First breath. First steps. First day of school.

For babies with RDS, tomorrow is
made possible by Infasurf® (calfactant).

Infasurf®
(calfactant)

Please see Important Safety Information on inside back cover.

For so many premature babies and their families, tomorrow is goal number one. And it's ONY Biotech's goal, too. As one of the leading surfactant choices to prevent and treat respiratory distress syndrome in newborns, Infasurf® (calfactant) turns todays into tomorrows by rapidly adsorbing, lowering surface tension, and improving lung compliance overall.

Infasurf® (calfactant), made to do more.

Infasurf® (calfactant) is the only natural, FDA approved surfactant manufactured in the U.S. by a unique calf lung lavage method. This process yields a surfactant that closely mirrors native calf lung surfactant in both composition and activity.

- Rapid onset of action[1]
- Sustained respiratory improvement[1,2]
- Demonstrates single-dose success[3,4,5]
- Proven safe and effective[1,2]
- Ready to use. No mixing or warming required[6]
- Cost effective[4]
- Highest SP-B to phospholipid ratio[6]
- Biophysically potent[7,8]
- Only surfactant that retains surfactant cholesterol[9]
- Lowest dynamic and surface viscosity[8,10]
- Lung lavage vs. minced manufacturing process[11]
- No preservatives[6]

INDICATION

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

PROPHYLAXIS

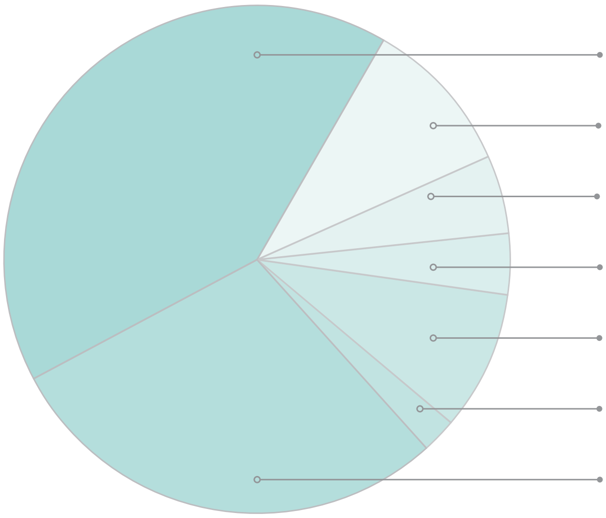
Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

TREATMENT

Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

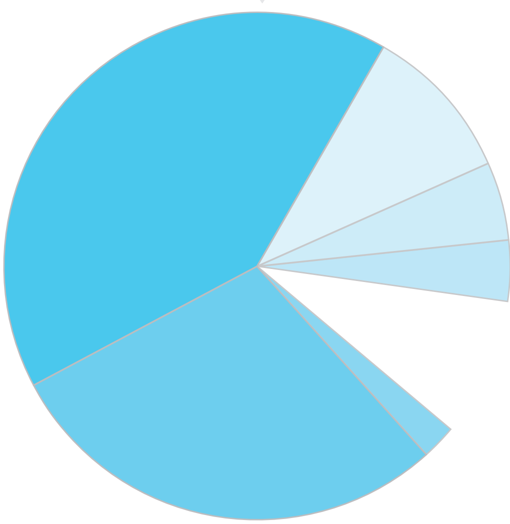
Mirrors native calf lung surfactant.

Infasurf® (calfactant) resembles native lung surfactant in both composition and activity due to our lung lavage manufacturing process.



Native Lung Surfactant[11]

41%	Disaturated Phosphatidylcholine (DSPC)
10%	Phosphatidyl Glycerol (PG)
5%	Cholesterol (Chol)
4%	Other Phospholipids (PLS)
9%	SP-A
2%	SP-B, SP-C
29%	Unsaturated Phosphatidylcholine (USPC)



Infasurf® (calfactant)[12]

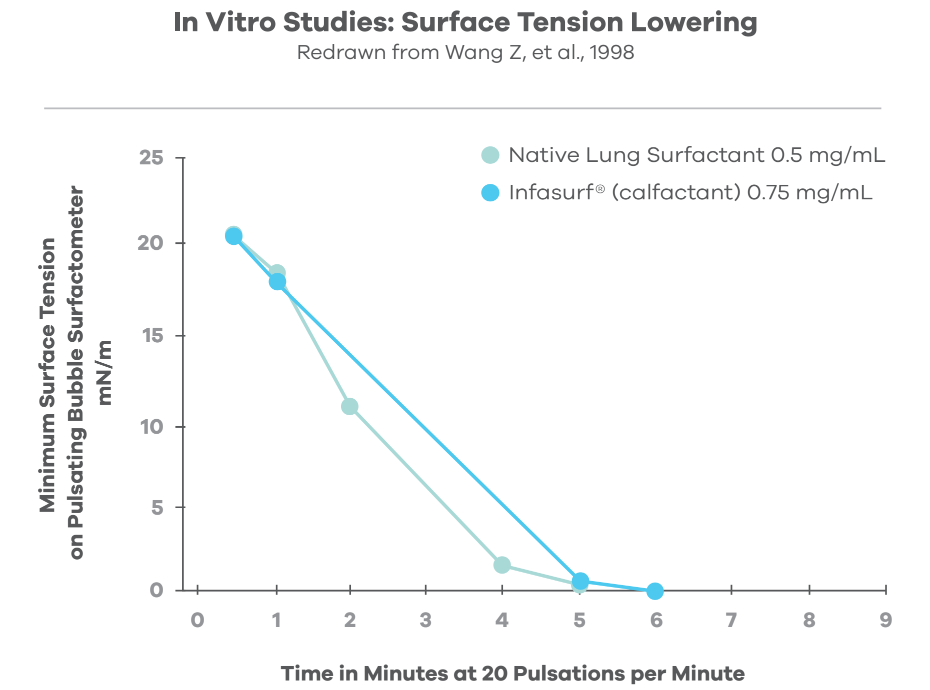
Infasurf® (calfactant) is native lung surfactant without SP-A

