. Riskin A, Hochwald O, Bader D, Sruogo I, Naftali G, Kugelman A, et al. The effects of lactulose supplementation to enteral feedings in premature infants: A pilot study. <i>Journal of Pediatrics.</i> 2010;156(2):209-14.</li> </ol>

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|  | 5. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database of Systematic Reviews. 2016(8):CD009118. |
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