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## Information for the Health Care Professional

In individual randomized clinical trials, physiological end points (e.g. faster reduction in  $\text{FiO}_2$  and lower respiratory support) have not been proven to impact key clinical outcomes due to respiratory distress syndrome (RDS). Clinical studies have not established that fewer doses result in superior safety or efficacy based on clinically relevant end points.

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.

Surfactant replacement therapy, including use of CUROSURF<sup>®</sup> (poractant alfa), is not indicated to reduce the incidence of patent ductus arteriosus. The evaluation of PDA hemodynamics was not a primary endpoint in this study. A direct correlation between short-term oxygenation improvement and lower incidence of PDA in infants with RDS has not been demonstrated.

## Indication

CUROSURF<sup>®</sup> (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.

## 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.

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 700-2000g birth weight with RDS requiring mechanical ventilation and  $\text{FiO}_2 \geq 0.60$  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 accompanying [Full Prescribing Information](#).

# A Randomized, Multicenter Masked Comparison Trial of Poractant Alfa (Curosurf) versus Beractant (Survanta) in the Treatment of Respiratory Distress Syndrome in Preterm Infants

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## ABSTRACT

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We compared the onset of clinical response and safety of two surfactants, poractant alfa (Curosurf, Chiesi Pharmaceuticals, Parma, Italy) and beractant (Survanta, Ross Laboratories, Columbus, OH), for treatment of respiratory distress syndrome (RDS) in preterm infants weighing 750 to 1750 g at birth and <35 weeks gestation. The study was performed as a 20-center prospective, randomized, masked comparison trial. Preterm infants ( $n = 293$ ) with RDS were randomized to receive an initial dose of either 100 ( $n = 96$ ) or 200 ( $n = 99$ ) mg/kg of poractant alfa or 100 ( $n = 98$ ) mg/kg of beractant. All repeat dosing was given at 100 mg/kg. The onset of clinical response after the first dose was studied by comparing changes in the fraction of inspired oxygen ( $F_{iO_2}$ ) between 0 and 6 hours measured using the area under the curve ( $F_{iO_2} AUC_{0-6}$ ); other outcomes were assessed for the entire cohort at 28 days and for infants born at  $\leq 32$  weeks gestation at 36 weeks postconceptional age. We found that the mean  $F_{iO_2} AUC_{0-6}$  values for the 100 and 200 mg/kg poractant alfa groups were both significantly lower than the mean  $F_{iO_2} AUC_{0-6}$  values for the beractant group ( $p < 0.005$ ) but were not different from each other. Other outcomes were not different among the three groups for the entire cohort, but in infants born at  $\leq 32$  weeks gestation, mortality up to 36 weeks

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postconceptional age was significantly less in the 200 mg/kg poractant alfa group than in either the beractant group (3% versus 11%;  $p = 0.034$ ) or in the 100 mg/kg poractant alfa group (3% versus 11%;  $p = 0.046$ ). Need for more than one dose of surfactant was significantly lower in infants treated with an initial dose of 200 mg/kg poractant alfa in comparison to the beractant-treated group ( $p < 0.002$ ). Treatment with poractant alfa (200 mg/kg initial dose) resulted in rapid reduction in supplemental oxygen with fewer additional doses of surfactant versus treatment with beractant in infants  $< 35$  weeks gestation with RDS, and significantly reduced mortality ( $p < 0.05$ ) than either beractant or poractant alfa (100 mg/kg dosing) in infants  $\leq 32$  weeks gestation with RDS.

**KEYWORDS:** Respiratory distress syndrome, surfactant, mortality, preterm

Respiratory distress syndrome (RDS) is caused by a deficiency of lung surfactant in prematurely born infants. This results in poor compliance, and inadequate gas exchange, requiring use of high ventilatory pressures. Use of high pressures and large tidal volumes in the presence of surfactant deficiency has been shown to result in lung injury, leading to a high incidence of bronchopulmonary dysplasia (BPD). Intratracheal administration of synthetic or biologically derived surfactants has been used extensively to improve lung function, and to decrease the morbidity and mortality associated with RDS.<sup>1-3</sup> Natural surfactants lead to faster weaning of ventilatory support during the acute phase of RDS,<sup>4,5</sup> and when used for the prevention of RDS they are more beneficial than synthetic surfactants. Meta-analysis of seven trials enrolling up to 4070 infants showed reduced mortality for natural surfactants (odds ratio, 0.80; 95% confidence interval [CI], 0.66 to 0.97) compared with synthetic surfactants.<sup>6</sup> Ainsworth et al<sup>7</sup> in a randomized trial showed that treatment with a natural surfactant, poractant alfa, was associated with a significant reduction in neonatal mortality when compared with a synthetic surfactant, pumactant (14.1% versus 31.0%;  $p = 0.006$ ; odds ratio, 0.37; 95% CI, 0.18 to 0.76]. The difference in mortality was sustained even after adjustment for center, gestation, birthweight, sex, plurality, and use of antenatal steroids, and this trial was stopped because mortality assumed a greater importance