SAME % OF SP-B TO TOTAL PHOSPHOLIPIDS

RETAINS NATURAL CHOLESTEROL LEVEL

- All essential components of native lung surfactant are maintained in Infasurf® (calfactant) due to our unique lavage manufacturing process[12]
- Surfactant protein B (SP-B) is essential for forming the surfactant film that lines the alveoli[13,14]
- Infasurf® (calfactant) is the only surfactant that retains natural cholesterol, which aids the rapid spread of the surfactant film during respiration[9]

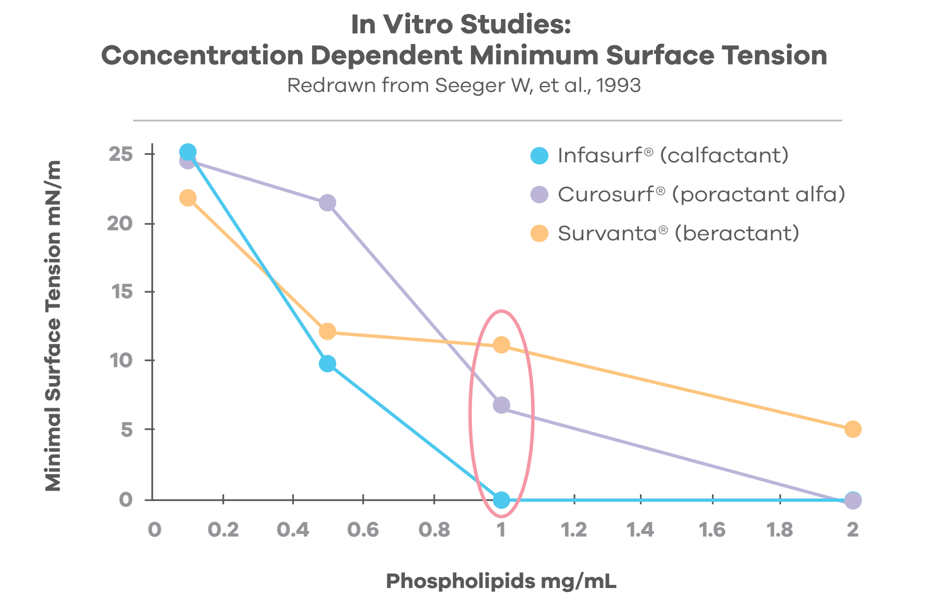
Safety Information: Infasurf® (calfactant) is intended for intratracheal use only.



Surface tension lowering ability of Infasurf® (calfactant) and Native Lung Surfactant

- Demonstrates surface tension lowering activity equal to that of native lung surfactant[8]
- Zero surface tension[7,8]
  - Helps prevent alveoli collapse
  - Increases the ability to achieve equal distribution of air throughout the lung
  - Aids rapid respiratory recovery by increasing lung compliance

Biophysically potent[7]



Concentration necessary to reach zero surface tension

- At a concentration of 1 mg/mL (circled area), Infasurf® (calfactant) reaches zero surface tension
- Higher concentrations are required by Curosurf® (poractant alfa) to reach zero surface tension; Survanta® (beractant) never reaches zero surface tension

Preclinical and biologic testing do not predict clinical effects.

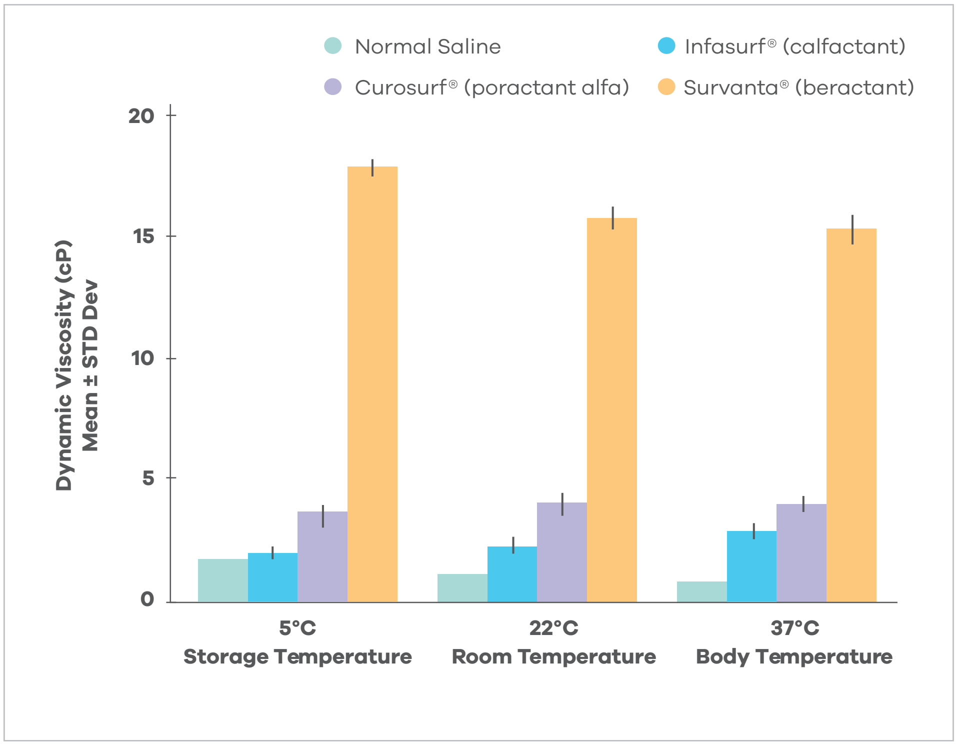
Safety Information: TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf® (calfactant) administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

There are no prospective, randomized clinical trials comparing Infasurf® and Curosurf® with respect to safety or efficacy.

