

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SURFAXIN® safely and effectively. See full prescribing information for SURFAXIN.

SURFAXIN (lucinactant) Intratracheal Suspension

Initial U.S. Approval: [year]

INDICATIONS AND USAGE

SURFAXIN is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of SURFAXIN is 5.8 mL per kg birth weight administered by intratracheal administration. (2.1)
- Up to 4 doses of SURFAXIN can be administered in the first 48 hours of life. (2.1)
- Doses should be given no more frequently than every 6 hours. (2.1)

DOSAGE FORMS AND STRENGTHS

Intratracheal Suspension: 8.5 mL suspension in a glass vial. Each mL contains 30 mg phospholipids (22.50 mg dipalmitoylphosphatidylcholine and 7.50 mg palmitoyloleoyl-phosphatidylglycerol, sodium salt), 4.05 mg palmitic acid, and 0.862 mg sinapulfotide. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Acute Changes in Lung Compliance: Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status. (5.1)
- Administration-Related Adverse Reactions: If adverse reactions including bradycardia, oxygen desaturation, reflux of SURFAXIN into the endotracheal tube (ETT), and airway/ETT obstruction occur during administration of SURFAXIN, dosing should be interrupted and the infant's clinical condition assessed and stabilized. Suctioning of the ETT or reintubation may be required if airway obstruction persists or is severe. (5.2)
- Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS): Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS. (5.3)

ADVERSE REACTIONS

Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Discovery Laboratories, Inc. at 1-877-SURFAXN or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

2.2 Directions for Use

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Acute Changes in Lung Compliance

5.2 Administration-Related Adverse Reactions

5.3 Increased Serious Adverse Reactions in Adults with ARDS

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Prevention of Neonatal Respiratory Distress Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SURFAXIN® (lucinactant) Intratracheal Suspension is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS. SURFAXIN reduces the incidence of RDS at 24 hours and mortality due to RDS.

2 DOSAGE AND ADMINISTRATION

For intratracheal administration only.

SURFAXIN should be administered by or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants.

2.1 Dosing

The recommended dose of SURFAXIN is 5.8 mL per kg birth weight. Up to 4 doses of SURFAXIN can be administered in the first 48 hours of life. Doses should be given no more frequently than every 6 hours.

No information is available on doses greater than 5.8 mL per kg birth weight, the effects of more than 4 doses, or dosing more frequently than every 6 hours.

Dosage may be determined from Table 1.

Table 1. Dosing Chart

Birth Weight (g)	Total Dose (mL)	Birth Weight (g)	Total Dose (mL)
600-649	3.5	950-999	5.5
650-699	3.8	1000-1049	5.8
700-749	4.1	1050-1099	6.1
750-799	4.4	1100-1149	6.4
800-849	4.6	1150-1199	6.7
850-899	4.9	1200-1250	7.0
900-949	5.2		

2.2 Directions for Use

Preparation

Before use, warm the vial for 15 minutes in a preheated dry block heater set at 44°C (111°F). After warming, *shake the vial vigorously* until SURFAXIN is a uniform and free-flowing suspension. The temperature of the product will be approximately 37°C (99°F) or less after the product is drawn into a syringe for administration.

For each vial of SURFAXIN that is warmed, record the date and time of warming in the space provided on the carton. If not used immediately after warming, SURFAXIN can be stored protected from light (i.e., in the carton) at room temperature for up to 2 hours. Do not return SURFAXIN to the refrigerator after warming. Discard the product if not used within 2 hours of warming. Vials are for single use only. Discard any unused portion of SURFAXIN.

Administration

Visually inspect SURFAXIN before use. After being warmed and vigorously shaken, SURFAXIN should be free-flowing and opaque white to off-white. Use aseptic technique to slowly draw up the appropriate amount of SURFAXIN into a single, appropriately sized syringe, depending on the total dose volume, using a 16- or 18-gauge needle.

Before administering SURFAXIN, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering SURFAXIN. The infant should be allowed to stabilize before proceeding with dosing.

Position the infant in the right lateral decubitus position with head and thorax inclined upward 30°. Attach the syringe containing SURFAXIN to a 5-French end-hole catheter. Thread the catheter through a Bodai valve or equivalent device that allows maintenance of positive end-expiratory pressure and then advance the tip of the catheter into the endotracheal tube. Position the catheter such that its tip is slightly distal to the end of the endotracheal tube.

