Alert	Unregistered product in Australia. Must be prescribed by TGA Special Access Scheme or via Authorised Prescriber Pathway, after obtaining parental consent. *Bifidobacterium breve M-16V* (*B. breve M-16V*) has not yet been shown in RCTs to reduce NEC or sepsis.
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] 3) 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.
Action	Probiotics promote 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 (stick) containing more than 1 billion *B. breve M-16V* per sachet at the end of shelf life.[6]
Dosage/Interval	Commence ½ sachet BD soon after birth irrespective of the feeds and continue until discharge [14] or considered no longer at risk of NEC.
Maximum daily dose	1 sachet
Route	Oral/Orogastric
Preparation/Dilution	The contents of ONE sachet should be dissolved 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 with or without food. Discard unused portion.
Monitoring	
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].
Stability	*Bifidobacterium breve* M-16V is particularly heat sensitive, so once the sachet is open it should be used immediately.
Storage	Store at room temperature.
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 summary	**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 (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) **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) **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] 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] ***Bifidobacteriumbreve M-16V*** **Efficacy:** In a comparative study with historical controls, *B. breve M-16V* 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 *B. breve M-16V* was associated with decreased NEC ≥ Stage II and 'NEC ≥ Stage II or all-cause mortality in neonates < 34 weeks [20]. *B. breve M-16V* has not yet been shown in RCTs to reduce NEC or sepsis. **Safety:** No adverse effects, particularly probiotic-induced sepsis, were reported in any of the studies using *B. breve M-16V* in term and preterm neonates. [16-22]
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