than the primary outcome. Soll and Blanco<sup>8</sup> compared outcomes after treatment with either synthetic or natural surfactant in infants at risk from RDS in a meta-analysis of 11 trials. Modified natural surfactants reduced relative risk of pneumothorax by 27% and of mortality by 13% compared with synthetic surfactants.

Only three randomized trials have compared different natural surfactants. Bloom et al<sup>9</sup> compared calf lung surfactant extract (Infasurf, Forrest Laboratories, New York, NY) with beractant in a randomized trial for prevention and treatment of RDS in preterm infants. They found no significant differences in air leaks, complications of prematurity, overall mortality, or survival without chronic lung disease in the prevention or treatment arm. A pilot study comparing poractant alfa with beractant showed a greater improvement in blood gases for 24 hours after treatment with poractant alfa.<sup>10</sup> More recently, Baroutis et al<sup>11</sup> reported in a comparison trial using poractant alfa, bovine lung lavage surfactant (Alveofact, Boehringer Ingelheim, Germany), and beractant that treatment with poractant alfa or Alveofact was associated with fewer days on the ventilator and supplemental oxygen, and a shorter length of stay when compared with beractant. Variations in outcome between different natural surfactants are most likely related to differences in the composition of phospholipids, surfactant-associated proteins, dosing volume, proportion of phospholipids to proteins, and their ability to resist inactivation

by various substances in the lung. Three natural surfactants, beractant, poractant alfa, and calf lung surfactant extract, are commercially available in the United States. Both poractant alfa and beractant have been carefully studied in large clinical trials.<sup>11–15</sup>

The primary objective of this multicenter, randomized, masked trial was to evaluate the effectiveness of a 100 mg/kg initial dose of poractant alfa, by comparing its onset of clinical response to that of a 200 mg/kg initial dose of poractant alfa or a 100 mg/kg initial dose of beractant, for treatment of RDS in infants weighing 750 to 1750 g. The secondary objectives were to evaluate other clinical outcomes.

## MATERIALS AND METHODS

### Trial Design

This was a prospective, randomized, masked trial comparing a 100 mg/kg initial dose of poractant alfa with a 200 mg/kg initial dose of poractant alfa or a 100 mg/kg initial dose of beractant for treatment of RDS. Following administration of the first dose of either poractant alfa or beractant, individuals who were blinded as to the type or dose of first dose of surfactant administered collected data to permit an unbiased assessment of the onset of clinical response to the different surfactants. The onset of clinical response was assessed for the first dose only. The total number of doses administered was also recorded. Adverse events were collected during the 7-day period following the first dose. The protocol also specified assessments of outcome at 28 days for all infants and at 36 weeks postconceptional age for those  $\leq 32$  weeks gestation. Outcomes included air leaks, patent ductus arteriosus, necrotizing enterocolitis, pulmonary hemorrhage, need for high-frequency ventilation,  $\geq$  grade III intraventricular hemorrhage, duration of mechanical ventilation, oxygen requirement at 28 days for all infants, oxygen requirement at 36 weeks postconceptional age for infants born  $\leq 32$  weeks gestation, and mortality.

### ELIGIBILITY CRITERIA

Subjects were eligible to participate if all inclusion criteria were met: birth weight 750 to 1750 g inclusive; gestational age  $< 35$  weeks; clinical or radiographic evidence of RDS; intubated and receiving conventional mechanical ventilation; fraction of inspired oxygen ( $F_{iO_2}$ )  $\geq 0.30$  to maintain oxygen saturation by pulse oximeter of 88% to 96% or an arterial to alveolar  $PaO_2$  ratio (a/A ratio) of  $\leq 0.33$ ; age of 6 hours or less at the time of randomization, and signed informed consent by a parent or legal guardian. Subjects were excluded if any of the following were present: respiratory failure not due to RDS; proven fetal lung maturity profile from amniocentesis prior to delivery; suspected lung hypoplasia; prior treatment with an exogenous surfactant; Apgar score  $\leq 3$  at 5 minutes; one or more major congenital anomalies considered to be life threatening; prolonged rupture of membranes, defined as  $\geq 3$  weeks in duration; untreated pneumothorax, hypotension, or hypoglycemia; use of high-frequency ventilation prior to first dose of surfactant; severe grades of intraventricular hemorrhage (grades III or IV) by cranial ultrasound (CUS) prior to surfactant (CUS not required); any condition believed by the investigator to place the subject at undue risk; and participation in another clinical trial.

