INFASURF ®
(calfactant)
Intratracheal Suspension
Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 06/11

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 within15 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, Inc.
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