# Statement on Prolacta Bioscience Human Milk Based Breastmilk Fortifier January 2020


**Summary**

- Breastmilk fortifier made from human milk (HMF) is being used in clinical trials but has also become commercially available in the UK.
- The human milk liquid fortifiers are marketed by Prolacta Bioscience under the name Humavant.TM
- Prolacta Bioscience is a commercial venture, the milk is sourced from women in the US who are paid for their milk. There are many ethical and practical issues associated with the commercialisation of human milk that are of concern and which require national debate.
- The process used to produce Prolacta products is not compliant with NICE clinical guidance (CG93, NICE 2010) on the operation of donor milk banks.
- Prolacta Bioscience estimate that it would cost between £94-£131.00/day to feed a very low birthweight infant an exclusive human milk diet using Prolacta human milk-based fortifier.
- This product is a liquid fortifier and therefore replaces a proportion of breastmilk which, in our opinion, makes it a breastmilk substitute and this would therefore be covered by the WHO Code of Marketing of Breastmilk Substitutes.
- Prolacta Bioscience claim that use of their human milk based fortifiers as part of a 100% human milk based diet offers improved health outcomes over bovine milk based fortifiers, and that the costs of using their products are more than offset by savings from reduced incidence of complications and medical interventions.
- The studies on which efficacy claims for their fortifiers are based do not, in our opinion, provide adequate evidence to determine whether human milk-based fortifier improves health outcomes.
- Further, appropriately powered randomised controlled trials in premature human milk fed infants are needed to more accurately determine whether there are significant differences in the incidence of necrotizing enterocolitis (NEC) and other morbidities where human milk-based fortifiers rather than bovine milk fortifiers are used.

**Background**

Breastmilk fortifiers derived from human milk have recently become commercially available in the UK and Ireland from the US Company Prolacta Bioscience. The breastmilk fortifiers are being used in clinical trials in the UK and the company have engaged a public affairs company called RPP. Representatives of the company have attended events for health professionals and approached them with information about their products and RPP has been in contact with people working in the field. Prolacta Bioscience now has a dedicated UK and Ireland website http://www.prolacta.uk/Home.

Whilst Prolacta also sell pasteurised human milk, fortified human milk and caloric fortifiers based on human milk cream, these products are not currently being marketed in the UK. This statement is designed to provide an independent review of the evidence offered by Prolacta and their representatives to support the use of their human milk-based breastmilk fortifier.

**1.0 What do we know about Prolacta Bioscience?**

Prolacta Bioscience is an American life sciences company founded in 1999. It is a for-profit company that screens, processes, pasteurises, stores and distributes large quantities of human milk which it markets as human milk formula. The human milk formula produced may be supplemented with additional vitamins and mineral to 'standardise' the composition of the milk. Different fractions of human milk are extracted and used in other products, for example, in breastmilk fortifier. The company has received large amounts of investment capital and human milk providers are paid for their expressed milk. In the UK donor human milk is supplied by a network of not-for-profit milk banks to which women donate their milk freely.

**2.0 What do we know about the human milk fortifiers produced by Prolacta Bioscience?**

Prolacta Bioscience fortification products assume the human milk being fortified has an energy content of around 67kcal/100ml (20 kcal /fl oz). The fortification products are processed human milk based liquid supplements that provide calories, protein, and minerals. The energy density of each fortifier is the same although they are supplied in volumes of either 10ml, 20ml, 40ml or 50ml. When mixed with human milk to a final volume of 100ml, the supplements are expected to increase the energy density of the final feed to 82kcal/100ml, 90kcal/100ml, 98 kcal/100ml and 105kcal/100ml respectively, and increase the protein content proportionally while keeping the mineral content similar. The product may need to be supplemented with some vitamins depending on local guidelines. Some of the protein levels could rise above that generally recommended.

The products are named according to the concentration of energy they add to human milk in kcal/fl oz, thus they are named Humavant™ +4 HMF (adds 4kcal/fl oz), Humavant™ +6 HMF (adds 6kcal/fl oz), Humavant™ +8 HMF (adds 8kcal/fl oz), and Humavant™ +10 HMF (adds 10kcal/fl oz). Each bottle of fortifier contains pooled expressed breastmilk that has been concentrated and pasteurised along with added sodium, potassium, chloride, calcium, phosphorus, magnesium, copper, and zinc and each bottle has the batch specific nutrients listed on the label.

