

Brand Name: Surfaxin ®

Generic Name: lucinactant

Manufacturer¹: Discovery Laboratories, Inc.

Drug Class^{2,3}: Synthetic lung surfactant

Uses^{1,2,3}:

- **Labeled:** Prevention of respiratory distress syndrome in premature infants

Mechanism of Action^{1,2,3}: Lucinactant is a synthetic replacement for endogenous surfactant that contains the proprietary peptide, sinapultide, which is designed to mimic the human surfactant protein B (SP-B), a fatty acid, and 2 phospholipids. SP-B acts to enhance the ability of phospholipids to lower surface tension. Following endotracheal administration, lucinactant acts to restore surface activity to the lungs at the terminal airways and alveolar surface. In premature infants, lucinactant compensates for the deficiency of surfactant that may lead to respiratory distress syndrome.

Pharmacokinetics^{1,2,3}: No studies have been performed to characterize the pharmacokinetics of lucinactant in humans. Lucinactant is administered directly to the lung where the biophysical effects occur at the terminal airways and alveolar surface.

Efficacy:

Moya F, et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics*. 2005;115(4):1081-1087.

Study Design: Multicenter, randomized, double-blind, active control study

Description of study: *Methods:* 1294 very preterm infants, weighing 600 to 1250g and between the ages of 24 and 32 weeks gestational age, who had undergone endotracheal intubation were randomly assigned in a 2:2:1 ratio to receive lucinactant (527), colfosceril palmitate (509), or beractant (258) within 20 to 30 minutes after birth. Patients were excluded if at 5 minutes their Apgar score was < 3, they had a major congenital malformation or chromosomal abnormality, had a need for chest compression/epinephrine/bicarbonate, or fluid bolus, or had a mother with ruptured membranes > 2 weeks. Patients were evaluated on an ongoing basis for up to 36 weeks postmenstrual age or discharge. Primary outcomes were the development of RDS at 24 hours and the occurrence of death related RDS through 14 days age. Secondary outcomes were all-cause mortality rates, bronchopulmonary dysplasia (BPD) rates, and rates of other complications of prematurity. *Outcome Results:* Lucinactant significantly reduced the incidence of RDS at 24 hours, compared with colfosceril (39.1% vs. 47.2%; OR:0.68, 95% CI: 0.52-0.89), but had no significant difference in comparison with beractant (33.3%). Lucinactant also significantly reduced the RDS-related mortality rates by 14 days of life, compared to both colfosceril (4.7% vs. 9.4%; OR 0.43, 95% CI: 0.25-0.73) and beractant (10.5%; OR: 0.35, 95% CI: 0.18-0.66). Also, BPD at 36 weeks postmenstrual age was significantly less common with lucinactant than with colfosceril (40.2% vs. 45%; OR 0.75, 95% CI: 0.56-0.99), and the all-cause mortality rate at 36 weeks postmenstrual age was lower with lucinactant than with beractant (21% vs 26%; OR: 0.67, 95% CI: 0.45-1.00).

Limitations: The study was funded by Discovery Laboratories the manufacturer of lucinactant.

Unblinding could have occurred during this study. The patients in this study were between the ages of 24 and 32 weeks of age and weighed between 600g and 1250g making it difficult to extrapolate this study

information to patients outside of these parameters. The study was only powered to test differences between lucinactant and colfosceril palmitate, with beractant being included as a reference arm. Also, the distinction between outcomes caused by the surfactants and those resulting from premature birth is not always clearly defined, making it difficult to attribute an event solely to one of these factors.

Conclusions: This study shows that lucinactant offers very preterm infants at high risk for RDS important advantages, compared with colfosceril palmitate and beractant by reducing RDS and RDS-related mortality rates. This study demonstrated that synthetic surfactants consisting only of phospholipids (colfosceril palmitate) could be improved with the addition of peptides that mimic the functions of human surfactant protein- B (SP-B). Due to the potential risks associated with animal-derived products, lucinactant, the first surfactant to contain a functional protein analog of SP-B, is an effective therapeutic option for very preterm infants at risk for RDS.

Sinha S, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics*. 2005;115(4):1030-1038.

