National Essential Medicine List Committee
Medication Review

Medication names: Poractant alfa and Beractant

Date of initial review: 24 July 2014

Date of update: March 2018

Indication: Respiratory Distress in the Newborn

Introduction and contextualisation:
Respiratory distress syndrome (RDS) is caused by a deficiency or dysfunction of pulmonary surfactant. Pulmonary surfactant forms a lipid-rich monolayer that coats the alveoli and airways of the lung and is essential for proper inflation inflation and function. Surfactant lowers surface tension and improves pulmonary dynamic compliance.[1] Surfactants from animal derivation include porcine (poractant alfa) and bovine (beractant) lung extracts.

The Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) have designated therapeutic classes. Therapeutic class means a group of medicines which have active ingredients with comparable therapeutic effects. Medicines in a therapeutic class may or may not belong to the same pharmacological class, may differ in chemistry or pharmacokinetic properties, and may possess different mechanisms of action, result in different adverse reactions, and have different toxicity, and drug interaction profiles. In most cases, these medicines have close similarity in efficacy and safety profiles, when administered in equipotent doses for a specific indication[2].

The Paediatric Hospital Level STGs and EML currently recommend animal-derived surfactant preparations for respiratory distress in the newborn if surfactant deficiency is suspected.[3]

During the past two tender evaluations for small volume parenterals (HP06-2014SVP, HP06-2017SVP) the cheapest member of the surfactant therapeutic class *i.e.* beractant was awarded.

In 2014 an objection to the exclusion of poractant alfa on tender HP06-2014SVP was received from Safeline Pharmaceuticals (supplier of poractant alfa); the United South African Neonatal Association (USANA); the Division of Neonatology, Groote Schuur Hospital and the Division of Neonatology, University of Witwatersrand. The motivations in support for the inclusion of poractant alfa on the tender were submitted to the Essential Drugs Programme for review.

The following is a summary of the key issues discussed in the motivations:

- Short and long-term benefits of poractant in terms of effectiveness and cost;
- Advantages of using poractant for infants > 1kg and < 1.2 kg;
- Concerns related to an interruption in the supply of beractant during the contract period;
- Difference in the composition of poractant *vs*. beractant;
- Administration advantages of poractant *vs*. beractant and;
- Availability of poractant for teaching and training requirements.

The motivations and supporting evidence for poractant was tabled for discussion at the Tertiary Expert Review Committee meeting on 17 July, 2014. Prof V. Davies, Head of the Division of Neonatology and Intensive Care, Charlotte Maxeke Johannesburg Academic Hospital, presented the case for poractant as well as the supporting evidence on behalf of USANA and the Division of Neonatology, University of Witwatersrand.

In 2017 a subsequent objection to the exclusion of poractant alfa on tender HP06-2017SVP was received from Safeline Pharmaceuticals (supplier of poractant alfa); and USANA. An appeal was made to consider poractant alfa and beractant as separate agents and not as therapeutically equivalent for the follow reasons:

- .Poractant and Beractant are not administered in therapeutically equivalent doses *(Poractant Alfa is licensed at a dose ranging from 100-200mg/kg and the majority of evidence is based on a 200mg/kg dose. As Beractant is only licensed at a dose of 100mg/kg, Poractant Alfa and Beractant cannot be classed as Therapeutic Equivalents and direct dosage comparisons are not possible).*
- Poractant and beractant do not have equivalent effectiveness
  (When compared with Beractant, Poractant Alfa at a dose of 200mg/kg, in addition to improving survival, has been shown to be associated with:
  - *Faster weaning and earlier extubation from mechanical ventilation;*
  - *Decreased need for re-dosing).*

This review document was initially prepared in 2014 and updated in 2018 to include subsequently relevant published data.

Evidence synthesis and quality:

The evidence evaluating the effectiveness and safety of poractant *vs*. beractant submitted in support for the inclusion of poractant on the tender is outlined in Table 1.

