Alert

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 has 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 (e.g. TLR4 receptor, nuclear factor-kB and inflammatory cytokines) to the advantage of the host. [5]

Drug Type
Probiotic bacteria

Trade Name
Infloran

Presentation
250 mg capsule containing Lactobacillus acidophilus [10⁹ colony-forming units, NCDO 1748; National Collection of Dairy Organisms] and Bifidobacterium bifidum [10⁹ colony-forming units, NCDO 1453; National Collection of Dairy Organisms, Reading, United Kingdom]; Laboratorio Farmaceutico, Italy. [6, 7]

Dosage/Interval
Commence the dose soon after birth irrespective of the feeds.

Birthweight < 1 kg: Commence with ½ capsule (125 mg) daily until neonate is on 40 mL/kg/day of oral feeds and then change to 1 capsule daily until 34–36 weeks or considered no longer at risk of NEC.

Birthweight ≥ 1 kg: Commence 1 capsule (250 mg) daily and continue until 34–36 weeks or considered no longer at risk of NEC.

Maximum daily dose
2 capsules (500 mg) daily

Route
Oral/Orogastric

Preparation/Dilution
The contents of ONE capsule should be dissolved in 2 mL of mother’s EBM/donor human milk/water for injection/formula. Draw up required volume (1 mL for 125 mg and 2 mL for 250 mg)

Administration
Oral: Administer with feeds if possible.

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.[8] 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. [8]

Stability
Bifidobacterium bifidum is particularly heat sensitive, so once the capsule is open it should be used immediately.

Storage
Store at 2–8°C.

Special Comments
Please note: There are 2 Infloran preparations. (1) Infloran and (2) Infloran infantis. Infloran infantis is not available in Australia. Infloran infantis contains Bifidobacterium bifidum and Lactobacillus acidophilus. Infloran infantis contains Bifidobacterium infantis and Lactobacillus acidophilus.

Median 2 to 3 x 10⁹ CFU dose has been shown to prevent NEC.[7] There is no known benefit in terms of prevention of NEC with doses higher than 3 x 10⁹ CFU. One capsule of
Infloran should provide minimum of $2 \times 10^9$ CFU. Studies have shown that up to 2 capsules/day dose is well tolerated by older premature neonates (> 1500 g).[8]

All probiotic preparations given to newborn infants should have undergone quality testing in an Australian TGA equivalent regulated system including batch to batch testing for colony count to rule out contamination.[8]

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.[8]

### Evidence summary

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. [9] (LOE 1, 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. Probiotics preparations containing either *Lactobacillus* alone or in combination with *Bifidobacterium* were found to be effective. Conclusions: Enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants. [1, 2, 9] (LOE I GOR A) Infloran containing *Bifidobacterium bifidum* and *Lactobacillus acidophilus* has been shown in a RCT to reduce the incidence of death and NEC. [7] Prospective observational studies of routine use of Infloran (*B. bifidum* and *L. acidophilus*) in preterm neonates, gestation < 32 weeks and < 1500 g, have documented its safety and potential efficacy. [10, 11]

**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 = .0007; NNT 44). [2, 3] (LOE I GOR A)

**Safety:** None of the included trials have reported probiotic-induced sepsis.[1-3, 9] Case reports of systemic infections caused by probiotic organisms are found in the literature. [8] Most adverse events and serious adverse events were considered unrelated to the study product and there were no major safety concerns.[8] Issues related to quality of probiotic products have been reported, including viability and contamination.[12, 13] Food and Drug Administration (FDA) USA issued an alert when a neonate died due to fungal sepsis from contaminated probiotic product. [13] Viability and contamination testing should be performed on every batch of probiotic product.[8]

**References**