#1 MOST USED SURFACTANT in the U.S.†*

For premature infants with respiratory distress syndrome (RDS)

DELIVER *FAST RDS* SUCCESS

with an initial dose containing
UP TO 2X MORE SURFACTANT[2-4†]



- ***FAST ONSET***[5-7†]
- ***SINGLE-DOSE SUCCESS***[7-12‡]
- ***LOWEST VOLUME***[2-4‡]

Important Safety Information

CUROSURF® (poractant alfa) is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

*Please note that this metric only provides insight into the surfactant selected by NICUs and does not imply equivalence or superiority between or among the products for any given clinical end point.

†Not proven to impact clinical outcomes such as mortality.

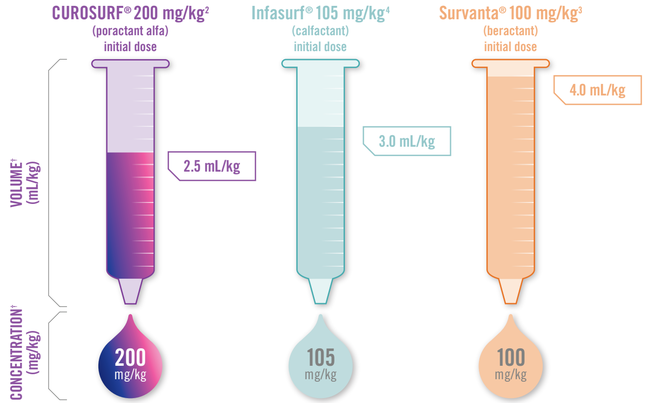
‡Not established to result in superior safety or efficacy.

Chiesi
in Neonatology for Life

CUROSURF®
(poractant alfa)
Intratracheal Suspension

CUROSURF (poractant alfa) 200 mg/kg*

UP TO 2X MORE SURFACTANT AND THE LOWEST VOLUME[2-4]



Clinical studies have not established that lower volume, fewer doses, or longer dosing intervals result in superior efficacy or safety based on clinically relevant end points.

The initial dose of CUROSURF 200 mg/kg provides a longer half-life than poractant alfa 100 mg/kg[13]*



Physiologic and pharmacokinetic end points (e.g., longer DSPC half-life) have not been proven to impact key clinical outcomes such as mortality due to RDS. A small amount of radiolabeled dipalmitoylphosphatidylcholine (DPPC) was added to facilitate this study.

*CUROSURF is FDA approved for an initial dose of 200 mg/kg (2.5 mL/kg). The 100 mg/kg (1.25 mL/kg) dose of CUROSURF is approved for repeat dosing only.
†Based on a 1000-g infant and manufacturer's dosing schedule. Volume of surfactant is measured in milliliters per kilogram of body weight at birth.

Indication

CUROSURF® (poractant alfa) Intratracheal Suspension is indicated for the rescue treatment of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

The long half-life seen with CUROSURF 200 mg/kg can lead to a long duration of clinical effect, which may impact the need for supplemental oxygen and redosing.[13]

CUROSURF (poractant alfa) 200 mg/kg*

THE ONLY SURFACTANT FDA-APPROVED FOR A 200 mg/kg INITIAL DOSE[2-4]

	CUROSURF 200 mg/kg[2,16] initial dose	Infasurf 105 mg/kg[4,16] initial dose	Survanta 100 mg/kg[3,16] initial dose
Source	Porcine	Bovine	Bovine
Phospholipid concentration (mg/mL)	76	35	25
Dipalmitoylphos-phatidylcholine (mg/mL)	30	16	11.0-15.5
SP-B (mg/mL)	0.45	0.26	Not Specified
SP-C (µg protein/ µmol · L^{-1} phospholipid)	5.0-11.6	8.1	1.0-20.0
Additives	No	No	Yes

- An initial dose of CUROSURF delivers more than twice the phospholipid concentration vs other exogenous surfactants[2-4]
  - And 44% more SP-B than Infasurf[2-4]
- There is no therapeutic or pharmaceutical equivalent to CUROSURF[2-4,16]

While clinical studies have demonstrated that SP-B, SP-C, and phospholipids are essential elements, they have not established the quantity required for optimal surfactant efficacy.

Important Safety Information

CUROSURF is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

There is no therapeutic equivalent to CUROSURF.[2-4,16]

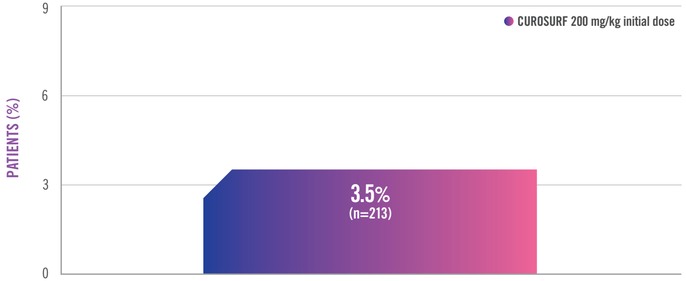
CUROSURF (poractant alfa) 200 mg/kg*

LOW REFLUX RATES[17]

CUROSURF® (poractant alfa) Intratracheal Suspension

Low reflux rate 5 to 15 minutes after administration[17]

It has been suggested that the thin suspension may help to minimize airway and endotracheal tube obstruction and associated complications such as transient hypercapnia.[17,18]



Administration traits or end points (eg, faster reduction in FiO_2, reflux or bradycardia rates, or oxygen desaturation) have not been proven to impact key clinical outcomes such as mortality or BPD due to RDS.