Infasurf® (calfactant) has lower dynamic viscosity.[10]

Low resistance to flow (dynamic viscosity) may improve the uniformity of distribution in the lung.

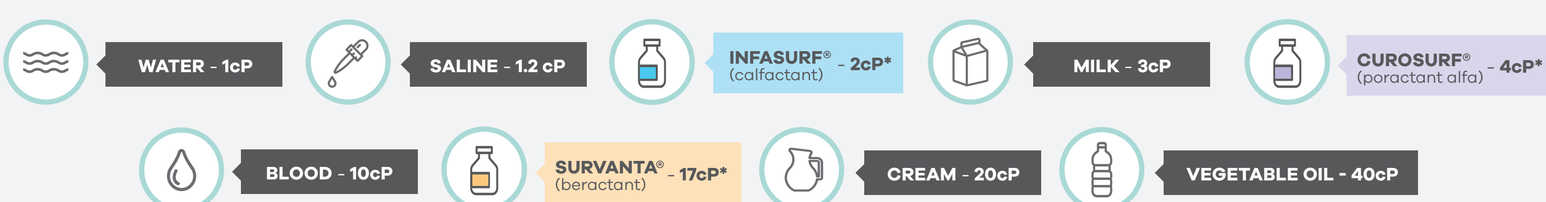
Dynamic Viscosities of Lung Surfactants[10]



Changes in dynamic viscosity with temperature measured by comparing force necessary to produce a constant flow through a conduit.

- Low dynamic viscosity may impact ease of flow down the trachea and distal airways
- Infasurf® (calfactant) has the lowest dynamic viscosity at all temperatures
- Temperature changes vary dynamic viscosity only slightly for all surfactants

Approximate Dynamic Viscosities of Common Substances[15,16]



*At room temperature.

Safety Information: THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

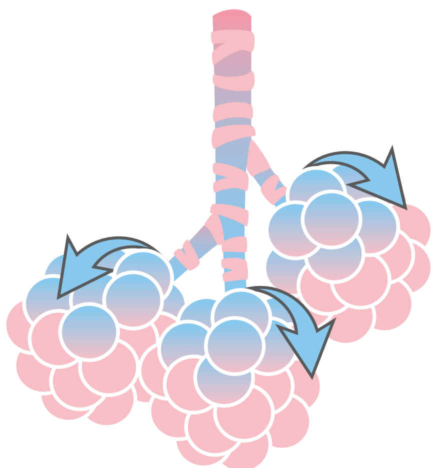
There are no prospective, randomized clinical trials comparing Infasurf® and Curosurf® with respect to safety or efficacy.

Please see Important Safety Information on inside back cover.

Infasurf® (calfactant) has lower surface viscosity.[9]

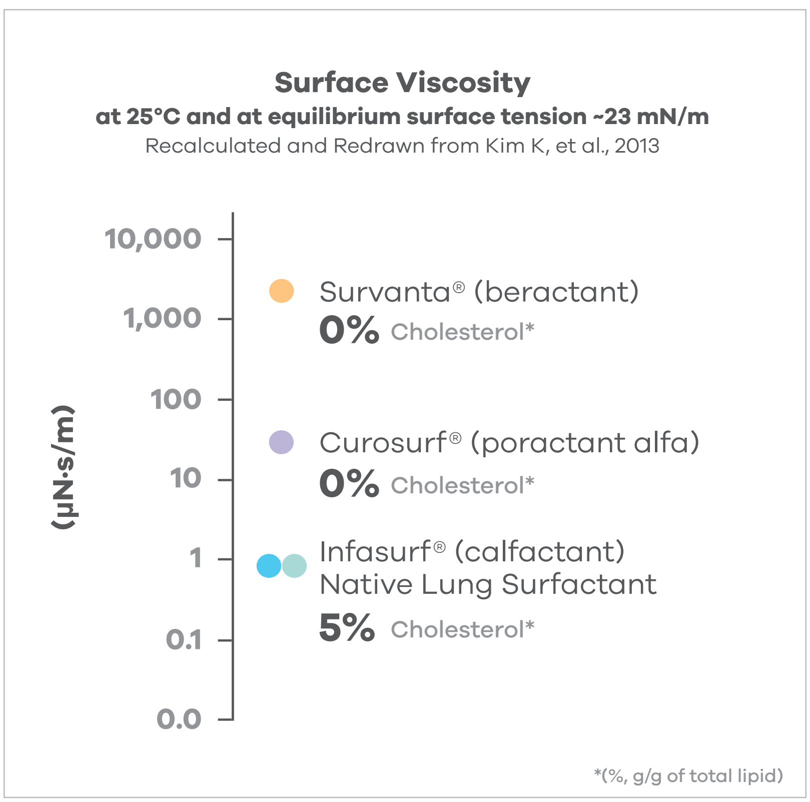
The presence of cholesterol induces low surface viscosity which aids the spreading of surfactant film during respiration.

Cholesterol in Surfactant



- Cholesterol contributes to the rapid spreading of native lung surfactant[9]
- The lavage manufacturing process retains natural cholesterol in Infasurf® (calfactant)[12]
- Infasurf® (calfactant) is the only surfactant available in the U.S. that contains a natural cholesterol level[9]

Impact of Cholesterol on Surface Viscosity[9]



- Native lung surfactant and Infasurf® (calfactant) contain the same level of cholesterol
- Cholesterol is removed from Survanta® (beractant) and Curosurf® (poractant alfa), which are produced by a minced lung manufacturing process

Retention of cholesterol in a surfactant has not been shown to have an effect on clinical outcomes.

Highest level of SP-B to phospholipid ratio makes Infasurf® (calfactant) less affected by inhibitory proteins.