Table 1: Summary of randomised studies comparing Poractant *vs*. Beractant

Study description	Patient inclusion criteria	Interventions/ Dose (no. of patients)	Primary outcome to assess clinical response	Results	Comment
Prospective, randomised, controlled trial[4]	Premature infants with BW ≤ 2.000g; GA of ≤ 32 weeks with RDS established within the first 24 h of life; ventilated with FiO_2 ≥ 0.30; surfactant given within 4 h of life	Alveofact/ 100mg/kg (27) Poractant/ 100mg/kg (26) Beractant/ 100mg/kg (27)	Various clinical outcomes compared (primary outcome not specified) Death before discharge Mean intubation days	Alveofact group: 7 deaths (25.9%) Poractant group: 5 deaths (18.5%) Beractant group: 6 deaths (23.1%) **Poractant *vs*. Beractant group:** **RR 0.89; CI 95% 0.44 to 1.79; ARR 5%; NNT = 18 (p=0.74)** Alveofact group: 6.6±2.1 Poractant group: 5.7±1.5 Beractant group: 11.5±2.3 **Poractant *vs*. Beractant group**: **p=0.043**	No significant differences found among the 3 groups when NICU-related morbidities such as chronic lung disease, PDA, air leaks, ROP, NEC, IVH were compared Study investigators reported that the numbers of patients in the study were to small in each group to draw any firm conclusions
Prospective, randomised controlled trial[5]	Infants < 37 wk GA with clinical signs and symptoms of RDS who required intubation and surfactant therapy	Poractant/ 200mg/kg (29) Beractant/ 100mg/kg (29)	Mean FiO_2 requirement in the first 48 h after the first surfactant dose	Poractant group: 0.47 Beractant group: 0.49 **Poractant *vs*. Beractant group:** **p=0.018**	Study reported a significant difference in the mean number of surfactant doses in the poractant group (1.2) compared to the beractant group (1.7); p < 0.004 No significant difference found between the groups with regard to age of first extubation, reintubation rate, total intubation time

Study description	Patient inclusion criteria	Interventions/ Dose (no. of patients)	Primary outcome to assess clinical response	Results	Comment
Multicentre, prospective, randomised controlled trial[6]	BW of 750 to 1750g; GA < 35 weeks; clinical or radiographic evidence of RDS; ventilated with $FiO_2 \geq 0.30$; surfactant given within 6 h of life	Poractant/ 100mg/kg (96) Poractant/ 200mg/kg (99) Beractant/ 100mg/kg (98)	Short-term Mean FiO_2 under the curve during the 6 h period after the first surfactant dose Long-term Mortality at 28 days Mortality at 36 weeks post-conceptional age for infants born ≤ 32 weeks gestation	Poractant 100mg/kg group: 1.956 hours (0.33) Poractant 200mg/kg group: 1.989 hours (0.33) Beractant group: 2.237 hours (0.37) **Poractant 100mg/kg group *vs.* Beractant:** **P < 0.001** **Poractant 200mg/kg *vs.* Beractant:** P < **0.005** Poractant 100mg/kg group: 6 deaths (6%) Poractant 200mg/kg group: 3 deaths (3%) Beractant group: 8 deaths (8%) **Poractant 100mg/kg group *vs.* Beractant:** **OR 0.75; CI 95% 0.25 to 2.25; ARR 2%; NNT = 50** **Poractant 200mg/kg group *vs.* Beractant:** **OR 0.35; CI 95% 0.09 to 1.37; ARR 5%; NNT = 20** Poractant 100mg/kg group: 9 deaths (11%) Poractant 200mg/kg group: 3 deaths (3%) Beractant group: 10 deaths (11%) **Poractant 100mg/kg group *vs.* Beractant:** **OR 0.95; CI 95% 0.36 to 2.46; ARR 0** **Poractant 200mg/kg group *vs.* Beractant:** **OR 0.26; CI 95% 0.07 to 0.98, ARR 8%; NNT = 13**	Study reported that 36% of infants received two or more doses of surfactant in the poractant 200mg/kg group compared with 68% in the beractant group (p = 0.002)

