

Bifidobacterium breve M-16V

Newborn use only

2020

Alert	Unregistered product in Australia. Must be prescribed by TGA Special Access Scheme or via Authorised Prescriber Pathway, after obtaining parental consent. <i>Bifidobacterium breve M-16V (B. breve M-16V)</i> has not yet been shown in RCTs to reduce NEC or sepsis. The safety and efficacy for other populations of infants at risk of NEC, sepsis or feed intolerance including infants with asphyxia, undergoing exchange transfusion, abdominal surgical conditions and congenital heart disease have not been assessed in clinical studies.
Indication	1. Preterm neonates < 32 weeks gestation or < 1800 g birth weight: For prevention of necrotising enterocolitis (NEC), late-onset sepsis, mortality and reduction in time to reach full feeds.[1-3] 2. Small for gestational age preterm neonates with abnormal umbilical artery Doppler for prevention of NEC and reduction in time to reach full feeds. [1, 4]
Action	Promotes colonisation of the gut with beneficial organisms, preventing colonisation by pathogens, improving the maturity and function of gut mucosal barrier, and modulating the immune system to the advantage of the host. [5]
Drug type	Probiotic bacteria
Trade name	Morinaga Bifidus M-16V
Presentation	1.0–1.2 g powder per sachet containing more than 1 billion <i>B. breve M-16V</i> per sachet at the end of shelf life.[6]
Dose	½ sachet twice a day to commence soon after birth irrespective of the feeds and continue until discharge [14] or considered no longer at risk of NEC.
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – Not applicable. Renal impairment – No information. Hepatic impairment – No information.
Maximum dose	1 sachet
Total cumulative dose	
Route	Oral Intragastric
Preparation	Dissolve ONE sachet in 2 mL of mother’s EBM/donor human milk/water for injection/formula. Draw up required volume (1 mL for ½ sachet and 2 mL for 1 sachet).
Administration	Oral: Administer prescribed amount with or without food. Discard unused portion.
Monitoring	Not applicable.
Contraindications	No known contraindications.
Precautions	Administration of the probiotics may be discontinued during periods when the integrity of the gut mucosa is considered compromised. The common scenarios include intestinal perforation, severe sepsis, critical illness, bile aspirates, NEC and surgical gut anomalies.[7] No efficacy or safety data available on use of probiotics in infants after definite NEC.
Drug interactions	None reported.
Adverse reactions	Rare. Probiotic sepsis has been reported in preterm neonates with surgical conditions, immune suppression and when gut barrier is compromised. [7].
Compatibility	No data available/ not applicable
Incompatibility	No data available/ not applicable
Stability	<i>Bifidobacterium breve M-16V</i> is particularly heat sensitive, so once the sachet is open it should be used immediately.
Storage	Store at room temperature.
Excipients	
Special comments	The intestinal barrier could be compromised during severe sepsis and critical illness. Probiotics may be discontinued in the initial stages of severe late onset sepsis, suspected NEC or critical illness.[7]
Evidence	Probiotics Several systematic reviews and randomised, controlled trials have shown that enteral probiotics significantly reduce the risk of NEC (≥ stage II), late-onset sepsis, all-cause mortality and time to full enteral feeds. [1-3] (LOE 1, GOR A) Multiple strains of probiotics may be more effective in preventing NEC and mortality than single strains. [8] (LOE I, GOR B) Probiotics for prevention of NEC in preterm infants: Enteral probiotic supplementation significantly reduced the incidence of severe NEC (RR 0.43, 95% CI 0.33 to 0.56; 20 studies, 5529 infants) and mortality