Plasma proteins can leak into alveolar space and inhibit surfactant function. Infasurf® (calfactant) was the most resistant to the three surfactant-inhibiting proteins studied.[7]

Comparison of SP-B in Exogenous Surfactants*

SP-B Content as a % of Phospholipids

Native Lung Surfactant (calf)	**Infasurf®** (calfactant)	**Curosurf®** (poractant alfa)	**Survanta®** (beractant)
0.74%[12]	0.74%[6]	0.59%[17]	Unspecified[18]

- Infasurf® (calfactant) contains the highest levels of SP-B as a percentage of total phospholipids (0.74%),[6,7] same as native calf lung surfactant[12]
- Lab bench testing has shown surfactant films high in SP-B may be less susceptible to inhibitory proteins[7]

Protein Inhibition Profile for Surfactants[7]

Adsorption and Surface Tension Lowering

Surfactant	**Inhibitory Protein** (8 mg/mL concentration)		
	Hemoglobin	**Albumin**	**Fibrinogen**
Infasurf® (calfactant)	Unaffected	Unaffected	Moderately Affected
Curosurf® (poractant alfa)	Severely Affected	Severely Affected	Severely Affected
Survanta® (beractant)	Severely Affected	Severely Affected	Severely Affected

- Even when exposed to high levels of inhibitory proteins, Infasurf® (calfactant) still rapidly adsorbs and lowers surface tension to near zero
- Adsorption and surface tension lowering properties of the other surfactants are inhibited by plasma proteins at low concentrations

* Chart does not imply clinical superiority of Infasurf® (calfactant).

While clinical studies have demonstrated that SP-B is an essential element, they have not determined the minimum SP-B to phospholipid ratio required for optimal surfactant efficacy.

Safety Information: Infasurf® (calfactant) should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation. Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

There are no prospective, randomized clinical trials comparing Infasurf® and Curosurf® with respect to safety or efficacy.

Please see Important Safety Information on inside back cover.

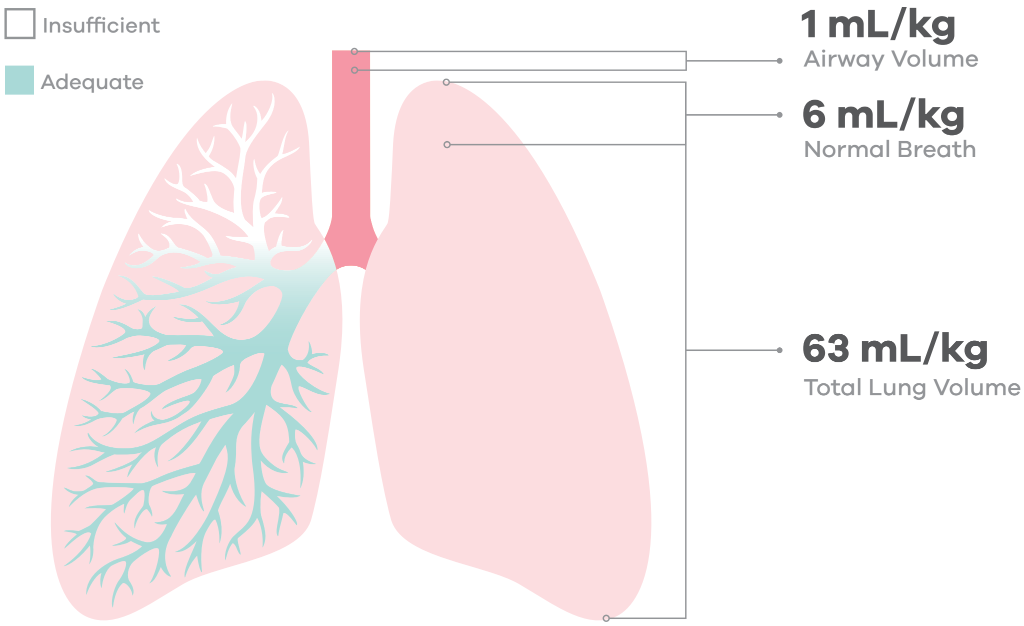
Infasurf® (calfactant) has an instillation volume for effective distribution.

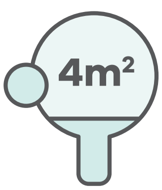
Volume should be sufficient to reach distal airways, yet small enough to be tolerated by the patient.[19]

Magnitude of Surfactant Distribution Challenge

- ~ **16** generations from trachea to respiratory bronchioles and saccules
- ~ **60,000** terminal bronchioles
- ~ **250,000** binary branch points
- ~ **50,000** distal airways leading to saccules
- ~ **3,000,000** terminal air spaces

Infant Lung[20]





The surface area of a baby's lung equals 4 square meters[20], about the size of a regulation ping-pong table

3 mL/kg
Infasurf®
(calfactant)
Dose

A dose of Infasurf® (calfactant) still leaves room for 60 mL/kg of air (95% of total lung capacity)