Study description	Patient inclusion criteria	Interventions/ Dose (no. of patients)	Primary outcome to assess clinical response	Results	Comment
Prospective, randomised, open label, controlled trial[7]	GA of 24 0/7 to 29 6/7 weeks, RDS requiring mechanical ventilation; surfactant and ventilation < 6 h after birth	Poractant/ 200mg/kg (25) Beractant/ 100mg/kg (27)	Outcomes for level of respiratory support for first 72h of life: MAP (cm H_20) FiO_2	**Poractant *vs.* Beractant group:** **P =0.003** **Poractant *vs.* Beractant group:** **P =0.762**	Study was terminated before completion of enrollment as differences between groups were more frequent than anticipated because of the young GA of infants enrolled Study investigators reported no difference in length of stay between groups Study was not powered to detect a difference in mortality
Prospective, open-label, randomised, controlled trial centres[8]	GA age < 37 weeks; clinical or radiographic evidence of RDS within 6 h of birth; ventilated with $FiO_2 \geq 0.30$	Poractant/ 200mg/kg (61) Beractant/ 100mg/kg (65)	Mean FiO_2 percentage requirement at 24 h post gestation	Poractant group: 67.4 Beractant group: 60.5 **Poractant *vs.* Beractant group:** **p=0.031** Days of hospitalisation and overall mortality was not significant between the groups Extubation rate within first 3 days after surfactant administration was found to be higher in Poractant group than the Beractant group (81% *vs.* 55.9%; p = 0.004)	Study investigators concluded that the results suggest some clinical benefit with the use of poractant over beractant but larger studies are necessary to confirm the impact of mortality

Study description	Patient inclusion criteria	Interventions/ Dose (no. of patients)	Primary outcome to assess clinical response	Results	Comment
Quasi-randomised single center clinical trial[9]	Preterm infants with RDS treated with exogenous surfactant.	Poractant (79) 200mg/kg Beractant (71) 100mg/kg	Mean duration of intubation	Poractant group: 3.13 ±1.80 days Beractant group: 4.06 ± 2.7 days **Poractant *vs.* Beractant group:** **p=0.05** The mean duration of need for oxygen and hospitalisation of patients in poractant group and beractant group were 17.73+/-22.25 vs 19.14+/-17.85 days (p=0.67) and 24.89+/-26.41 vs 29.14+/-23.54 days (p= 0.32), respectively	No significant difference between groups with respect to mortality and morbidity.
Randomised prospective study[10]	Preterm infants with RDS	Beractant (46) Poractant (46)	Perfusion index (PI) variability	Median oxygenation index (OI) before surfactant were similar, but improvement in OI was more prominent at 6th hour of surfactant in poractant group (p = 0.001) Both groups had similar preductal PI values before surfactant. PI was higher at 6th hour of surfactant in poractant group (p = 0.001) Pulmonary haemorrhage, intraventricular haemorrhage, PDA, NEC, and mortality were more frequent in infants whose PI values lower than 0.7 within the first 5 days of life (p = 0.001)	Repeated doses were more needed in beractant group (p = 0.04).

Birth Weight (BW), Gestational age (GA), Respiratory Distress Syndrome (RDS), Mean fraction of inspired oxygen (FiO_2), Patent ductus arteriosus (PDA), Retinopathy of prematurity (ROP), Necrotizing enterocolitis (NEC), Intraventricular haemorrhage (IVH),
Neonatal Intensive Care Unit (NICU), Mean airway pressure (MAP), Relative risk (RR), Odds ratio (OR), Absolute risk reduction (ARR), Number needed to treat (NNT)

Other studies:

Singh *et.al.* Meta-analysis

A systematic review and meta-analysis comparing the efficacy of porcine versus bovine surfactants found a statistically significant decrease in mortality when poractant 100mg/kg or 200mg/kg was compared with beractant 100mg/kg (RR 0.51, 95% CI 0.30 to 0.89) and when poractant 200mg/kg was compared with beractant 100mg/kg (RR 0.29, 95% CI 0.12 to 0.66).[11] Of the 5 studies included in the review, 4 have been described in Table 1 (Refer to study references 4, 5, 6, 8). The 5th study (75 patients) was designed as a pilot trial.[12]

The review also found that the length of hospital stay was significantly shorter for infants treated with poractant compared with those treated with beractant. However the study investigators reported that the finding was on the basis of only 2 studies with significant heterogeneity (I^2 = 75%) between the study groups (Refer to Table 1; study references 4 and 7).