Each SURFAXIN dose should be delivered in 4 aliquots. Instill the first aliquot of the dose (one-quarter of the total volume) as a bolus while continuing positive pressure mechanical ventilation and maintaining positive end-expiratory pressure of 4 to 5 cm H₂O. Ventilator settings may be adjusted at the discretion of the clinician to maintain appropriate oxygenation

and ventilation. Ventilate until the infant is stable, that is, has an oxygen saturation of at least 90% and a heart rate greater than 120 beats per minute. Repeat the procedure with the infant in the left decubitus position while maintaining adequate positive pressure ventilation. Repeat the procedure with the infant in the right, then left decubitus position to deliver a total of 4 aliquots. A pause should separate administration of the aliquots to allow for an evaluation of the infant's respiratory status.

After instillation of the last aliquot, remove the catheter and resume usual ventilator management and critical care while keeping the head of the infant's bed elevated at least 10 degrees for at least 1-2 hours. Do not suction the infant during the first hour after dosing unless signs of significant airway obstruction occur.

Use the same technique for additional doses, if indicated.

3 DOSAGE FORMS AND STRENGTHS

Intratracheal Suspension: 8.5 mL suspension in a glass vial. Each mL contains 30 mg phospholipids [22.50 mg dipalmitoylphosphatidylcholine (DPPC) and 7.50 mg palmitoyloleoyl-phosphatidylglycerol, sodium salt (POPG, Na)], 4.05 mg palmitic acid (PA), and 0.862 mg sinapltide.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Changes in Lung Compliance

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

5.2 Administration-Related Adverse Reactions

Frequently occurring adverse reactions related to the administration of SURFAXIN include bradycardia, oxygen desaturation, reflux of drug into the endotracheal tube (ETT), and airway/ETT obstruction. If any of these events occur, dosing with SURFAXIN should be interrupted and the infant's clinical condition assessed and stabilized. Suctioning of the ETT or reintubation may be required if airway obstruction persists or is severe. After the patient is stable, dosing may proceed with appropriate monitoring.

5.3 Increased Serious Adverse Reactions in Adults with ARDS

In a two-part clinical trial in adult patients with ARDS, compared to standard of care, patients who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in the treatment of ARDS.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Studies in Premature Infants at Risk for Respiratory Distress Syndrome

The safety data described below reflect exposure to SURFAXIN at a dose of 5.8 mL per kg (up to 4 doses) administered in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 infants 32 weeks gestational age or less in 2 randomized double-blind, active-controlled clinical studies in which infants could receive up to 4 doses of surfactant intratracheally [see *Clinical Studies (14)*]. Study 1 was conducted in 1294 premature infants who weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants received 1 of 3 surfactants, SURFAXIN (N = 524), colfosceryl palmitate (N = 506), or beractant (N = 258). Study 2 was conducted in 252 premature infants who weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants received SURFAXIN (N = 119) or poractant alfa (N = 124).

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Administration-related adverse reactions (endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption) were assessed in both SURFAXIN controlled clinical studies. Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 2) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively. These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 3).

Table 2. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies^a

	Study 1 ^b			Study 2 ^c	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
Total Number of Events (Events per 100 Doses)					
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

^a Table includes only infants who received study treatment.

^b In Study 1 doses were administered in 4 aliquots.

^c In Study 2 doses were administered in 2 aliquots.

Table 3. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceryl palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
- Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

Follow-up Evaluations

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceryl palmitate, beractant, or poractant alfa).

Clinical Study in Adults with ARDS

The safety and efficacy of lucinactant administered in 2 doses separated by 48 hours via segmental bronchoscopic lavage in adults with ARDS was evaluated in a two-part clinical trial in

124 adult patients. Twenty-two patients were studied in the initial open-label portion of the trial (Part A) and 102 patients participated in a subsequent randomized controlled portion (Part B). Compared to standard of care, patients who received treatment with lucinactant via segmental bronchoscopic lavage at doses up to 50 mL per lung segment had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia/decreased oxygen saturation, pneumothorax, hypotension, and pulmonary embolism compared to those patients receiving standard of care. SURFAXIN is not indicated for use in the treatment of ARDS.