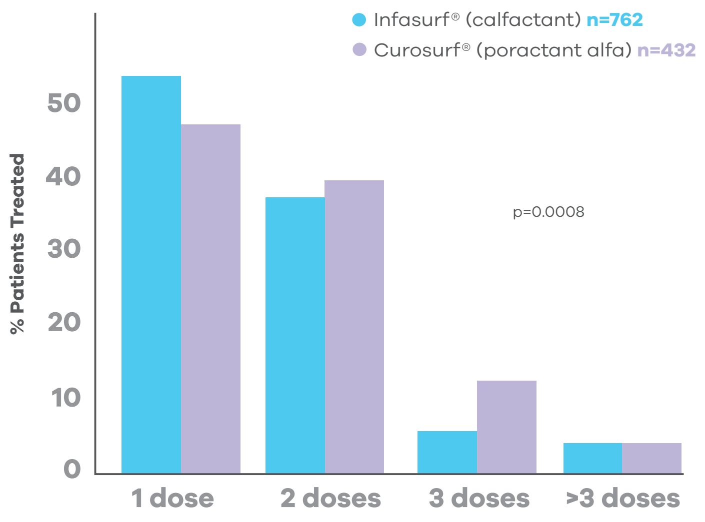
Variables that Contribute to Surfactant Distribution in the Lungs[19]	
Property	**Effect**
Surface Activity	Essential for rapid adsorption and spreading
Gravity	Surfactant distributed with fluid by gravity in large airways
Volume	The higher the volume, the better the distribution
Rate of Administration	Rapid administration results in better distribution
Ventilator Settings	Pressure and positive end-expiratory pressure clear airways of fluid
Fluid Volume in Lung	Higher volumes of fetal lung fluid or edema fluid may result in a better distribution

- Higher surfactant instillation volumes result in more uniform distribution[22,23]

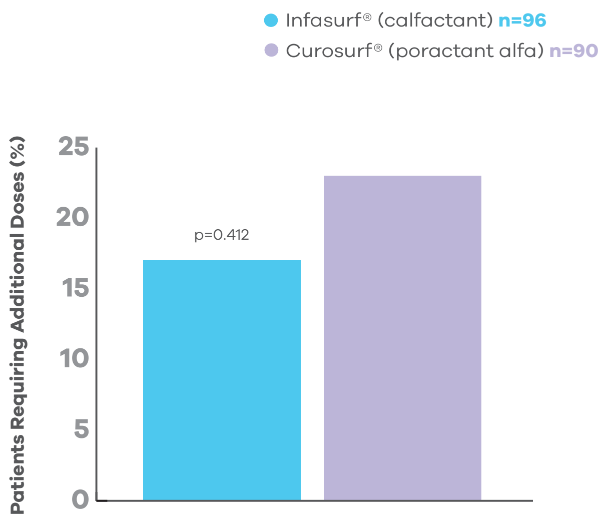
Clinical studies have not established that lower volume results in superior efficacy or safety based on clinically relevant endpoints.[21]

Infasurf® (calfactant) can result in fewer doses and high rates of single-dose success.

Low Re-Dose Rates*

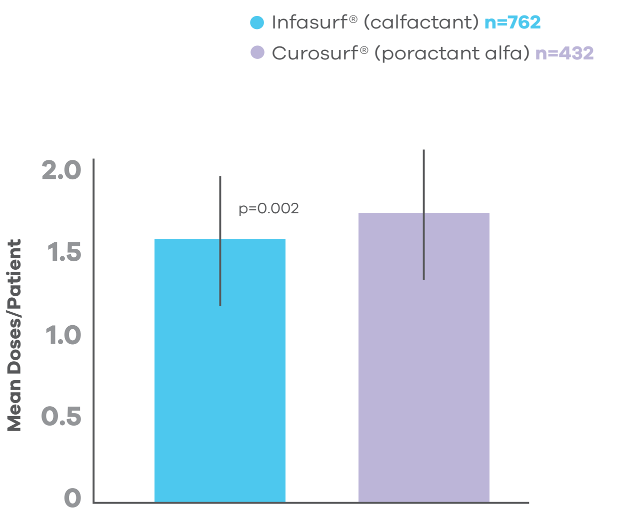


All treated patients
Zayek M, et al.

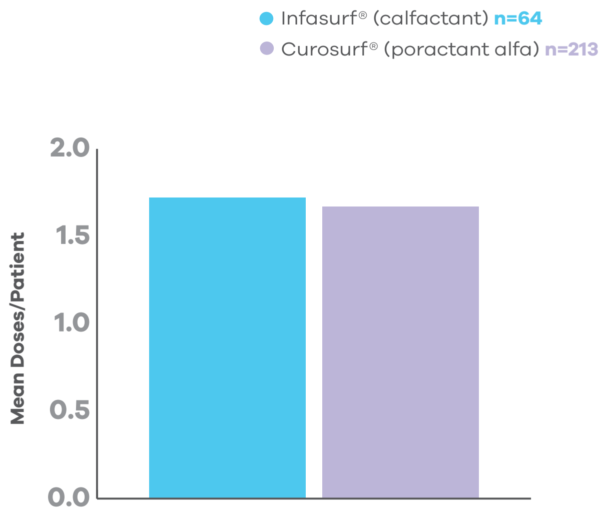


All treated patients
Jeon G, et al.

Number of Doses per Patient*



All treated patients
Zayek M, et al.



All treated patients
Gerdes J, et al.

*Infasurf® (calfactant) All Doses 105 mg/kg, Curosurf® (poractant alfa) Initial Dose 200 mg/kg, Repeat Doses 100 mg/kg

- Repeat dosing rates varied depending on patient demographics, surfactant utilized, hospital protocols and established practices.[4] Clinical studies have not determined superior safety or efficacy with fewer doses.

