Infloran

Newborn Use Only

2017

Alert	Unregistered product in Australia. Must be prescribed by TGA Special Access Scheme or via Authorised Prescriber Pathway, after obtaining parental consent. Please note: There are 2 Infloran preparations. (1) Infloran and (2) Infloran infantis. Infloran infantis is not available in Australia. Infloran contains *Bifidobacterium bifidum* and *Lactobacillus acidophilus*. Infloran infantis contains *Bifidobacterium infantis* and *Lactobacillus acidophilus*.
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* [10^9 colony-forming units, NCDO 1748; National Collection of Dairy Organisms] and *Bifidobacterium bifidum* [10^9 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	1) Median 2 to 3 x 10^9 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 10^9 CFU. One capsule of Infloran should provide minimum of 2 x 10^9 CFU. Studies have shown that up to 2

	capsules/day dose is well tolerated by older premature neonates (> 1500 g).[8] 2) 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 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. 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	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. Dermyshi 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. Infloran. Product information. Laboratorio Farmaceutico, Italy. 2002. 7. Lin HC, Hsu CH, Chen HL, Chung MY, Hsu JF, Lien RI, Tsao LY, Chen CH, Su BH. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics. 2008;122:693-700. 8. Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. BMC medicine. 2011;9:92. 9. Chang HY, Chen JH, Chang JH, Lin HC, Lin CY, Peng CC. Multiple strains probiotics appear

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