CUROSURF- poractant alfa suspension
Chiesi USA, Inc.

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

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 after briefly disconnecting endotracheal tube from ventilator; or
  - A single aliquot 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: 4/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 intracheal 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 after briefly disconnecting the endotracheal tube from the ventilator; or
- Intratracheally in a single aliquot 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 (see Table 1), 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 who remain intubated and 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.

Table 1: CUROSURF Weight-Based Dosing Chart for Rescue Treatment of RDS

Weight (grams)	**Initial Dose 2.5 mL/kg**	**Repeat Dose 1.25 mL/kg**	**Weight (grams)**	**Initial Dose 2.5 mL/kg**	**Repeat Dose 1.25 mL/kg**
	Each Dose (mL)			**Each Dose (mL)**	
600-650	1.60	0.80	1301-1350	3.30	1.65
651-700	1.70	0.85	1351-1400	3.50	1.75
701-750	1.80	0.90	1401-1450	3.60	1.80
751-800	2.00	1.00	1451-1500	3.70	1.85
801-850	2.10	1.05	1501-1550	3.80	1.90
851-900	2.20	1.10	1551-1600	4.00	2.00
901-950	2.30	1.15	1601-1650	4.10	2.05
951-1000	2.50	1.25	1651-1700	4.20	2.10
1001-1050	2.60	1.30	1701-1750	4.30	2.15
1051-1100	2.70	1.35	1751-1800	4.50	2.25
1101-1150	2.80	1.40	1801-1850	4.60	2.30
1151-1200	3.00	1.50	1851-1900	4.70	2.35
1201-1250	3.10	1.55	1901-1950	4.80	2.40
1251-1300	3.20	1.60	1951-2000	5.00	2.50

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 pre-cut 8-cm 5 end-hole French catheter 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.

3. When administering CUROSURF using a 5 French end-hole catheter, administer in two divided aliquots:
   - For the first dose: 1.25 mL/kg (birth weight) per aliquot
     For each repeated dose: 0.635 mL/kg (birth weight) per aliquot
4. 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, change the infant's ventilator settings to a rate of 40-60 breaths/minute, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain SaO_2 > 92%.
   3. Briefly disconnect the endotracheal tube from the ventilator.
   4. Insert the pre-cut 5 French catheter into the endotracheal tube and instill the first aliquot of CUROSURF suspension.
   5. After the first aliquot is instilled, remove the catheter from the endotracheal tube and manually ventilate the infant with 100% oxygen at a rate of 40-60 breaths/minute for one minute.
5. 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.
6. After completion of the dosing procedure, resume usual ventilator management and clinical care. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur. Post dosing, consider maintenance of PaO_2 of about 55 mmHg, $PaCO_2$ of 35-45, and pH > 7.3 *[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 2.

Table 2: 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 ≤ 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 3.

Table 3: 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	18%	22%	N.S.

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 4.

Table 4: 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.

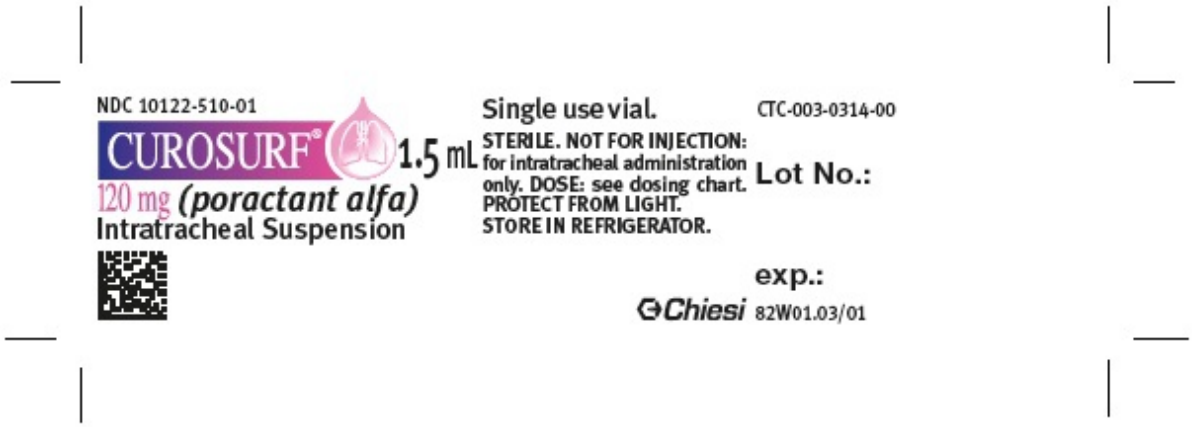
Cary, NC 27518

Manufactured by and licensed from:

Chiesi Farmaceutici, S.p.A.

Parma, Italy 43100

CTC-007-1214-01-SPL-1



CUROSURF 1.5 mL Bottle Label

Curosurf 1.5 mL Box

CUROSURF

poractant alfa suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:10122-510
Route of Administration	ENDOTRACHEAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PORACTANT ALFA (UNII: KE3U2023NP) (PORACTANT ALFA - UNII:KE3U2023NP)	PORACTANT ALFA	80 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM BICARBONATE (UNII: 8MDF5V39QO)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10122-510-01	1.5 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:10122-510-03	3.0 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020744	11/18/1999	

Labeler - Chiesi USA, Inc. (088084228)

Registrant - Chiesi USA, Inc. (088084228)

Revised: 4/2015 Chiesi USA, Inc.