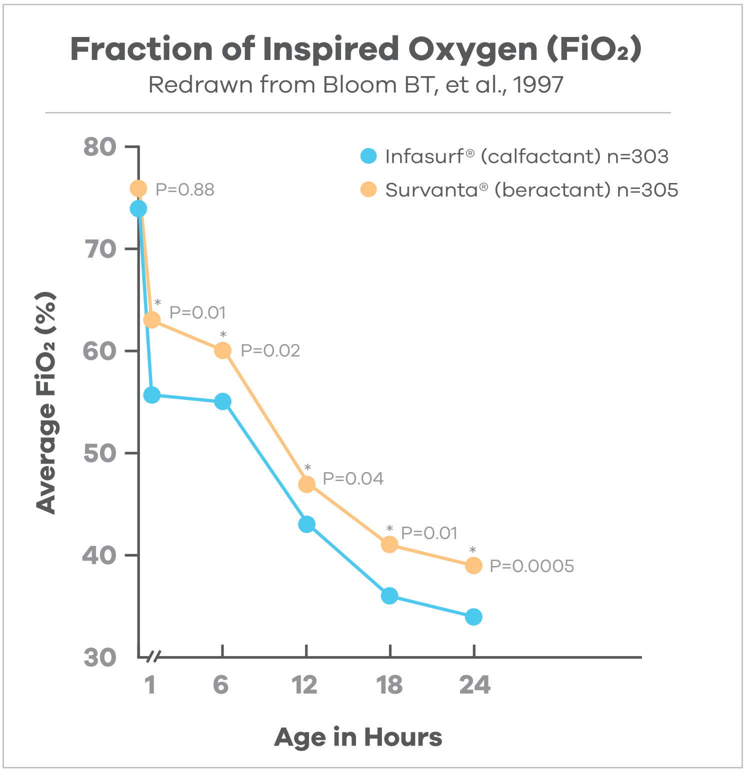
There are no prospective, randomized clinical trials comparing Infasurf® and Curosurf® with respect to safety or efficacy.

Please see Important Safety Information on inside back cover. Refer to list of Re-Dose Rate Publications included in back pocket.

With the first dose, Infasurf® (calfactant) delivers a rapid, sustained response.

Potential for single-dose success and fewer doses.

Lowered FiO_2 significantly in the critical first 24 hours



*Significant difference (*P*<.05) between groups at time indicated.

GOLDEN HOUR	24 HOURS
Supplemental Oxygen 1/3	Supplemental Oxygen 3/4

- Potential for less oxygen requirement and less days on mechanical ventilation[1]
- Infasurf® (calfactant) demonstrates a long duration of action[1,2]
- Improvements in FiO_2 requirements may not necessarily reduce dosing or predict long-term outcomes

Safety Information: Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf® (calfactant) instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Infasurf® (calfactant) is cost effective.

A key factor affecting cost is the surfactant's first-dose regimen, based on weight, combined with vial sizes available.

Infasurf® (calfactant) - Each Dose[6]

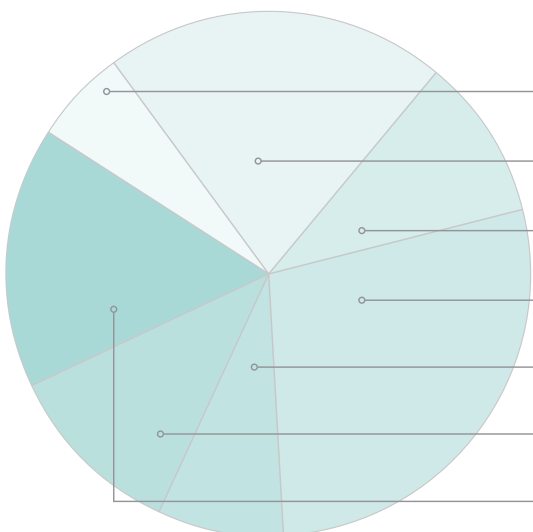
Vial	Treats up to:
Small 3 mL	**1000g**
Large 6 mL	**2000g**

Curosurf® (poractant alfa) - Initial Dose[17]

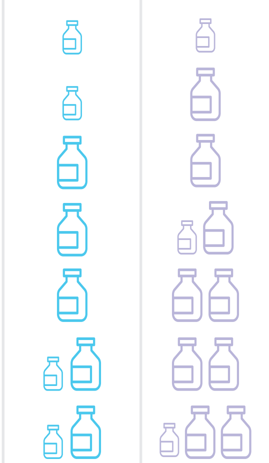
Vial	Treats up to:
Small 1.5 mL	**600g**
Large 3 mL	**1200g**

Patient Demographics of Treated Infants 2005-2010*

Birth weight determines the dose required.



Birth Weight Distribution*		Vials Needed[6,17] Infasurf®	Curosurf®
6%	≤ 600g		
21%	601 - 1000g		
10%	1001 - 1200g		
28%	1201 - 1800g		
8%	1801 - 2000g		
11%	2001 - 2400g		
16%	2401 - 3000g		
Number of vials required to treat a 100-patient population with an initial dose:		**127**	**179**



- All patients receive an initial dose
- 29% fewer vials of Infasurf® (calfactant) needed on the initial dose than Curosurf® (poractant alfa)
- Fewer vials have shown to lower total surfactant costs[4]

29%

Safety Information: Infasurf® (calfactant) therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and newborn infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

*Calculation of cohorts is based upon a large national sample which described birth weight distribution of 51,282 surfactant-treated patients from 322 neonatal intensive care units over six years.[24] Birth weight cohorts were defined where a change in vial size or vial count is required by each drug's respective prescribing information.

There are no prospective, randomized clinical trials comparing Infasurf® and Curosurf® with respect to safety or efficacy.

INDICATION

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis
Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment
Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

IMPORTANT SAFETY INFORMATION

Infasurf is intended for intratracheal use only. THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and newborn infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES that required stopping Infasurf and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal controlled trials. These observations were not associated with increased mortality.

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). These events were generally transient and not associated with serious complications or death.

The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in the Table. Prophylaxis and treatment study results for each surfactant are combined.

Please see accompanying full prescribing information.