Gerdes JS, et al. *J Pediatr Pharmacol Ther.* 2006;11:92-100.
An open-label, observational study of 277 (CUROSURF 200 mg/kg, n=213; calfactant 100 mg/kg, n=64) infants compared the two surfactants with respect to their technical aspects of administration, short-term clinical observations, and the implications of any differences observed. The study was not randomized or blinded. Birth weight averaged 1410 ± 676 grams for CUROSURF and 1649 ± 87 grams for Infasurf. The gestational age was 29.4 ± 3.5 weeks for CUROSURF and 30.2 ± 4.2 weeks for Infasurf. Data for calfactant 100 mg/kg is not shown. The study was not powered to determine statistically significant differences between the short-term clinical outcomes, including reflux rate.[17]

Important Safety Information

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported with CUROSURF. The rates of common complications of prematurity observed in a multicenter single-dose study that enrolled infants 700–2000 g birth weight with RDS requiring mechanical ventilation and $FiO_2 \geq 0.60$ are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) (n=78) and control (n=66; no surfactant) respectively: acquired pneumonia (17% vs. 21%), acquired septicemia (14% vs. 18%), bronchopulmonary dysplasia (18% vs. 22%), intracranial hemorrhage (51% vs. 64%), patent ductus arteriosus (60% vs. 48%), pneumothorax (21% vs. 36%) and pulmonary interstitial emphysema (21% vs. 38%).

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

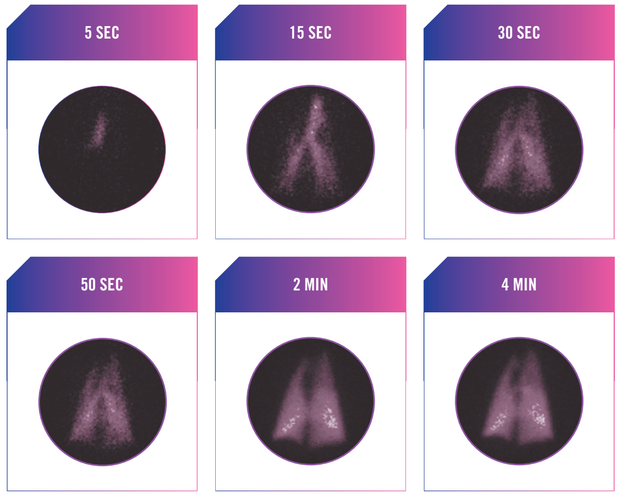
Low reflux rates may improve tolerability and ease of administration.[17]



CUROSURF (poractant alfa) 200 mg/kg*

SPREADS FAST AND EVENLY[14]

CUROSURF distribution in lamb lungs over 4 minutes[14†‡]



- Quickly forms a stable surfactant monolayer inside alveoli[15]
- Suctioning of airways permitted after 1 hour[2]
- Preclinical data may not be predictive of clinical results

†Unpublished photos presented during the 15th International Workshop on Surfactant Replacement, 2000.
‡It is unknown if CUROSURF was delivered as a single bolus in this study.

Important Safety Information

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

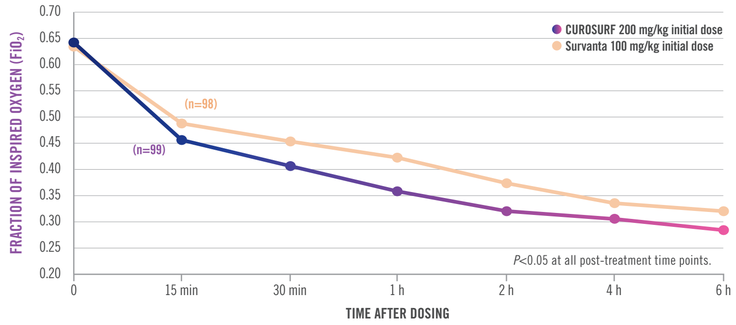
Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

CUROSURF is the ONLY surfactant with an FDA-approved single bolus delivery option.[2-4]



CUROSURF (poractant alfa) 200 mg/kg*

FASTER REDUCTIONS IN FiO_2 VS SURVANTA (beractant) 100 mg/kg[7†]



*CUROSURF is FDA approved for an initial dose of 200 mg/kg (2.5 mL/kg). The 100 mg/kg (1.25 mL/kg) dose of CUROSURF is approved for repeat dosing only.
†Primary end point was FiO_2 AUC_{0-6} defining onset of clinical response.
FiO_2=Fraction of inspired oxygen.

Physiological end points (eg, faster reduction in FiO_2) have not been proven to impact key clinical outcomes such as mortality due to RDS.

Ramanathan R, et al. *Am J Perinatol.* 2004;21:109-119.
A randomized, multi-center, masked comparison trial of CUROSURF vs Survanta in the treatment of RDS in 293 preterm infants weighing 750 to 1750 grams at birth and < 35 weeks gestation (CUROSURF 200 mg/kg, n=99; poractant alfa 100 mg/kg, n=96; beractant 100 mg/kg, n=98). Randomization was stratified by birth weight and site. The onset of clinical response after the first dose was studied by comparing changes in the FiO_2 between 0 and 6 hours measured using the area under the curve (FiO_2 AUC_{0-6}). Data for poractant alfa 100 mg/kg is not shown.[7]

Important Safety Information

CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of preterm infants.