Fortifier is supplied frozen and must be kept frozen until use. Expressed human milk must be added to the bottle of liquid fortifier prior to use.

Human milk from which the human milk fortifier is made is purchased from women in the US. The Prolacta Bioscience milk banking operation does not comply with NICE guidance (CG93, 2010) as milk from different women is pooled. In addition, the handling of the human milk following the pasteurisation process does not conform to the NICE guidelines. Prolacta Bioscience have estimated the cost of feeding a very low birthweight baby on an exclusively human milk diet using human milk-based fortifier is between £94-£131/day.

**3.0 Is a liquid fortifier a breastmilk substitute?**

In our opinion the use of a liquid fortifier which replaces a proportion of maternal breastmilk is clearly a breastmilk substitute and is therefore covered by the WHO Code of Marketing of Breastmilk Substitutes.

**4.0 What claims does Prolacta Bioscience make for the human milk based fortifiers they market in the UK?**

Prolacta Bioscience claim on their UK and Ireland website that their fortification product:

- *'Provides concentrated nutrition to help support the developing immune system and provide essential calories, protein, and minerals'*
- *'Retains human milk oligosaccharide content similar to that of fresh human milk'*

No references are given to support these statements. It should be noted however that replacing maternal, non-heat treated human milk with a pasteurised product, as happens when the liquid fortifier replaces some of the mother's own milk, will reduce the available immune system supporting components. It will also reduce the amount of bile salt stimulated lipase the baby receives potentially reducing fat digestion.

- *'Humavant™ HMF, when used as part of an exclusive human milk diet (EHMD), can reduce the incidence of medical complications and interventions.'*

The claim that their breastmilk fortifier, Humavant™ HMF, can reduce medical complications and interventions as part of an exclusively human milk diet is supported by reference to a retrospective cohort study of 1,587 premature infants. The study examined rates of necrotizing enterocolitis (NEC), mortality and other morbidities in premature infants 2-3 years before, and after, the introduction of an exclusively human milk feeding protocol (Hair et al, 2016).

Infants with a birth weight <1,250g who received a diet of mother's own milk fortified with bovine fortifier and/or preterm formula (BOV) were compared to infants who received an exclusive human milk feeding protocol (HUM). Statistically significant differences were found between the primary outcome measures of NEC and mortality between groups with lower rates for both outcomes

reported for the group fed an exclusively human milk diet. Secondary outcomes included late-onset sepsis, retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD). All were reported as significantly lower in the HUM group.

There were however a number of methodological limitations to this study. All 4 study centres had slightly different feeding protocols resulting in differences in the stage of introduction and rate of fortification and the criteria for transition off the HUM diet onto receiving bovine milk-based products. The authors reported that an increase in awareness of central line infection reduction protocols during the study period may have impacted to reduce NEC rates. Furthermore, the bovine group had statistically significant lower birthweights and use of antenatal steroids both of which are generally accepted as potential risk factors for NEC. No control group of infants fed unfortified human milk was included. The study manuscript was reviewed by the MD of Prolacta and several of the authors were affiliated in some way with Prolacta.

The relevance of this study to the use of Humavant™ human milk-based fortifiers as part of an otherwise exclusively human milk-based diet versus a human milk-based diet with bovine milk based fortifiers is limited because of differences in feeding protocols and the inclusion of bovine milk based infant formula in the BOV group diet.

- *Early and appropriate advancement of fortification is achievable with an exclusive human milk diet (EHMD) and has been associated with weight gain exceeding targeted standards.*

This claim is supported by an earlier study by Hair et al, 2013. This single centre observational study evaluated growth velocities and the incidence of extrauterine growth restriction in 104 premature infants ≤ 1250g birthweight. Fortification was commenced when enteral intake reached 60ml/kg/day and was advanced by 20ml/kg/day to reach a goal of 140-150ml/kg/day. The results were compared to human milk fed cohorts from another study that examined the growth of premature infants with a birthweight <1,250g.

The authors reported that weight gain in the study group exceeded targeted growth standards and length and head circumference gain met targeted standards. Weight gain from birth to discharge was significantly affected by the day of fortification of feeds and the total number of days to reach full enteral feeds. Infants achieved greater growth in weight and length but not head circumference when compared to human milk fed cohorts from a clinical trial reported by Sullivan et al, 2010.