Common Complications of Prematurity and RDS in Controlled Trials	Infasurf® (n=1001), %	Exosurf Neonatal® (n=978), %	Infasurf® (n=553), %	Survanta® (n=566), %
Apnea	61	61	76	76
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage[a]	12	10	9	7
IVH and PVL[b]	7	3	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	17	18

[a] Grade III and IV by the method of Papile.
[b] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

References:

1. Bloom BT, Kattwinkel J, Hall RT, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of Respiratory Distress Syndrome. Pediatrics. 1997;100:31-38. **2.** Attar M, Becker M, Dechert R, et al. Immediate changes in lung compliance following natural surfactant administration in premature infants with Respiratory Distress Syndrome: a controlled trial. J Perinatol. 2004;24:626-630. **3.** Jeon GW, Oh M, Sin JB. Efficacy of surfactant-TA, calfactant and poractant alfa for preterm infants with Respiratory Distress Syndrome: A retrospective study. Yonsei Med J. 2015;56(2):433-439. **4.** Zayek MM, Eyal FG, Smith RC. Comparison of the pharmacoeconomics of calfactant and poractant alfa in surfactant replacement therapy. JPPT. 2018;23(2):146-151. **5.** Gerdes JS, Seiberlich W, Sivieri EM, et.al. An open label comparison of calfactant and poractant alfa administration traits and impact on neonatal intensive care unit resources. J Pediatr Pharmacol Ther. 2006;11(2):92-100. **6.** Infasurf® (calfactant) Intratracheal Suspension Prescribing Information, ONY Biotech, March 2018. **7.** Seeger W, Gruba C, Gunther A, et al. Surfactant inhibition by plasma proteins: differential sensitivity of various surfactant preparations. Eur Respir J. 1993;6:971-977. **8.** Wang Z, Notter RH. Additivity of protein and nonprotein inhibitors of lung surfactant activity. Am J Respir Crit Care Med. 1998;158:28-35. **9**. Kim K, Choi S, Zell Z, et al. Effect of cholesterol nanodomains on monolayer morphology and dynamics. Proc Natl Acad Sci USA. 2013;110:E3054-60. **10.** Swartz D, Klein W, Row S, et al. Comparison of dynamic viscosities of lung surfactant drugs. Poster presented Hot Topics. 2017. **11.** Notter RH. Lung Surfactants. Michael Dekker, New York, 2000, pp 171-232; 319-345. **12.** Data on file, ONY Biotech. **13.** Mizuno K, Ikagami M, Chen C-M, et al. Surfactant protein-B supplementation improves in vivo function of a modified natural surfactant. Pediatr Res. 1995;37: 271-276. **14.** Hall SB, Vemkitaraman AR, Whitsett JA, et al. Importance of hydrophobic apoproteins as constituents of clinical exogenous surfactants. Am Rev Respir Dis. 1992;145:24-30. **15.** Retrieved from https://epakmachinery.com/viscosity-chart-1/ **16.** Retrieved from https://en.wikipedia.org/wiki/Saline_water **17.** Curosurf® (poractant alfa) Intratracheal Suspension Prescribing Information, Chiesi USA, Inc. December 2014. **18.** Survanta® (beractant) Intratracheal Suspension Prescribing Information, AbbVie, Inc. December 2012. **19.** Jobe A. Pharmacology review: why surfactant works for Respiratory Distress Syndrome; NeoReviews. 2006;7:e95-e106. **20.** Strang, LB. Neonatal Respiration: Psychological and Clinical Studies. JB Lippincott Company, Philadelphia, 1978, pp 66-81. **21.** Retrieved from https://curosurf.com/conventional-treatment-strategies/administration/ **22.** Ueda T, Ikegami M, Rider E, et al. Distribution of surfactant and ventilation in surfactant-treated preterm lambs. J Appl Physiol. 1994;76(1):45-55. **23.** Gillard N, Richman PM, Merritt TA, et al. Effect of volume and dose on pulmonary distribution of exogenous surfactant administered to normal rabbits or to rabbits with oleic acid lung injury. Am Rev Respir Dis. 1990;141(3):743-747. **24**. Trembath A, Hornik CP, Clark R, et al. Comparative effectiveness of surfactant preparations in premature infants. J Pediatr. 2013;163(4):955-960.

Infasurf®
(calfactant)
Helping babies breathe since 1998.
ONY Biotech is a leader in the creation of critically important products for the treatment of premature infants. Since 1998, we have made tomorrow possible for so many premature babies and their families, thanks to Infasurf® (calfactant).
onybiotech
Manufactured by ONY Biotech
1576 Sweet Home Road | Amherst, NY 14228 | 716.636.9096 | 877.274.4669
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Survanta® is a registered trademark of Abbott Laboratories, Inc.
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INFASURF ® (calfactant)
Intratracheal Suspension
Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 03/18

DESCRIPTION

Infasurf® (calfactant) Intratracheal Suspension is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives.

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg proteins including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of Respiratory Distress Syndrome (RDS) in premature infants. Infasurf restores surface activity to the lungs of these infants.

Activity: Infasurf adsorbs rapidly to the surface of the air:liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤3 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. Ex vivo, Infasurf restores the pressure volume mechanics and compliance of surfactant-deficient rat lungs. In vivo, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, its site of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and 25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 30% of instilled Infasurf is present in the lung lining after 24 hours.

Clinical Studies: The efficacy of Infasurf was demonstrated in two multiple-dose controlled clinical trials involving approximately 2,000 infants treated with Infasurf (approximately 100 mg phospholipid/kg) or Exosurf Neonatal®. In addition, two controlled trials of Infasurf versus Survanta®, and four uncontrolled trials were conducted that involved approximately 15,500 patients treated with Infasurf.

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1,126 infants ≤72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 < 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in Table 1.