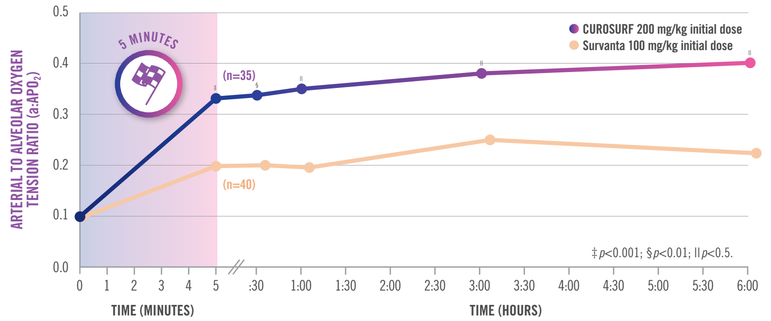
Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

CUROSURF improves oxygenation within 5 minutes and rapidly reduces FiO_2 requirements over the initial treatment period.[2,7]

CUROSURF (poractant alfa) 200 mg/kg*

AND FASTER IMPROVEMENT IN OXYGENATION[5]

CUROSURF® (poractant alfa) Intratracheal Suspension



a:APO_2=Arterial to alveolar oxygen tension ratio.

Physiological end points (eg, faster reduction in FiO_2) have not been proven to impact key clinical outcomes such as mortality due to RDS.

Speer CP, et al. *Arch Dis Child.* 1995;72:F8-F13.
A randomized, nonblinded clinical trial of CUROSURF and Survanta in the treatment of RDS in 75 preterm infants requiring artificial ventilation with an $FiO_2 \geq 0.4$, weighing 700 to 1500 grams at birth and aged 1–24 hours (CUROSURF 200 mg/kg, n=35; beractant 100 mg/kg, n=40). Randomization was stratified by birth weight. The effects of the two treatment regimens on gas exchange, ventilatory requirements, and 28-day outcome were compared. Study patients received rescue surfactant and mechanical ventilation as primary intervention.[5]

Important Safety Information

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported with CUROSURF. The rates of common complications of prematurity observed in a multicenter single-dose study that enrolled infants 700–2000 g birth weight with RDS requiring mechanical ventilation and $FiO_2 \geq 0.60$ are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) (n=78) and control (n=66; no surfactant) respectively: acquired pneumonia (17% vs. 21%), acquired septicemia (14% vs. 18%), bronchopulmonary dysplasia (18% vs. 22%), intracranial hemorrhage (51% vs. 64%), patent ductus arteriosus (60% vs. 48%), pneumothorax (21% vs. 36%) and pulmonary interstitial emphysema (21% vs. 38%).

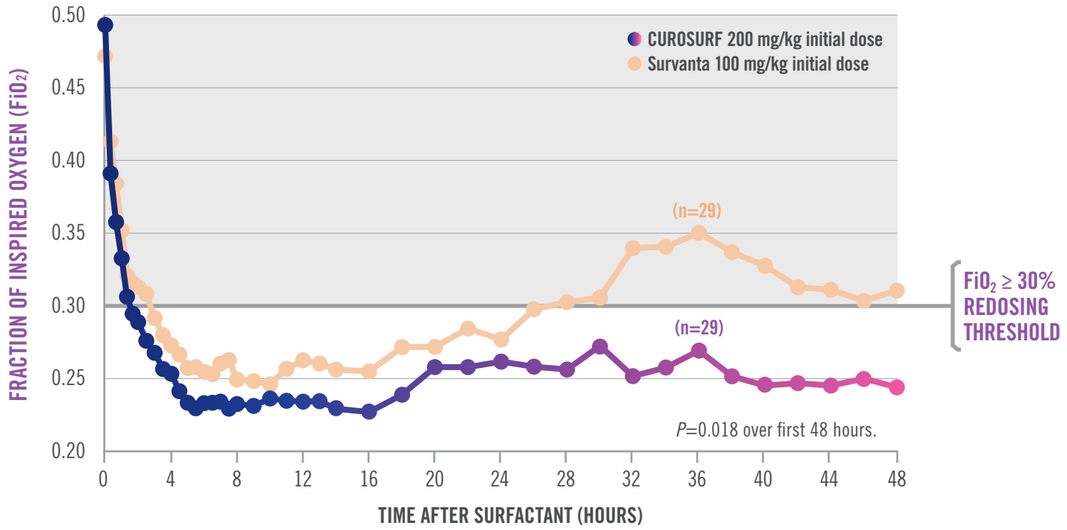
Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

It has been suggested that faster oxygenation supports the treatment goal of weaning infants from mechanical ventilation (MV) more rapidly.[7]



CUROSURF (poractant alfa) 200 mg/kg*

PROVEN FiO_2 REDUCTIONS SUSTAINED OVER TIME VS SURVANTA (beractant) 100 mg/kg[19]



- In a clinical trial, oxygen requirements did not rebound above redosing threshold (FiO_2 ≥ 0.30) after first dose of CUROSURF during the first 48 hours[19]

*CUROSURF is FDA approved for an initial dose of 200 mg/kg (2.5 mL/kg). The 100 mg/kg (1.25 mL/kg) dose of CUROSURF is approved for repeat dosing only.
FiO_2=Fraction of inspired oxygen.
Shading indicates FiO_2 range in which redosing was required.