Study Design: Multicenter, randomized, double-blind, noninferiority active control study

Description of study: *Methods:* 252 infants born between 24 and 28 weeks of gestation, with birth weights between 600g and 1250g were randomly assigned to receive either lucinactant (124) or poractant alfa (128) within 30 minutes of life. Patients were excluded if their 5 minute Apgar score was <3, they were diagnosed with a major congenital malformation, had a known or suspected chromosomal abnormality, or were delivered > 2 weeks after ruptured membranes. Patients were eligible to receive additional doses if they met pre-determined criteria at the 6-hour interval. The primary outcome was the incidence of survival without bronchopulmonary dysplasia (BPD) through 28 days of age. Secondary outcomes included death at day 28 and 36 weeks postmenstrual age (PMA), air leaks, neuroimaging abnormalities, and other complications related to either prematurity or respiratory distress syndrome (RDS). *Outcome Results:* At 28 days, 45 of 119 infants given lucinactant were alive without BPD (37.8%; 95% CI: 29.1-46.5%), compared with 41 of 124 given poractant alfa (33.1%; 95% CI: 24.8-41.3%); at 36 weeks PMA, the rates were 64.7% and 66.9%, respectively. The corresponding mortality rate through day 28 for the lucinactant group was lower than that for the poractant alfa group (11.8%; 95% CI: 6.0-17.6% vs. 16.1%; 95% CI: 9.7-22.6%), as was the rate at 36 weeks PMA, 16% vs. 18.5%, respectively.

Limitations: This study was funded by Discovery Laboratories the manufacturer of lucinactant. The study did not enroll enough patients in order to achieve statistical noninferiority. The usual dose of lucinactant is divided into 4 equal aliquots that are each administered with the patient in a different position. In this study the lucinactant dose was divided into only 2 aliquots. The patients in this study were between the ages of 24 and 28 weeks gestation weighing between 600g to 1250g which makes it difficult to extrapolate this information to patients outside of these parameters. The distinction between outcomes caused by the surfactants and those resulting from premature birth is not always clearly defined, making it difficult to attribute an event solely to one of these factors.

Conclusion: Poractant alfa is an animal derived surfactant that contains trace amounts of surfactant protein-B, while lucinactant is a synthetic surfactant that contains a functional protein analog of SP-B, sinapultide. While this study was designed as a noninferiority type, the evidence is suggestive of the fact that using an exogenous surfactant with a greater amount of SP-B may be beneficial in the prevention and

treatment of RDS in very preterm infants. Further studies, that are appropriately powered, are needed to be able to detect if lucinactant decreases BPD and mortality for preterm infants more than beractant.

Moya F, et al. One-year follow-up of very preterm infants who received lucinactant for prevention of respiratory distress syndrome. *Pediatrics*. 2007;119(6):1361-1370.

Study Design: Prospective one-year follow-up of the SELECT and STAR trials

Description of study: *Methods:* All infants from the SELECT (Safety and Effectiveness of Lucinactant Versus Exosurf in a Clinical Trial) and STAR (Surfaxin Therapy Against Respiratory Distress Syndrome) trials who were randomly assigned lucinactant, colfosceril palmitate, beractant, or poractant alfa were prospectively followed through 1 year corrected age, at which point masked assessment of outcomes was performed for surviving infants. One-year survival was a key outcome of interest. Other parameters assessed included rates of rehospitalization, respiratory morbidity, and gross neurologic status. Data were analyzed by comparing the different surfactants within each trial and, in secondary analysis, combining data from both trials to compare lucinactant versus the animal-derived surfactants (beractant and poractant) used in these trials. Survival rates over time were compared by using the Wilcoxon test for survival through 1 year corrected age and logistic regression for comparison of fixed time points.

Outcome Results: In the primary analysis of the SELECT trial comparing lucinactant to either colfosceril or beractant, there were no significant differences in the proportion of infants who were alive through 1 year corrected age. By using raw data without attributing loss to follow-up as a death, mortality estimates at 1 year corrected age were computed to be 26.6% for lucinactant, 29.1% for colfosceril, and 28.3% for beractant. In the primary analysis of the STAR trial, significantly more infants treated with lucinactant were alive through 1 year corrected age compared with those who received poractant alfa. The estimates using raw data that did not attribute loss to follow-up as a death were 18.6% for lucinactant and 21.9% for poractant alfa. In the combined analysis, survival through 1 year corrected age was higher for infants in the lucinactant group versus that of infants in the animal derived surfactants group. The incidence of post-discharge rehospitalizations, total number of rehospitalizations, incidence of respiratory illnesses, and total number of respiratory illnesses were generally similar, as well as neurologic status at 1 year corrected age.

Limitations: This study was funded by Discovery Laboratories the manufacturer of lucinactant. Only short-term mortality data from previously published surfactant-comparison trials are available, and none of them evaluated survival at 1 year corrected age, which limits the comparison of conclusions. Analysis in which a raw incidence estimate was used may be biased since counting premature withdrawals as a death can overestimate the event rate, whereas counting premature withdrawals as survival can underestimate the event rate. The assumption that surfactant use played a role in either the rehospitalization or neurological status of these patients cannot be completely justified as these events could be due to premature birth in general.