Cochrane 2015

A subsequent Cochrane systematic review and meta-analysis[13] comparing the effect of administration of different animal-derived surfactant extracts did not demonstrate any significant effect of surfactant preparation on the risk of neonatal mortality from any cause (RR 1.48, 95% CI 0.72 to 3.07; Risk Difference (RD) 0.03, 95% CI −0.03 to 0.10; 2 studies and 320 infants), see *Annexure 1*. However, there was statistically significant increase in the risk of mortality prior to hospital discharge reported by 9 studies with beractant as compared to poractant (RR 1.44, 95% CI 1.04 to 2.00, RD 0.05 95% CI 0.01 to 0.10; NNTH = 20, 95% CI 10 – 100), see *Annexure 2*.

The review also found an increase in risk of death or oxygen requirement at 36 weeks' postmenstrual age (RR 1.30, 95% CI 1.04 to 1.64; RD 0.11, 95% CI 0.02 to 0.20; NNTH 9, 95% CI 5 to 50; 3 studies and 448 infants; moderate quality evidence) *see Annexure 3*, an increased risk of receiving more than one dose of surfactant (RR 1.57, 95% CI 1.29 to 1.92; RD 0.14, 95% CI 0.08 to 0.20; NNTH 7, 95% CI 5 to 13; 6 studies and 786 infants) *see Annexure 4*, and an increased risk of patent ductus arteriosus (PDA) requiring treatment (RR 1.86, 95% CI 1.28 to 2.70; RD 0.28, 95% CI 0.13 to 0.43; NNTH 4, 95% CI 2 to 8; 3 studies and 137 infants), *see Annexure 5*, in infants treated with beractant compared with poractant. The differences in these outcomes was limited to studies using a higher initial dose of poractant (>100mg/kg).

This Cochrane review included all studies included by Singh *et.al*, in addition to 3 other studies, 2 have been described in Table 1 (Refer to study references 9 and 10). The third study was a PhD thesis.[14]

Table 2: Quality assessment of randomised studies comparing Poractant *vs*. Beractant

Study reference	Method of randomisation	Method of concealment of allocation	Blinding of intervention/ outcome assessors	Were treatment and control groups similar	Intention to treat analysis
4	Not stated	Sealed envelopes	No No	Yes	Yes
5	Stratified by birth weight	Sealed envelopes	No Yes	Yes	No
6	Stratified by birth weight and site	Sealed, opaque envelopes	No Yes	Yes	No
7	Not stated	Not stated	No No	Yes	Not stated
8	Computer-generated block	Sealed, opaque envelopes	No No	Yes	Yes
9	Odd or even number admission code	Odd or even number admission code	Not reported Outcome reported by 2 senior neonatologists who did not know the group	Yes	Unclear
10	Random number generation	Sealed envelopes contained cards that were not randomly assigned to groups	Not reported	Yes	Unclear

Previous NEMLC recommendation (2014):

After all the published data was presented and reviewed, understanding all the operational issues, the committee was still unable to discern difference in terms of benefit. Although there may be a trend towards benefit in small patients using high doses, this is unquantifiable. The committee did raise concern about the supply, and were informed about the letter from Biotech.

The Committee recommended that:

- Beractant and poractant be considered as a class.
- Cost minimisation principles apply.

NEMLC Recommendation (2018)

After review of additional evidence (Cochrane 2015), it was resolved that there were insufficient grounds to overturn the previous recommendation; and poractant alfa and beractant should be retained as a therapeutic class.

References:

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[10] Karadag N, Dili D, Zenciroglu A, Aydin B, Beken S, Okumus N. Perfusion index variability in preterm infants treated with two different natural surfactants for respiratory distress syndrome. American Journal of Perinatology 2014, 31 (11):1015-1022.