Malloy CA, et al. *Acta Paediatr.* 2005;94:779-784.
A randomized trial comparing CUROSURF and Survanta treatment in neonatal RDS. The primary outcome measure was FiO_2 requirement in the first 48 hours after surfactant therapy. A total of 58 infants completed the study and were included in the analysis (CUROSURF 200 mg/kg, n=29; beractant 100 mg/kg, n=29). The mean gestational ages for the CUROSURF and Survanta groups were 29.6 ± 3.6 and 29.3 ± 2.9 weeks, with average birth weights of 1394 ± 699 and 1408 ± 534 grams, respectively.[19]

Important Safety Information

CUROSURF® (poractant alfa) is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

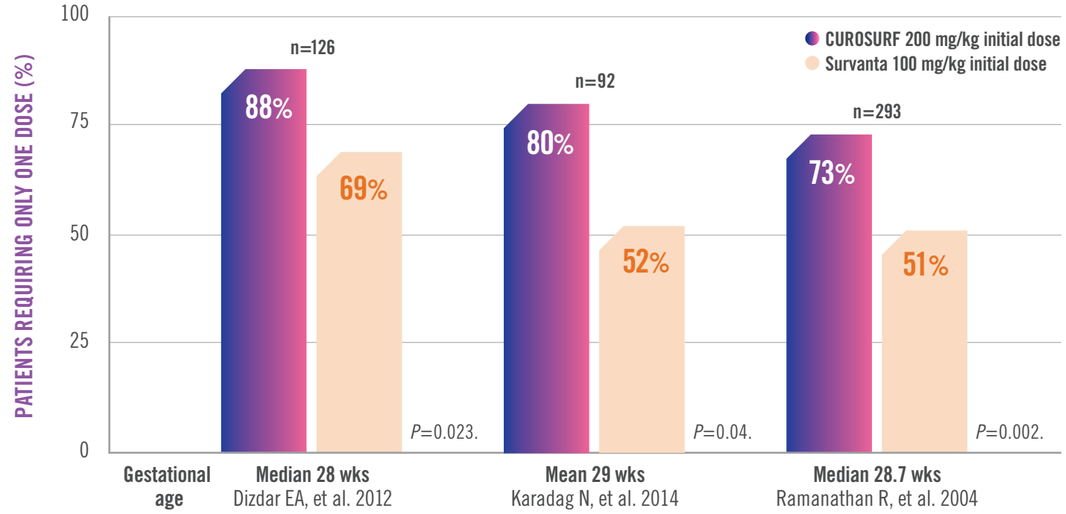
Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

Sustained reduction of FiO_2 levels over 48 hours may reduce the need for redosing.[19]

CUROSURF (poractant alfa) 200 mg/kg*

HIGH RATES OF SINGLE-DOSE SUCCESS ACROSS MULTIPLE STUDIES[7-9]

CUROSURF® (poractant alfa) Intratracheal Suspension



Clinical studies have not established that fewer doses or longer dosing intervals result in superior safety or efficacy based on clinically relevant end points.

Dizdar EA, et al. *Am J Perinatol.* 2012;29:95-100.
A randomized, controlled trial of CUROSURF vs Survanta in the treatment of RDS in 126 preterm infants (CUROSURF 200 mg/kg, n=61; beractant 100 mg/kg, n=65). FiO_2 after surfactant treatment, need for repeat doses, and duration of respiratory support and hospitalization were evaluated between groups. Differences in baseline patient demographics between the two treatment groups were reported for antenatal steroid use and gender distribution.[8]

Karadag N, et al. *Am J Perinatol.* 2014;31:1015-1022.
A prospective study on 92 preterm infants with RDS, randomized to receive CUROSURF or Survanta (CUROSURF 200 mg/kg, n=46; beractant 100 mg/kg, n=46). The study compared the effects of the two treatment regimens on perfusion index and oxygenation.[9]

Ramanathan R, et al. *Am J Perinatol.* 2004;21:109-119.
A randomized, multi-center, masked comparison trial of CUROSURF vs Survanta in the treatment of RDS in 293 preterm infants weighing 750 to 1750 grams at birth and < 35 weeks gestation (CUROSURF 200 mg/kg, n=99; poractant alfa 100 mg/kg, n=96; beractant 100 mg/kg, n=98). Randomization was stratified by birth weight and site. The onset of clinical response after the first dose was studied by comparing changes in the FiO_2 between 0 and 6 hours measured using the area under the curve (FiO_2 AUC_{0-6}). Total number of doses of surfactant and duration of respiratory support were also evaluated between groups. Data for poractant alfa 100 mg/kg is not shown.[7]

Important Safety Information

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

In clinical studies, most infants required only one dose of CUROSURF, which may reduce complications associated with reintubation and subsequent MV.[7,12]



CUROSURF (poractant alfa) 200 mg/kg*

SUPPORTS THE GOALS OF RAPID EXTUBATION AND LESS INVASIVE VENTILATION[10-12,20]

In some clinical studies, infants treated with CUROSURF using the INSURE strategy were generally extubated within approximately 5 to 10 minutes following administration.[10-12,20]

RAPID EXTUBATION
following surfactant administration



The INSURE strategy provides the benefits of surfactant while avoiding prolonged MV[21]



INtubation



SURfactant



Rapid **E**xtubation

- Extubation should be performed when the infant is stable at the discretion of the clinician
- Rapid extubation after surfactant administration may not be achievable or desirable in the most immature infants, and decisions to extubate should be individualized

It is important to note that the INSURE strategy may not be appropriate for all infants. Infants with RDS may vary markedly in the severity of respiratory disease, maturity, and presence of other complications, and thus it is necessary to individualize patient care.

*CUROSURF is FDA approved for an initial dose of 200 mg/kg (2.5 mL/kg). The 100 mg/kg (1.25 mL/kg) dose of CUROSURF is approved for repeat dosing only.