Conclusion: The findings of this 1 year follow-up strongly suggest that the administration of lucinactant to very preterm infants at risk for RDS results in survival that is at least comparable with, if not superior to that of infants given animal-derived surfactants. The data from this study also strongly support the long term safety of using lucinactant for the prevention of RDS in very preterm infants.

Contraindications^{1,2,3} :

- **Adult patients with ARDS:** In clinical trials, adult patients receiving lucinactant for the treatment of ARDS had an increased incidence of death, multi-organ failure, sepsis, anoxic

encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism compared to patients receiving standard of care.

- **Infants, Children and Adolescents with ARDS:** Safety and efficacy data on the use of lucinactant in this population have not been established

Precautions ^{1,2,3}:

- Intrathecal use **ONLY**
- Administration of lucinactant requires an experienced clinician trained in the care, resuscitation, and stabilization of pre-term neonates
- Bradycardia, hypoxemia, reflux of lucinactant into the endotracheal tube, and airway obstruction may occur during administration. If these occur, stop the treatment and alleviate the condition. Suctioning may be required if obstruction is persistent or severe. Once stable, treatment can be resumed.

Adverse effects ^{1,2,3} : The distinction between adverse events associated with lucinactant and those that are the result of premature birth is not always clear.

Occurring at a greater frequency than in comparator surfactants (colfosceril, beractant, and poractant alfa) during clinical trial:

Cardiovascular

Bradyarrhythmia (3% to at least 10%)
Hypotension (at least 10%)
Patent ductus arteriosus (37% to 43%)

Dermatologic

Pallor

Endocrine

Hyperglycemia (at least 10%)
Hyponatremia (at least 10%)
Metabolic acidosis (at least 10%)
Respiratory acidosis (at least 10%)

Gastrointestinal

Necrotizing enterocolitis in fetus OR newborn (13% to 17%)

Hematologic

Anemia (at least 10%)

Hepatic

Jaundice (at least 10%)

Immunologic

Sepsis (44%)

Neurologic

Perinatal intraventricular hemorrhage (39% to 52%)
Periventricular leukomalacia (4% to 10%)

Ophthalmic

Retinopathy of prematurity (27% to 32%)

Respiratory

- Abnormal blood oxygen level (8% to 17%)
- Airway constriction
- Apnea (52% to 66%)
- Blocked endotracheal tube
- Neonatal pulmonary air leak (9% to 15%)
- Perinatal interstitial emphysema (3% to 9%)
- Pneumonia (at least 10%)
- Pneumothorax (3% to 4%)
- Pulmonary hemorrhage (6% to 10%)
- Reflux of drug into endotracheal tube

Drug Interactions²: Specific drug interaction studies have not been done with lucinactant. Theoretically, interactions may exist based off of data from the other exogenous pulmonary surfactants (beractant, poractant, colfosceril palmitate). Some surfactant anti-infective mixtures have been shown to affect the in vivo activity of other exogenous pulmonary surfactants when administered by inhalation. A reduced activity of tobramycin has been reported in the presence of surfactant, but was most apparent when used with the highest surfactant concentrations. This suggests that the surplus of phospholipids in the higher concentrations could potentially inactivate all aminoglycosides, considering their susceptibility to changes in pH. Interactions also occurred in vivo with amphotericin B surfactant mixtures. The mentioned interactions may be conditional and dependent on the concentrations and diluents used for the antimicrobial surfactant mixtures. These interactions may not prevent the delivery of surfactants and antimicrobials together as long as the interactions are carefully considered and the methods of delivery are chosen to minimize or overcome the interaction.

Dosing/Administration^{1,2,3}:

Intratracheally dosage for premature neonates:

The recommended dose for the prevention of RDS is 5.8mL/kg (birth weight) administered intratracheally. The total dose is divided and administered in 4 equal aliquots that are each administered separately followed by positive pressure mechanical ventilation until the infant is stable. Each aliquot (quarter dose) is administered with the infant in a different position to ensure even distribution throughout the lungs. The dose may be repeated up to 4 times during the first 48 hours of life; do not give doses more frequently than every 6 hours.