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[12] Speer CP, Gefeller O, Groneck P, Laufkotter E, Roll C, Hanssler L, Harms K, Herting E, Boenisch H, Windeler J, Robertson B. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child 1995;72:F8 – 13.

[13] Singh N, Halliday HL, Stevens TP, Suresh, G, Soll R, Rojas-Reyes MX. Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews. 2015, Issue 12, CD010249.

[14] Halahakoon WL. A study of cerebral function following surfactant treatment for respiratory distress syndrome (Doctoral dissertation). Queens University of Belfast (UK). 1999.

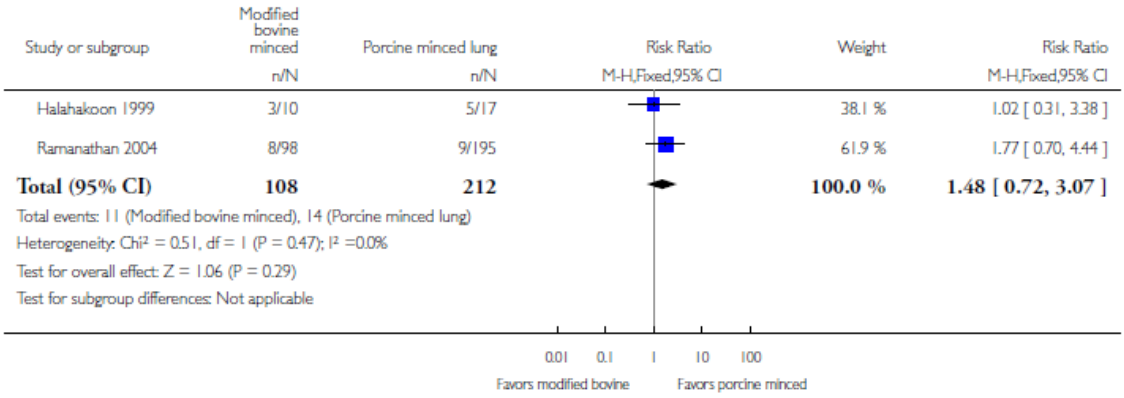
Annexure 1

Analysis 3.1. Comparison 3 Modified bovine minced lung vs. porcine minced lung, Outcome 1 Neonatal mortality.

Review: Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants

Comparison: 3 Modified bovine minced lung vs. porcine minced lung

Outcome: 1 Neonatal mortality



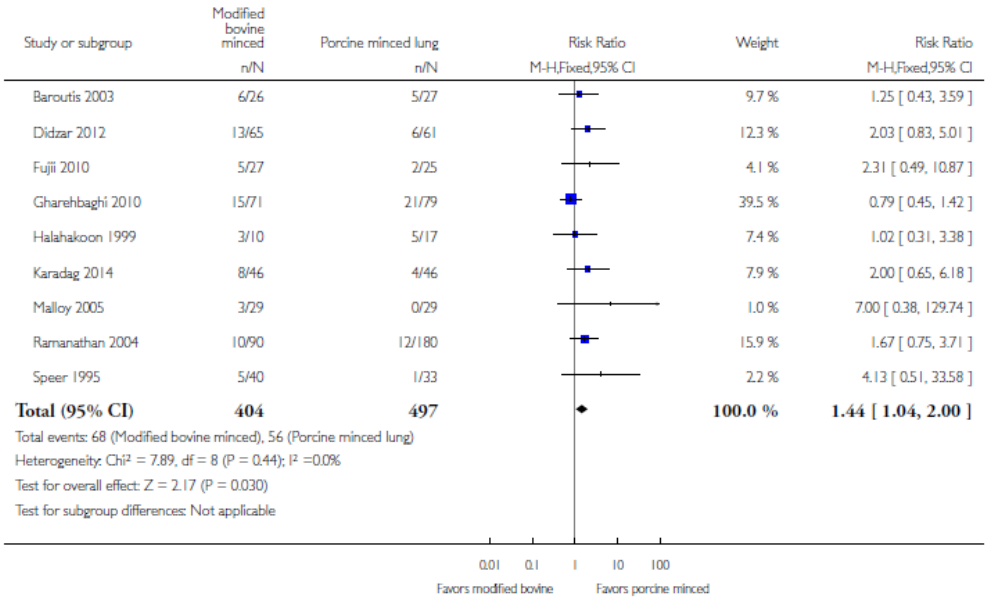
Annexure 2

Analysis 3.2. Comparison 3 Modified bovine minced lung vs. porcine minced lung, Outcome 2 Mortality prior to discharge.