10 OVERDOSAGE

There have been no reports of overdose following the administration of SURFAXIN.

If respiration, ventilation, or oxygenation is clearly affected after an accidental overdose, aspirate as much of the suspension as possible and provide the infant with supportive treatment.

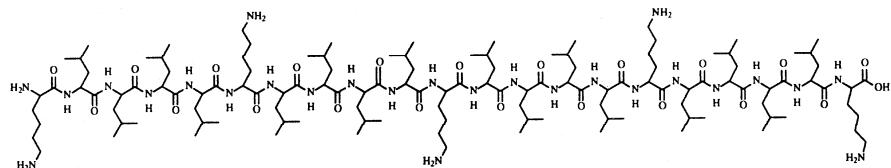
11 DESCRIPTION

SURFAXIN (lucinactant) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a synthetic formulation consisting of phospholipids, a fatty acid, and sinapultide (KL₄ peptide), a 21-amino acid hydrophobic synthetic peptide. The chemical names, structures, and empirical formulas of the 4 active components of SURFAXIN are:

Sinapultide (KL₄ acetate)

Chemical Name: L-Lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl-L-leucyl-L-lysine, acetate

Structure:



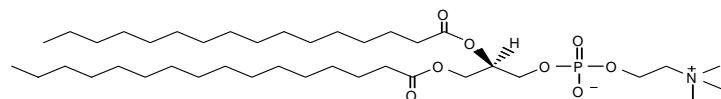
Empirical Formula: C₁₂₆H₂₃₈N₂₆O₂₂

Molecular Weight: 2469.46

DPPC

Chemical Name: 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine

Structure:



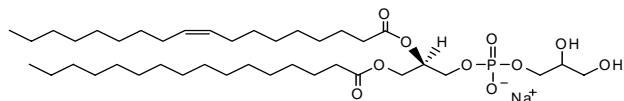
Empirical Formula: C₄₀H₈₀NO₈P

Molecular Weight: 734.06

POPG, Na

Chemical Name: 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphoglycerol, sodium salt

Structure:



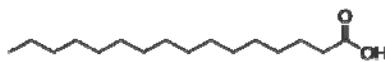
Empirical Formula: C₄₀H₇₆O₁₀PNa

Molecular Weight: 771.00

PA

Chemical Name: Palmitic acid (hexadecanoic acid)

Structure:



Empirical Formula: C₁₆H₃₂O₂

Molecular Weight: 256.43

SURFAXIN is a white to off-white opaque gel-like suspension at 2° to 8°C (36° to 46°F), which becomes a free-flowing suspension upon warming for 15 minutes in a dry block heater set at 44°C (111°F). Each mL of SURFAXIN provides 30 mg phospholipids (22.50 mg DPPC and 7.50 mg POPG, Na), 4.05 mg PA, and 0.862 mg sinapuntide in tromethamine and sodium chloride. Glacial acetic acid is used to adjust the pH of the buffer to 7.4 (range 7.0 to 8.0). SURFAXIN contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous pulmonary surfactant lowers surface tension at the air-liquid interface of the alveolar surfaces during respiration and stabilizes the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in premature infants results in RDS. SURFAXIN compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

Activity

In vitro

Lucinactant lowers minimum surface tension to ≤ 6 dynes per cm, as assessed by the pulsating bubble surfactometer.

In vivo

Lucinactant improves lung compliance and respiratory gas exchange in premature fetal rabbits, lambs and non-human primates with RDS under experimental conditions with controlled airflow and oxygen pressure. The clinical relevance of these animal findings to humans is unknown.

12.2 Pharmacokinetics

SURFAXIN is administered directly to the lung, where biophysical effects occur at the terminal airways and alveolar surface. No human pharmacokinetic studies have been performed to characterize the absorption, distribution, metabolism, or elimination of SURFAXIN.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess potential carcinogenic effects of SURFAXIN have not been conducted.

Lucinactant was not mutagenic in the bacterial reverse mutation assay (Ames test), chromosomal aberration assay in Chinese hamster ovary cells, or mouse micronucleus assay.