Dosing Chart by Birth Weight^{1,3}			
Birth Weight	Total Dose	Birth Weight	Total Dose
600 to 649 g	3.5 mL	950 to 999 g	5.5 mL
650 to 699 g	3.8 mL	1000 to 1049 g	5.8 mL
700 to 749 g	4.1 mL	1050 to 1099 g	6.1 mL
750 to 799 g	4.4 mL	1100 to 1149 g	6.4 mL
800 to 849 g	4.6 mL	1150 to 1199 g	6.7 mL
850 to 899 g	4.9 mL	1200 to 1250 g	7 mL

900 to 949 g	5.2 mL	---
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Storage requirements^{1,3}:

- Refrigerate unused vials between 36 and 46 degrees F (2 and 8 degrees C), protected from light. Do not freeze
- After warming, vials can be stored at room temperature and protected from light for up to 2 hours. Do not place warmed vials under refrigeration. Discard any unused portion or if not used within 2 hours.

Warming the vials^{1,2,3} :

- Record the date and time of warming in the space provided on the carton for each vial that is warmed. Warm the lucinactant vial for 15 minutes in a preheated dry block heater set at 111 degrees F (44 degrees C). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. The temperature of the suspension will be about 99 degrees F (37 degrees C) after drawn into a syringe for administration. Warmed vials should not be refrigerated after warming but may be stored in the carton (i.e.protected from light) at room temperature for no more than 2 hours

Intratracheal administration for premature neonates ^{1,2,3}:

- 1) For intratracheal administration only. Using a 16- or 18-gauge needle, slowly draw up the dose of warmed and vigorously shaken lucinactant intratracheal suspension into an appropriately sized syringe.
- 2) Before administration of the suspension, ensure patency and proper placement of the endotracheal tube. The endotracheal tube may be suctioned before lucinactant administration if necessary. Allow the infant to stabilize before administration.
- 3) The infant should be positioned in the right lateral decubitus position with head and thorax at a 30 degree upward inclined position. A 5-French end-hole catheter with the syringe of lucinactant attached should be threaded through a Bodai valve (or equivalent device) to allow maintenance of positive end-expiratory pressure. The tip of the catheter should be advanced into the endotracheal tube and positioned so that it is slightly distal to the end of the endotracheal tube.
- 4) The lucinactant dose should be delivered in 4 equal aliquots (each aliquot equal to one-fourth of the total dose). Administer the first aliquot while continuing positive pressure mechanical ventilation and maintaining a positive end-expiratory pressure of 4 to 5 cm H₂O. Adjust ventilator settings as necessary to maintain appropriate oxygenation and ventilation until the infant is stable (oxygen saturation of at least 90% and heart rate greater than 120 beats/minute).
- 5) Maintain adequate positive pressure ventilation, move the infant to the left decubitus position, and repeat the administration procedure for the second aliquot. Pause between administration of each aliquot to evaluate the infant's respiratory status. Move the infant to the right decubitus position for administration of the third aliquot, and to the left decubitus position for administration of the fourth aliquot.
- 6) Remove the catheter after administration of the fourth aliquot, and resume usual ventilator management. Keep the head of the infant's bed elevated at least 10 degrees for at least 1 to 2 hours. Unless the infant develops significant airway obstruction, do not suction the infant for the first hour after dosing.

Renal Impairment²: Specific guidelines for dosage in renal impairment are not available; it appears that no dosage adjustments are needed.

Hepatic Impairment²: Specific guidelines for dosage in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Use in special circumstances²:

- Pregnancy category risk and breastfeeding precautions are not relevant for this product since it is ONLY intended for use in neonates.

Conclusion:

Lucinactant is a safe and efficacious surfactant therapy for preterm infants at risk for RDS. Lucinactant is an advantageous option when compared to surfactants that contain only phospholipids (colfosceril) and those that have minimal amounts of SP-B, but carry potential risks due to being animal-derived (beractant and poractant). Lucinactant is superior to other synthetic surfactants that are available for RDS because it combines the valuable properties of the current options, phospholipids and sinapultide, a peptide analog of SP-B, while being void of the supply limitations that can be encountered with animal-derived products. Also, lucinactant has been proven to be equally efficacious to the other surfactants for survival in the preterm infants at 1 year follow-up. There is a likelihood that lucinactant does not cause the same immune reactions that are seen with animal-derived products; however, further studies are needed to determine such risks.

Recommended References:

1. Lucinactant [package insert]. Warrington, PA: Discover Laboratories, Inc.; March 2012
2. Lucinactant. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2012. Available at: <http://www.clinicalpharmacology.com> Accessed April 5, 2012.
3. Lucinactant. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Accessed April 5, 2012.
4. Moya F, et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics*. 2005;115(4):1081-1087.
5. Sinha S, et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics*. 2005;115(4):1030-1038.
6. Moya F, et al. One-year follow-up of very preterm infants who received lucinactant for prevention of respiratory distress syndrome. *Pediatrics*. 2007;119(6):1361-1370.

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