In clinical studies, early rescue INSURE strategy ($FiO_2 \leq 0.45$) was associated with improved outcomes vs late selective therapy ($FiO_2 > 0.45$)[21]

Important Safety Information

CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of preterm infants.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

Early rescue INSURE strategy may help avoid potential for respiratory insufficiency and the need for subsequent MV.[21]

CUROSURF®
(poractant alfa)
Intratracheal Suspension

FiO_2 IS THE STRONGEST PREDICTOR OF CPAP FAILURE IN EARLY LIFE[22]

Predicting CPAP failure earlier using an FiO_2 that is ≥ 30% may help optimize the timing of surfactant treatment and improve outcomes for preterm infants.[22]

Gestational age: 25–28 weeks[22†]

An $FiO_2 \geq 30\%$ within **2 HOURS** correctly identified

83% of infants who failed on CPAP

n=66

†Data from ROC curves showed that FiO_2 in early life appeared to be a good predictor of CPAP failure (OR 1.19, 95% CI 1.06, 1.33; *P*=0.002), with an AUC of at least 0.8 in both GA ranges. A threshold of $FiO_2 \geq 0.3$ provided a balance between adequate sensitivity and an acceptable false-positive rate on ROC analysis.

Dargaville PA, et al. *Neonatology.* 2013;104(1):8-14.

A retrospective and observational study of data collected from June 2006 to June 2009 at the Royal Hobart Hospital and from May 2009 to April 2010 at the Royal Women's Hospital, Melbourne. Preterm infants (25–32 weeks' gestation, n=297) who were admitted to the NICU for respiratory support in the first 24 hours of life and managed initially with CPAP (maximum CPAP pressure of 8 cm H_2O and FiO_2 0.45–0.50) were included. CPAP failure was defined as the need for intubation before 72 hours. Data was separated into two gestation ranges (25–28 weeks and 29–32 weeks) and grouped according to whether the infants were successfully managed on or failed CPAP. Logistic regression models were used to investigate the effects of FiO_2 and CPAP levels in early life in the prediction of CPAP failure. The highest values for FiO_2 and CPAP in the first 2 hours (25–28 weeks) or 6 hours (29–32 weeks) were used.[22]

Clinical consequences for infants who failed early on CPAP[22-24]

- Increased risk of mortality and morbidities, including pneumothorax, bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH)[22,23]
- Prolonged duration of respiratory support could lead to serious AEs related to oxygen toxicity[24]

Important Safety Information

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported with CUROSURF. The rates of common complications of prematurity observed in a multicenter single-dose study that enrolled infants 700–2000 g birth weight with RDS requiring mechanical ventilation and $FiO_2 \geq 0.60$ are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) (n=78) and control (n=66; no surfactant) respectively: acquired pneumonia (17% vs. 21%), acquired septicemia (14% vs. 18%), bronchopulmonary dysplasia (18% vs. 22%), intracranial hemorrhage (51% vs. 64%), patent ductus arteriosus (60% vs. 48%), pneumothorax (21% vs. 36%) and pulmonary interstitial emphysema (21% vs. 38%).

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

Predicting CPAP failure using an $FiO_2 \geq 30\%$ may help optimize the timing of surfactant treatment and improve outcomes for preterm infants.[22]



IMPORTANT SAFETY INFORMATION

CUROSURF® (poractant alfa) is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of preterm infants.

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported with CUROSURF. The rates of common complications of prematurity observed in a multicenter single-dose study that enrolled infants 700–2000 g birth weight with RDS requiring mechanical ventilation and $FiO_2 \geq 0.60$ are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) (n=78) and control (n=66; no surfactant) respectively: acquired pneumonia (17% vs. 21%), acquired septicemia (14% vs. 18%), bronchopulmonary dysplasia (18% vs. 22%), intracranial hemorrhage (51% vs. 64%), patent ductus arteriosus (60% vs. 48%), pneumothorax (21% vs. 36%) and pulmonary interstitial emphysema (21% vs. 38%).

INDICATION

CUROSURF® (poractant alfa) Intratracheal Suspension is indicated for the rescue treatment of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

Please see accompanying Full Prescribing Information.

CUROSURF®
(poractant alfa)
Intratracheal Suspension

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Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