Infants in the Hair et al (2013) study achieved full feeds earlier and had less days on total parenteral nutrition as compared to human milk fed cohorts from Sullivan et al, 2010 where feeding strategies involved lower intakes of calories and protein. Whereas the human milk fed cohorts in the study by Sullivan et al, 2010 failed to achieve the target growth standard of 17-20g/kg/day suggested by ESPGHAN, 2018, infants in the Hair et al (2013) study achieved mean weight gain of about 25 g/kg/d. Excessive weight gain, over and above standards is not however considered to be desirable and rapid weight gain for premature infants, particularly small for gestational infants may be associated with later adverse metabolic effects including increased risk of obesity and non-communicable diseases, although more evidence is needed (Martin et al, 2016)

Hair et al (2013) reported that their study *'provided data showing that infants can achieve and mostly exceed targeted growth standards when receiving an exclusive human milk-based diet...with early and rapid advancement of fortification of feeds'.* There were however methodological limitations to this study. It compared results to cohorts of human milk fed infants from other studies which means that it is likely that there were methodological differences between the groups other than the feeding protocols. Furthermore, weight gains were not sustained. At discharge, or 40 weeks gestational age, 43% of infants experienced extrauterine growth restriction.

Whilst this study does provide some evidence that target weight gain can be achieved with human milk-based fortifiers, it does not support any role for human milk-based fortifiers over bovine milk-based fortifiers in otherwise human milk-based diets.

**5.0 Are there any studies that compare the efficacy of human milk-based fortifiers versus bovine milk-based fortifiers in otherwise exclusively human milk diets?**

Two recent studies have compared the use of human or bovine milk-based fortifiers in otherwise human milk-based diets in order to evaluate their efficacy in terms of feeding tolerance and growth. The first of these studies, by O'Connor et al (2018) is a triple blinded randomized controlled trial conducted in Canada in which 127 infants with a birthweight <1250g were randomised to a feeding protocol including human milk fortified with either human milk based fortifier (HMBF) or bovine milk based fortifier (BMBF).

The study outcomes were measures of feeding tolerance. The primary outcome was to identify any differences between groups in the incidence of feeding interruptions for > or = 12 hours or a >50% reduction in feeding volume. Secondary outcomes included days on parenteral nutrition (PN), a dichotomous mortality and morbidity index, faecal calprotectin as a measure of gut inflammation and growth.

No statistically significant differences were found in the percentage of infants with a feeding interruption. In addition, no statistically significant differences were identified between groups for days of PN, days to full enteral feeding, and percent of infants who had their enteral feeds discontinued with resumption of PN. There were 5 of 64 (8%) infants in the HMBF group who discontinued the feeding intervention early because of feeding intolerance, compared to no infants in the BMBF group.

No significant differences were observed between groups for faecal calprotectin or between absolute growth or z scores for growth at day 1 and at the end of the intervention. Infants in the BMBF group had more rapid weight gain during the intervention than infants in the HMBF group. No significant differences were reported between groups for the dichotomous mortality and morbidity index. Although the study was not powered to detect differences in individual morbidities, planned exploratory analysis reported no significant differences between groups for NEC, late-onset sepsis or chronic lung disease. The incidence of severe retinopathy of prematurity was significantly higher in the group fed bovine milk-based fortifier than in the group fed human milk based fortifier, however, it is important to remember that this data was from an exploratory

analysis. The authors concluded that the use of HMBF did not improve feeding tolerance or reduce mortality and morbidity compared with BMBF.

In a subsequent retrospective observational study in Austria data from the hospital records of 192 infants with a birthweight <1000g (extremely low birthweight (ELBW) infants) across 2 study centres were analysed in order to investigate the impact of human milk based fortifier versus a bovine milk based fortifier on growth up to 37 weeks gestational age (Eibensteiner et al, 2019). At 32 weeks the group receiving human milk-based fortifier transitioned to bovine milk based fortifier. Both groups may have received formula milk after 32 weeks if insufficient human milk was available. The primary outcome of the study was growth. Secondary outcomes included time to full enteral feeds, fortifier tolerance, morbidities including NEC, retinopathy and focal intestinal perforation.