Table 1- Infasurf vs Exosurf Neonatal®
Treatment Trial

Efficacy Parameter	Infasurf (N=570) %	Exosurf Neonatal® (N=556) %	p-Value
Incidence of air leaks [a]	11	22	≤0.001
Death due to RDS	4	4	0.95
Any death to 28 days	8	10	0.21
Any death before discharge	9	12	0.07
BPD [b]	5	6	0.41
Crossover to other surfactant [c]	4	4	1

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 96 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Prophylaxis Trial

A total of 853 infants <29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2- Infasurf vs Exosurf Neonatal®
Prophylaxis Trial

Efficacy Parameter	Infasurf (N=431) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	47	≤0.001
Incidence of air leaks [a]	10	15	0.01
Death due to RDS	2	5	≤0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.56
BPD [b]	16	17	0.60
Crossover to other surfactant [c]	0.2	3	<0.001

[a] Pneumothorax and/or pulmonary interstitial emphysema.
[b] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[c] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 72 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10

Infasurf versus Survanta®

Treatment Trial

A total of 662 infants with RDS who required endotracheal intubation and had an a/A PO_2 <0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). Repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Results for the major efficacy parameters evaluated at 28 days or to discharge (incidence of air leaks, death due to respiratory causes or to any cause, BPD, or treatment failure) for all treated patients from this treatment trial were not significantly different between Infasurf and Survanta®.

Prophylaxis Trial

A total of 457 infants ≤30 weeks gestation and <1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). The initial dose was administered within 15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days (p=0.03) and in death due to respiratory causes (p=0.005) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group (p = 0.07 and 0.03, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

Acute Clinical Effects: As with other surfactants, marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (F_IO_2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

INDICATIONS AND USAGE

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis

Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment

Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

WARNINGS

Infasurf is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and new born infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

PRECAUTIONS

When repeat dosing was given at fixed 12-hour intervals in the Infasurf vs. Exosurf Neonatal® trials, transient episodes of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction were observed more frequently among infants in the Infasurf-treated group.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials. These observations were not associated with increased mortality.

No data are available on the use of Infasurf in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Data from controlled trials on the efficacy of Infasurf are limited to doses of approximately 100 mg phospholipid/kg body weight and up to a total of 4 doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies and animal reproduction studies have not been performed with Infasurf. A single mutagenicity study (Ames assay) was negative.

ADVERSE REACTIONS

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). These events were generally transient and not associated with serious complications or death.

The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in Table 3. Prophylaxis and treatment study results for each surfactant are combined.

Table 3 - Common Complications of Prematurity and RDS in Controlled Trials

Complication	Infasurf (N=1001) %	Exosurf Neonatal® (N=978) %	Infasurf (N=553) %	Survanta® (N=566) %
Apnea	61	61	76	76
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage [a]	12	10	9	7
IVH and PVL [b]	7	3	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	17	18

[a] Grade III and IV by the method of Papile.
[b] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 415 infants enrolled in 5 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

There have been no reports of overdosage with Infasurf. While there are no known adverse effects of excess lung surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

Infasurf should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation.

Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Dosage

Each dose of Infasurf is 3 mL/kg body weight at birth. Infasurf has been administered every 12 hours for a total of up to 3 doses.

Directions for Use

Infasurf is a suspension which settles during storage. Gentle swirling or agitation of the vial is often necessary for redispersion. DO NOT SHAKE. Visible flecks in the suspension and foaming at the surface are normal for Infasurf. Infasurf should be stored at refrigerated temperature 2° to 8°C (36° to 46°F). THE 3mL VIAL MUST BE STORED UPRIGHT. Date and time need to be recorded on the carton when Infasurf is removed from the refrigerator. Warming of Infasurf before administration is not necessary.

Unopened, unused vials of Infasurf that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Infasurf should not be removed from the refrigerator for more than 24 hours. **Infasurf should not be returned to the refrigerator more than once.** Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

INFASURF DOES NOT REQUIRE RECONSTITUTION. DO NOT DILUTE OR SONICATE.

Dosing Procedures

General

Infasurf should only be administered intratracheally through an endotracheal tube. The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Infasurf suspension into the endotracheal tube.

Administration for Treatment of RDS

When used to treat RDS, Infasurf may be administered using either of the following 2 methods:

Exosurf Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Exosurf® trials, Infasurf was administered intratracheally through a side-port adapter into the endotracheal tube. Two attendants, one to instill the Infasurf, the other to monitor the patient and assist in positioning, facilitated the dosing. The dose (3 mL/kg) was administered in two aliquots of 1.5 mL/kg each. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Administration was made while ventilation was continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning separated the two aliquots. Repeat doses of 3 mL/kg of birth weight, up to a total of 3 doses 12 hours apart, were given if the patient was still intubated.

Survanta Active Control Trials: Initial and Repeat Dosing

In the Infasurf vs. Survanta® trials, Infasurf was administered through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a $P_aO_2 \leq 80$ torr.

Administration for Prophylaxis of RDS at Birth

Dosing procedures are described under Administration for Treatment of RDS. The amount of a prophylaxis dose of Infasurf should be based on the infant's birth weight. Administration of Infasurf for prophylaxis should be given as soon as possible after birth. Usually the immediate care and stabilization of the premature infant born with hypoxemia and/or bradycardia should precede Infasurf prophylaxis.

Dosing Precautions

During administration of Infasurf liquid suspension into the airway, infants often experience bradycardia, reflux of Infasurf into the endotracheal tube, airway obstruction, cyanosis, dislodgement of the endotracheal tube, or hypoventilation. If any of these events occur, the administration should be interrupted and the infant's condition should be stabilized using appropriate interventions before the administration of Infasurf is resumed. Endotracheal suctioning or reintubation is sometimes needed when there are signs of airway obstruction during the administration of the surfactant.

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61938-456-03) and 6 mL (NDC 61938-456-06) off-white suspension.

Store Infasurf (calfactant) Intratracheal Suspension at refrigerated temperature 2° to 8°C (36° to 46°F) and protect from light. **THE 3 mL VIAL MUST BE STORED UPRIGHT.** Vials are for single use only. After opening, discard unused drug.

Rx only

Manufactured by:
ONY Biotech Inc.
Amherst, NY 14228

Rev. 03/18

REDOSE RATE PUBLICATIONS

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