	<p>(typical RR 0.65, 95% CI 0.52 to 0.81; 17 studies, 5112 infants). The included trials reported no systemic infection with the supplemental probiotics organism. Conclusions: Enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants. [1, 2, 8] (LOE I GOR A)</p> <p>Probiotics for prevention of late onset sepsis (LOS) in preterm infants: Enteral probiotics supplementation significantly reduced the incidence of LOS (37 RCTs, 9416 infants; 13.9% vs 16.3%; RR 0.86; 95% CI 0.78–0.94; P = 0.0007; NNT 44). [2, 3] (LOE I GOR A)</p> <p>Safety: None of the included trials have reported probiotic-induced sepsis.[1-3, 8] Case reports of systemic infections caused by probiotic organisms are found in the literature. [7] Most adverse events and serious adverse events were considered unrelated to the study product and there were no major safety concerns.[7]</p> <p>Issues related to quality of probiotic products have been reported, including viability and contamination.[11,12] Food and Drug Administration (FDA) USA issued an alert when a neonate died due to fungal sepsis from contaminated probiotic product.[12] Viability and contamination testing should be performed on every batch of probiotic product.[7]</p> <p><i>Bifidobacterium breve M-16V</i></p> <p>Efficacy: In a comparative study with historical controls, <i>B. breve M-16V</i> was associated with a reduced incidence of NEC, sepsis and mortality from sepsis. (LOE III-3 GOR C) [14]. A before and after retrospective study showed that <i>B. breve M-16V</i> was associated with decreased NEC ≥ Stage II and 'NEC ≥ Stage II or all-cause mortality in neonates < 34 weeks [20]. <i>B. breve M-16V</i> has not yet been shown in RCTs to reduce NEC or sepsis.</p> <p>Safety: No adverse effects, particularly probiotic-induced sepsis, were reported in any of the studies using <i>B. breve M-16V</i> in term and preterm neonates. [16-22]</p>
Practice points	
References	<ol style="list-style-type: none"> 1. Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2011;CD005496. 2. Dermyshe E, Wang Y, Yan C, Hong W, Qiu G, Gong X, Zhang T. The "Golden Age" of Probiotics: A Systematic Review and Meta-Analysis of Randomized and Observational Studies in Preterm Infants. Neonatology. 2017;112:9-23. 3. Rao SC, Athalye-Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic Supplementation and Late-Onset Sepsis in Preterm Infants: A Meta-analysis. Pediatrics. 2016;137:e20153684. 4. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics. 2010;125:921-30. 5. Martin CR, Walker WA. Probiotics: role in pathophysiology and prevention in necrotizing enterocolitis. Semin Perinatol. 2008;32:127-37. 6. Morinaga Bifidus M16V. Manufactured by Morinaga Milk Industry Co Ltd. 7. Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. BMC medicine. 2011;9:92. 8. Chang HY, Chen JH, Chang JH, Lin HC, Lin CY, Peng CC. Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: An updated meta-analysis. PLoS One. 2017;12:e0171579. 9. Deshpande G, Shingde V, Downe L, Leroi M, Xiao J. Routine probiotics for preterm neonates: experience in a tertiary australian neonatal intensive care unit. J Paediatr Child Health. 2013;49:50. 10. Samuels N, Van De Graaf R, Been JV, De Jonge RCJ, Hanff LM, Wijnen RMH, Kornelisse RF, Reiss IKM, Vermeulen MJ. Necrotising enterocolitis and mortality in preterm infants after introduction of routine probiotics in a NICU setting. Eur J Pediatr. 2016;175 (11):1733-4. 11. Canganella F, Paganani S, Ovidi M, Vettraino AM, Bevilacqua L, Massa S, Trovatelli LD. A microbiological investigation on probiotic pharmaceutical products used for human health. Microbiological research. 1997;152:171-9. 12. Drago L, Rodighiero V, Celeste T, Rovetto L, De Vecchi E. Microbiological evaluation of commercial probiotic products available in the USA in 2009. J Chemother. 2010;22:373-7. 13. https://www.fda.gov/food/recallsoutbreaksemergencies/outbreaks/ucm423830.htm. 14. Satoh Y, Shinohara K, Umezaki H, Shoji H, Satoh H, Ohtsuka Y, Shiga S, Nagata S, Shimizu T, Yamashiro Y. Bifidobacteria prevent necrotizing enterocolitis and infection in preterm infants. International Journal of Probiotics and Prebiotics. 2007;2(2/3):49. 15. Burks A, Harthoorn LF, Van Ampting MT, Oude Nijhuis MM, Langford JE, Wopereis H, Goldberg SB, Ong PY, Essink BJ, Scott RB, Harvey BM. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. Pediatric Allergy and Immunology. 2015 Jun 1;26(4):316-22.

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