No differences in either absolute growth or growth velocity from birth to 32 or 37 weeks of gestation were reported, however growth velocity was reported as greater in the group fed bovine milk-based fortifier between its introduction and 32 weeks gestational age. Although according to the authors this was the most sensitive time period to detect differences in growth velocity, the sample size was not powered to detect differences in growth velocity during this time frame but to detect growth velocity from birth to 37 weeks gestational age. The authors suggest that although both types of fortifier contained optimal protein-energy ratios for growth, the human milk fortifier is characterised by a lower carbohydrate and higher fat content than the bovine based fortifier. Intestinal fat digestion in premature infants is suboptimal and the carbohydrate to energy ratio of the human milk-based fortifier was lower than 10.5g/100kcal recommended by ESPGHAN. The authors suggest that this might explain the slower growth velocity observed for infants fed human milk-based fortifier.

Time to full enteral feedings, duration of parenteral nutrition and central line days were significantly longer in the group fed human milk-based fortifier than in the bovine fortifier group. Signs of feeding intolerance were similar between groups. There was no difference in NEC, other major morbidities, and mortality or glucose and fat metabolism between groups. The authors concluded that overall, the results of their study, and those of others do not support the superiority of human milk-based fortifier over bovine milk-based fortifier.

**6.0 Is there any evidence that Prolacta products are cost effective?**

Prolacta suggest on their website that the costs of their products are more than offset by savings from a reduced incidence of complications and medical interventions. This claim is supported by reference to Assad et al, 2016 and Ganapathy et al, 2012. The retrospective chart review by Assad et al, was carried out independently of commercial interest. Infants were allocated to one of four groups depending on how they were fed and the data was used to inform a cost of treatment analysis that reported that total overall charges were lowest when infants were fed an exclusively human milk diet, despite the costs involved in buying processed human milk and human milk based fortifier. The reliability of the outcomes used to calculate costs are questionable as the study had several limitations: it was not powered to detect differences between groups for all parameters

that were used as drivers for the cost calculations and the infants in the formula group were significantly older than in the other groups.

The study by Ganapathy et al (2012) was sponsored by Prolacta. Their analysis evaluated the cost effectiveness of a 100% human milk-based diet with human donor milk and human milk-based fortifier versus a human milk-based diet fortified with bovine milk-based fortifier. The parameters used to develop the cost calculator included the probabilities of developing NEC and surgical NEC by feeding regime observed from a key clinical trial (NCT00506584 reported by Sullivan et al, 2010), costs of the feeding products used and the incremental costs of NEC over and above average neonatal intensive care unit costs incurred for an extremely premature infant without NEC.

The reliability of the outcomes used to calculate costs are questionable as the study they were based upon (Sullivan et al, 2010) had several limitations. The trial evaluated the health benefits of an exclusively human milk-based diet compared with a diet that contained both human milk and bovine milk-based products in 207 extremely premature infants. It was not powered to be able to detect real differences in the incidence of NEC between study groups. Only a small number of cases of NEC were reported and so the reported 50% and 90% reductions in cases may not be reliable. In addition, the incidence of NEC in infants fed according to standard guidelines with mother's milk, bovine milk-based fortifiers and preterm formula when no mothers milk was available, although small in number, was much higher than that seen in the UK (Embleton et al, 2013) and so it is likely that the cost effectiveness reported is not applicable to the situation in the UK.

In addition, the composition of the bovine milk-based fortifier used in the trial differed from those currently in use in the UK in particular the US products are based on whole cows' milk protein while the predominant fortifier in the UK is based on hydrolysed cows' milk. These differences may have had a role to play in the development of NEC. It is not surprising that the treatment costs calculated by Ganapathy et al. for extremely premature infants fed a diet that included bovine milk-based products were higher than those for infants fed only human milk as human milk feeding is understood to be protective against NEC and therefore the costs associated with NEC.

In a letter to the editor of the journal in which the Sullivan et al 2010 paper was published, Embleton et al, 2013 commented that '*an unequivocal case for use of a HM fortifier has not been determined*' Embleton et al, 2013.

In our opinion there is insufficient conclusive evidence that human milk-based fortifiers have clinical advantages over bovine milk-based fortifiers in otherwise human milk based diets for extremely premature infants. Prolacta Bioscience is a commercial venture, lactating women are paid for their milk and Prolacta claim that their milk supply is secure. There are many ethical and practical issues associated with the commercialisation of human milk that are of concern and which require national debate.

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