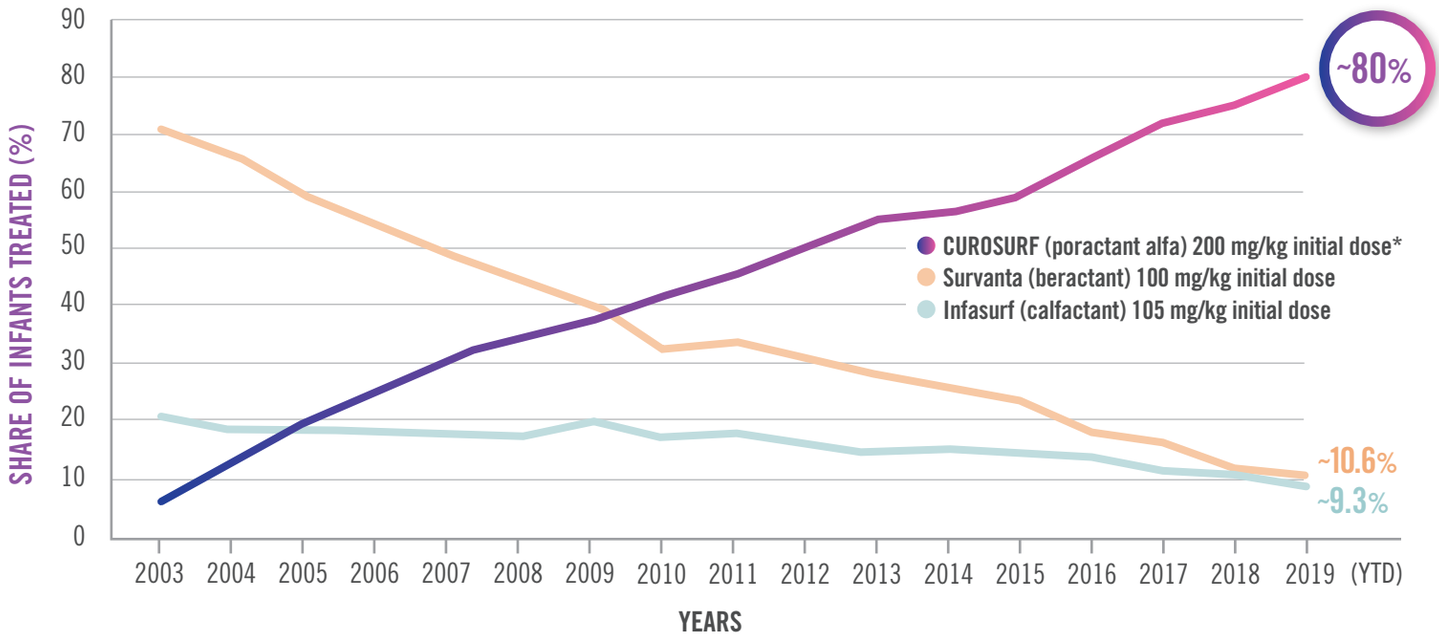


CUROSURF (poractant alfa) 200 mg/kg*

CHOOSE THE MOST USED SURFACTANT IN THE UNITED STATES FOR 10 YEARS AND COUNTING[1,25]

#1 MOST USED SURFACTANT in the U.S.††

CUROSURF is chosen by more NICUs than all other surfactants combined[25-27†]



*CUROSURF is FDA approved for an initial dose of 200 mg/kg (2.5 mL/kg). The 100 mg/kg (1.25 mL/kg) dose of CUROSURF is approved for repeat dosing only.

†The number of patients treated with each surfactant is calculated by dividing the total amount of each surfactant sold by the average amount of surfactant each patient receives. Please note that this metric only provides insight into the surfactant selected by NICUs and does not imply equivalence or superiority between or among the products for any given clinical end point.

4.2 MILLION

***INFANTS TREATED WITH CUROSURF WORLDWIDE*[25]**

80%

***CHOSEN BY MORE THAN 80% OF THE MAJORITY OF TOP HOSPITALS THAT USE SURFACTANT*[25,28,29]**

- 50 Best Hospitals for Neonatology | US News and World Report‡
- U.S. Member Hospitals | Children's Hospital Association§



Important Safety Information

CUROSURF® (poractant alfa) is intended for intratracheal use only. The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

Please see Important Safety Information on page 12 and accompanying Full Prescribing Information.

‡Based on US News and World Report's "50 Best Hospitals for Neonatology" and Data on File, Chiesi Farmaceutici S.p.A. and Chiesi USA, Inc., 2018.

§Based on hospitals listed in the Children's Hospital Association's "Children's Hospital Directory" and Data on File, Chiesi Farmaceutici S.p.A. and Chiesi USA, Inc., 2018.

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CUROSURF®
(poractant alfa)
Intratracheal Suspension

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CUROSURF (poractant alfa) intratracheal suspension
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Dosage and Administration, Important Administration Instructions (2.1)	12/2019
Dosage and Administration, Recommended Dosage (2.2)	12/2019
Dosage and Administration, Administration (2.4)	12/2019

INDICATIONS AND USAGE

CUROSURF is a surfactant indicated for the rescue treatment, including the reduction of mortality and pneumothoraces, of Respiratory Distress Syndrome (RDS) in premature infants. (1)

DOSAGE AND ADMINISTRATION

- Before administering CUROSURF, assure proper placement and patency of endotracheal tube (2.1)
- Administer intratracheally either in (2.1):
  - Two divided aliquots through a 5 French end-hole catheter; or
  - A single bolus through secondary lumen of a dual lumen endotracheal tube without interrupting mechanical ventilation
- Initial recommended dose is 2.5 mL/kg birth weight (2.2)
- Up to two repeat doses of 1.25 mL/kg birth weight may be administered at approximately 12-hour intervals (2.2)
- Maximum total dose (initial plus repeat doses) is 5 mL/kg (2.2)
- See Full Prescribing Information for instructions on preparation and administration of the CUROSURF suspension (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Intratracheal Suspension: 80 mg poractant alfa (surfactant extract) in 1 mL of suspension includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Acute Changes in Lung Compliance: Frequently assess need to modify oxygen and ventilatory support to respiratory changes (5.1)
- Administration-Related Adverse Reactions: Transient adverse effects include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition (5.2)

ADVERSE REACTIONS

- Common adverse reactions associated with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

Revised: 12/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CUROSURF® (poractant alfa) Intratracheal Suspension is indicated for the rescue treatment of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

For intratracheal administration only.

CUROSURF should be administered by, or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants. Before administering CUROSURF, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering CUROSURF. Allow the infant to stabilize before proceeding with dosing.

Administer CUROSURF either:

- Intratracheally by instillation in two divided aliquots through a 5 French end-hole catheter or
- Intratracheally in a single bolus through the secondary lumen of a dual lumen endotracheal tube without interrupting mechanical ventilation.

2.2 Recommended Dosage

The initial recommended dose is 2.5 mL/kg birth weight, administered as one or two aliquots depending upon the instillation procedure *[see Dosage and Administration (2.3)]*.

Up to two repeat doses of 1.25 mL/kg birth weight each may be administered at approximately 12-hour intervals in infants in whom RDS is considered responsible for their persisting or deteriorating respiratory status. The maximum recommended total dosage (sum of the initial and up to two repeat doses) is 5 mL/kg.