No studies to assess reproductive effects of SURFAXIN have been performed.

14 CLINICAL STUDIES

14.1 Prevention of Neonatal Respiratory Distress Syndrome

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). This study included 646 males and 648 females who weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Seventy-eight percent of the infants were white, 1% black, and 21% classified as other. Study participants were from Europe and Latin America. Within the first 30 minutes after birth, infants were randomized to receive 1 of 3 surfactants, SURFAXIN (N = 527), colfosceril palmitate (N = 509), or beractant (N = 258). SURFAXIN was administered at a dose of 5.8 mL per kg, colfosceril palmitate at a dose of 5.0 mL per kg, and beractant at a dose of 4.0 mL per kg. Infants in the SURFAXIN and beractant groups could be given up to 3 additional doses between 6 and 24 hours of birth, as often as every 6 hours, if they subsequently developed RDS and required mechanical ventilation with an $\text{FiO}_2 \geq 0.30$ and a mean airway pressure (MAP) $\geq 6 \text{ cm H}_2\text{O}$. Infants in the colfosceril palmitate group could receive up to 2 additional doses at least 12 hours apart if they met the retreatment criteria. Some infants received sham air to maintain blinding of the study. All doses were calculated based on birth weight. Infants were followed through 12-months corrected age.

Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an $\text{FiO}_2 \geq 0.30$) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. Results for the primary endpoint comparisons and other relevant endpoints are shown in Table 4.

Table 4. Results from a Controlled Prophylaxis Study in Preterm Infants (Study 1)

	SURFAXIN (N = 527) n (%)	Colfosceryl palmitate (N = 509) n (%)	P-value SURFAXIN vs. Colfosceryl palmitate
RDS at 24 hours	206 (39)	240 (47)	<0.01
RDS-related mortality through Day 14	25 (5)	48 (9)	<0.01
Non-RDS-related mortality through Day 14	59 (11)	37 (7)	0.04
Sepsis-related mortality through Day 14	21 (4)	17 (3)	0.70
All-cause mortality			
Through Day 28	100 (19)	108 (21)	0.23
Through 36-weeks PCA	111 (21)	121 (24)	0.18
Pulmonary air leak through Day 7, all types	82 (16)	93 (18)	0.15
Oxygen requirement			
At Day 28	304 (58)	316 (62)	0.06
At 36-weeks PCA	210 (40)	227 (45)	0.05

A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted (Study 2). The study included 126 males and 126 females who weighed between 600 g and 1250 g at birth with a gestational age \geq 24 weeks but < 29 weeks. Eighty-three percent of the infants were white and 5% black. Study participants were from North America and Europe. Within the first 30 minutes after birth, infants were randomized to receive 1 of 2 surfactants, SURFAXIN (N = 124) or poractant alfa (N = 128). SURFAXIN was administered at a dose of 5.8 mL per kg and poractant alfa was dosed at 2.2 mL per kg for the first dose and 1.25 mL per kg for subsequent doses. Infants in each group could be given up to 2 additional doses during the first 48 hours of life if they continued to require mechanical ventilation with an FiO₂ \geq 0.30 to maintain arterial PaO₂ \geq 50 mmHg or an oxygen saturation \geq 90% and a chest radiograph consistent with RDS. The primary endpoint was the incidence of being alive without bronchopulmonary dysplasia at Day 28 of life. Bronchopulmonary dysplasia was defined as a requirement for mechanical ventilation or use of supplemental oxygen in order to maintain oxygen saturation \geq 90%. The study was designed with the intent of demonstrating non-inferiority between SURFAXIN and poractant alfa with a planned sample size of 248 infants per treatment group. However, the basis of the non-inferiority margin could not be justified; the study was also terminated prematurely. As such, Study 2 can only be used to support the safety of SURFAXIN relevant to another surfactant product.

There is no controlled experience with the use of SURFAXIN in conjunction with experimental therapies for RDS (e.g., high-frequency ventilation or extracorporeal membrane oxygenation).

16 HOW SUPPLIED/STORAGE AND HANDLING

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming [*see Directions for Use (2.3)*].

Manufactured by Discovery Laboratories, Inc.
Warrington, PA 18976