Review: Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants

Comparison: 3 Modified bovine minced lung vs. porcine minced lung

Outcome: 2 Mortality prior to discharge



Annexure 3

Analysis 3.5. Comparison 3 Modified bovine minced lung vs. porcine minced lung, Outcome 5 Death or oxygen requirement at 36 weeks postmenstrual age.

Review: Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants

Comparison: 3 Modified bovine minced lung vs. porcine minced lung

Outcome: 5 Death or oxygen requirement at 36 weeks postmenstrual age

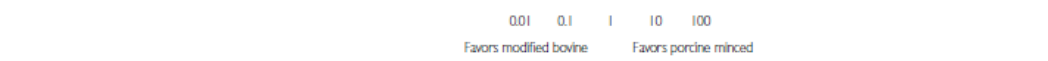
Study or subgroup	Modified bovine minced n/N	Porcine minced lung n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Didzar 2012	27/65	13/61		17.7 %	1.95 [1.11, 3.42]
Fujii 2010	16/27	10/25		13.7 %	1.48 [0.84, 2.63]
Ramanathan 2004	43/90	78/180		68.6 %	1.10 [0.84, 1.45]
Total (95% CI)	**182**	**266**		**100.0 %**	**1.30 [1.04, 1.64]**

Total events: 86 (Modified bovine minced), 101 (Porcine minced lung)

Heterogeneity: $Chi^2 = 3.61$, $df = 2$ ($P = 0.16$); $I^2 = 45\%$

Test for overall effect: $Z = 2.30$ ($P = 0.022$)

Test for subgroup differences: Not applicable



Annexure 4

Analysis 3.6. Comparison 3 Modified bovine minced lung vs. porcine minced lung, Outcome 6 Received > one dose of surfactant.

Review: Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants

Comparison: 3 Modified bovine minced lung vs. porcine minced lung

Outcome: 6 Received > one dose of surfactant

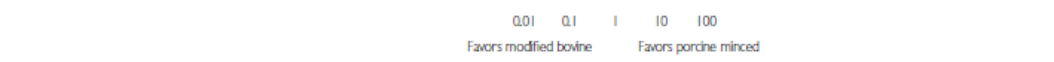
Study or subgroup	Modified bovine minced n/N	Porcine minced lung n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Didzar 2012	20/65	7/61		7.8 %	2.68 [1.22, 5.89]
Fujii 2010	15/27	9/25		10.0 %	1.54 [0.83, 2.87]
Gharehbaghi 2010	4/71	5/79		5.1 %	0.89 [0.25, 3.19]
Karadag 2014	22/46	9/46		9.7 %	2.44 [1.26, 4.73]
Ramanathan 2004	48/98	66/195		47.4 %	1.45 [1.09, 1.92]
Speer 1995	25/40	17/33		20.0 %	1.21 [0.81, 1.83]
Total (95% CI)	**347**	**439**		**100.0 %**	**1.57 [1.29, 1.92]**

Total events: 134 (Modified bovine minced), 113 (Porcine minced lung)

Heterogeneity: $Chi^2 = 6.14$, $df = 5$ ($P = 0.29$); $I^2 = 19\%$

Test for overall effect: $Z = 4.42$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



Annexure 5

Analysis 3.10. Comparison 3 Modified bovine minced lung vs. porcine minced lung, Outcome 10 Treated patent ductus arteriosus (PDA).

Review: Comparison of animal-derived surfactants for the prevention and treatment of respiratory distress syndrome in preterm infants

Comparison: 3 Modified bovine minced lung vs. porcine minced lung

Outcome: 10 Treated patent ductus arteriosus (PDA)