2.3 Preparation of the CUROSURF Suspension

1. Remove the vial of CUROSURF suspension from a refrigerator at +2 to +8°C (36 to 46°F) and slowly warm the vial to room temperature before use.
2. Visually inspect the CUROSURF suspension for discoloration prior to administration. The color of the CUROSURF suspension should be white to creamy white. Discard the CUROSURF vial if the suspension is discolored.
3. Gently turn the vial upside-down, in order to obtain a uniform suspension. DO NOT SHAKE.
4. Locate the notch (FLIP UP) on the colored plastic cap and lift the notch and pull upwards.
5. Pull the plastic cap with the aluminum portion downwards.
6. Remove the whole ring by pulling off the aluminum wrapper.
7. Remove the rubber cap to extract content.
8. Unopened, unused vials of CUROSURF suspension that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Do not warm to room temperature and return to refrigerated storage more than once. Protect from light.

2.4 Administration

For endotracheal tube instillation using a 5 French end-hole catheter

1. Slowly withdraw the entire contents of the vial of CUROSURF suspension into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Enter each single-use vial only once.
2. Attach the 5 French end-hole catheter of appropriate length to position the catheter tip proximal to the distal portion of the endotracheal tube, to the syringe. Fill the catheter with CUROSURF suspension. Discard excess CUROSURF through the catheter so that only the dose to be given remains in the syringe.
    - For the first dose: 1.25 mL/kg (birth weight) per aliquot
    - For each repeated dose: 0.625 mL/kg (birth weight) per aliquot
3. First aliquot of CUROSURF suspension:
    1. Position the infant in a neutral position (head and body in alignment without inclination), with either the right or left side dependent.
    2. Immediately before CUROSURF administration, ventilate the infant with supplemental oxygen sufficient to maintain SaO_2 > 92%.
    3. Insert the catheter into the endotracheal tube and instill the first aliquot of CUROSURF suspension.
    4. After the first aliquot is instilled, remove the catheter from the endotracheal tube and manually ventilate with supplemental oxygen until clinically stable.
4. Second aliquot of CUROSURF suspension:
    1. When the infant is stable, reposition the infant such that the other side is dependent.
    2. Administer the remaining aliquot using the same procedures as the first aliquot.
5. After completion of the dosing procedure, do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur *[see Clinical Studies (14.1)]*.

For endotracheal instillation using the secondary lumen of a dual lumen endotracheal tube

1. Slowly withdraw the entire contents of the vial of CUROSURF suspension into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Do not attach 5 French end-hole catheter. Remove the needle and discard excess CUROSURF so that only the dose to be given remains in the syringe.
2. Keep the infant in a neutral position (head and body in alignment without inclination).
3. Administer CUROSURF suspension through the proximal end of the secondary lumen of the endotracheal tube as a single dose, given over 1 minute, and without interrupting mechanical ventilation.
4. After completion of this dosing procedure, ventilator management may require transient increases in FiO_2, ventilator rate, or PIP. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

3 DOSAGE FORMS AND STRENGTHS

CUROSURF (poractant alfa) is an intratracheal suspension available in vials:

- 1.5 mL [120 mg poractant alfa (surfactant extract)], or
- 3 mL [240 mg poractant alfa (surfactant extract)].

CUROSURF is a white to creamy white suspension. Each mL of suspension contains 80 mg poractant alfa (surfactant extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Changes in Oxygenation and Lung Compliance

The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

5.2 Administration-Related Adverse Reactions

Transient adverse reactions associated with administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

Adverse Reactions in Studies in Premature Infants with Respiratory Distress Syndrome

The safety data described below reflect exposure to CUROSURF at a single dose of 2.5 mL/kg (200 mg/kg), in 78 infants of 700-2000 grams birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ (Study 1) *[see Clinical Studies (14.1)]*. A total of 144 infants were studied after RDS developed and before 15 hours of age; 78 infants received CUROSURF 2.5 mL/kg single dose (200 mg/kg), and 66 infants received control treatment (disconnection from the ventilator and manual ventilation for 2 minutes).

Transient adverse effects seen with the administration of CUROSURF included bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. The rates of the most common serious complications associated with prematurity and RDS observed in Study 1 are shown in Table 1.

Table 1: Most Common Serious Complications Associated with Prematurity and RDS in Study 1

	CUROSURF 2.5 mL/kg n=78	**CONTROL* n=66**
Acquired Pneumonia	17%	21%
Acquired Septicemia	14%	18%
Bronchopulmonary Dysplasia	18%	22%
Intracranial Hemorrhage	51%	64%
Patent Ductus Arteriosus	60%	48%
Pneumothorax	21%	36%
Pulmonary Interstitial Emphysema	21%	38%

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Seventy-six infants (45 treated with CUROSURF) from study 1 were evaluated at 1 year of age and 73 infants (44 treated with CUROSURF) were evaluated at 2 years of age to assess for potential long-term adverse reactions. Data from follow-up evaluations for weight and length, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment, or auditory impairment was similar between treatment groups. In 16 patients (10 treated with CUROSURF and 6 controls) evaluated at 5.5 years of age, the developmental quotient, derived using the Griffiths Mental Developmental Scales, was similar between groups.

6.2 Immunogenicity

Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

6.3 Postmarketing Experience

Pulmonary hemorrhage, a known complication of premature birth and very low birth-weight, has been reported both in clinical trials with CUROSURF and in postmarketing adverse event reports in infants who had received CUROSURF.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

CUROSURF is indicated for the rescue treatment, including the reduction of mortality and pneumothoraces, of Respiratory Distress Syndrome (RDS) in premature infants *[see Indications and Usage (1) and Dosage Administration (2)]*.

The safety and efficacy of CUROSURF in the treatment of full term infants or older pediatric patients with respiratory failure has not been established.

10 OVERDOSAGE

There have been no reports of overdosage following the administration of CUROSURF.

In the event of accidental overdosage, and if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, aspirate as much of the suspension as possible and provide the infant with supportive treatment, with particular attention to fluid and electrolyte balance.

11 DESCRIPTION

CUROSURF (poractant alfa) is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. CUROSURF is an extract of natural porcine lung surfactant consisting of 99% polar lipids (mainly phospholipids) and 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C).

CUROSURF is a white to creamy white suspension of poractant alfa. Each milliliter of suspension contains 80 mg of poractant alfa (surfactant extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.45 mg is SP-B and 0.59 mg is SP-C. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine. It is suspended in 0.9% sodium chloride solution. The pH is adjusted with sodium bicarbonate to a pH of 6.2 (5.5 to 6.5).

CUROSURF contains no preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous pulmonary surfactant reduces surface tension at the air-liquid interface of the alveoli during ventilation and stabilizes the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in preterm infants results in Respiratory Distress Syndrome (RDS) characterized by poor lung expansion, inadequate gas exchange, and a gradual collapse of the lungs (atelectasis).

CUROSURF compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

12.2 Pharmacodynamics

In vitro - CUROSURF lowers minimum surface tension to $\leq$ 4mN/m as measured by the Wilhelmy Balance System.

12.3 Pharmacokinetics

CUROSURF is administered directly to the lung, where biophysical effects occur at the alveolar surface. No human pharmacokinetic studies have been performed to characterize the absorption, biotransformation, or elimination of CUROSURF.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Poractant alfa was negative for genotoxicity in the following assays: bacterial reverse mutation assay (Ames test), gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovary cells, unscheduled DNA synthesis in HELA S3 cells, and in vivo mouse micronucleus assay.

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

14 CLINICAL STUDIES

14.1 Rescue Treatment of Respiratory Distress Syndrome

The clinical efficacy of CUROSURF in the treatment of established Respiratory Distress Syndrome (RDS) in premature infants was demonstrated in one single-dose study (Study 1) and one multiple-dose study (Study 2) involving approximately 500 infants. Each study was randomized, multicenter, and controlled.

In study 1, premature infants 700 to 2000 grams birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ were enrolled. CUROSURF 2.5 mL/kg single dose (200 mg/kg) or control (disconnection from the ventilator and manual ventilation for 2 minutes) was administered after RDS developed and before 15 hours of age. The results from Study 1 are shown below in Table 2.

Table 2: Study 1 Results in Premature Infants with Respiratory Distress Syndrome

Efficacy Parameter	**Single Dose CUROSURF n=78**	**Control n=67**	**p-Value**
Mortality at 28 Days (All Causes)	31%	48%	≤0.05
Bronchopulmonary Dysplasia*	18%	22%	N.S.
Pneumothorax	21%	36%	≤0.05
Pulmonary Interstitial Emphysema	21%	38%	≤0.05

*Bronchopulmonary dysplasia (BPD) diagnosed by positive x-ray and supplemental oxygen dependence at 28 days of life.
N.S.: not statistically significant

In Study 2, premature infants 700 to 2000 g birth weight with RDS requiring mechanical ventilation and a $FiO_2 \geq 0.60$ were enrolled. In this two-arm trial, CUROSURF was administered after RDS developed and before 15 hours of age, as a single-dose or as multiple doses. In the single-dose arm, infants received CUROSURF 2.5 mL/kg (200 mg/kg). In the multiple-dose arm, the initial dose of CUROSURF was 2.5 mL/kg followed by up to two 1.25 mL/kg (100 mg/kg) doses of CUROSURF. The results from Study 2 are shown below in Table 3.

Table 3: Study 2 Results in Premature Infants with Respiratory Distress Syndrome

Efficacy Parameter	**Single Dose CUROSURF n=184 Rate (%)**	**Multiple Dose CUROSURF n=173 Rate (%)**	**p-Value**
Mortality at 28 Days (All Causes)	21	13	0.048
Bronchopulmonary Dysplasia*	18	18	N.S.
Pneumothorax	17	9	0.03
Pulmonary Interstitial Emphysema	27	22	N.S.

*Bronchopulmonary dysplasia (BPD) diagnosed by positive x-ray and supplemental oxygen dependence at 28 days of life.
N.S.: not statistically significant

There is no controlled experience on the effects of administering initial doses of CUROSURF other than 2.5 mL/kg (200 mg/kg), subsequent doses other than 1.25 mL/kg (100 mg/kg), administration of more than three total doses, dosing more frequently than every 12 hours, or initiating therapy with CUROSURF more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation or extracorporeal membrane oxygenation.

16 HOW SUPPLIED/STORAGE AND HANDLING

CUROSURF (poractant alfa) intratracheal suspension is available in sterile, rubber-stoppered clear glass vials containing (one vial per carton):

- 1.5 mL [120 mg poractant alfa (surfactant extract)] of suspension: NDC Number: 10122-510-01
- 3 mL [240 mg poractant alfa (surfactant extract)] of suspension. NDC Number: 10122-510-03

Store CUROSURF intratracheal suspension in a refrigerator at +2 to +8°C (36 to 46°F). PROTECT FROM LIGHT. Do not shake. Vials are for single use only. After opening the vial discard the unused portion *[see Dosage and Administration (2.3)]*.

Manufactured for:
Chiesi USA, Inc.
Cary, NC 27518



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