### SURFACTANT PREPARATIONS

Poractant alfa was supplied in ready-to-use, single-use vials containing 1.5 mL (120 mg phospholipid) of surfactant (poractant alfa is licensed through Chiesi Pharmaceuticals to Dey, L.P., Napa, CA, for North American distribution). Prepared from minced porcine lung, poractant alfa is a creamy white, sterile suspension containing the surfactant in normal saline at a concentration of 80 mg/mL phospholipid. Poractant alfa is prepared by chloroform-methanol extraction, and liquid-gel affinity chromatography, and contains  $\sim 99\%$  polar lipids.<sup>16</sup> Beractant was supplied in ready-to-use, single-dose glass vials containing 8.0 mL (200 mg phospholipid) of surfactant (Ross Laboratories, Columbus, OH). Prepared from bovine lung extract, beractant is an off-white to light brown, sterile

suspension. Beractant is supplemented with synthetic dipalmitoyl-phosphatidylcholine, palmitic acid, and tripalmitin. Cholesterol is removed and the final preparation of beractant contains 25 mg/mL phospholipid.

#### INFORMED CONSENT

The protocol, study design, and informed consent were reviewed and approved by the institutional review boards at each institution.

#### RANDOMIZATION

Randomization was stratified by birth weight and site. The three birth weight strata were 750 to 1150 g, 1151 to 1450 g, and 1451 to 1750 g. Within each birth weight stratum, infants were randomized to receive poractant alfa at an initial dose of 100 or 200 mg/kg, or beractant at 100 mg/kg. Randomization was done using random numbers contained in sealed, opaque envelopes provided to each site. When subjects qualified for study entry, their birth weight was used to determine which of the three sets of randomization envelopes were used.

#### DOSING

The first dose of the surfactant was administered intratracheally as soon as possible after randomization, which was to occur within 6 hours of birth. Additional doses of surfactant were given if the infant continued to require mechanical ventilation and an  $F_{IO_2}$  of 0.30 or greater to maintain an oxygen saturation by pulse oximetry of 88% or greater. Repeat doses, if necessary, were given within 48 hours of the first dose without regard to masking the administration of doses. Repeat doses of poractant alfa were given not less than 12 hours after the previous dose, and for beractant, not less than 6 hours after the previous dose. All repeat dosing was given at 100 mg/kg of poractant alfa or beractant in accordance with the manufacturer's drug package insert.

#### SHORT-TERM END POINTS

The primary end point, used to define the onset of clinical response, was area of  $F_{IO_2}$  under the curve during the 6-hour period ( $F_{IO_2}$  AUC<sub>0-6</sub>) after the

first dose of poractant alfa or beractant. Six hours following surfactant administration was chosen because beractant was given every 6 hours. Secondary end points to assess onset of clinical response included changes in  $F_{IO_2}$  and mean airway pressure (MAP), measured at baseline, at 15 and 30 minutes, and at 1, 2, 4, and 6 hours after the initial dose of surfactant. Other specified secondary end points included total number of doses of surfactant and the median durations of oxygen dependence and mechanical ventilation.

#### LONG-TERM END POINTS

Long-term end points were complications of prematurity and overall clinical outcomes, assessed from days 7 to 28. Infants born at  $\leq 32$  weeks gestation also had outcomes assessed at 36 weeks postconceptional age.

#### CALCULATIONS AND COMPARISONS OF THE PRIMARY END POINT: $F_{IO_2}$ AUC<sub>0-6</sub>

The  $F_{IO_2}$  AUC<sub>0-6</sub> was calculated using the linear trapezoidal rule for the 6 hours immediately after the first dose of surfactant. Mathematical integration was performed using all nonmissing values, and interpolating or carrying forward the last observation for missing values. Mean values of the primary end point  $F_{IO_2}$  AUC<sub>0-6</sub> were compared among treatment groups using the Kruskal-Wallis test. A  $p$  value of less than 0.05 was considered significant.

Changes in  $F_{IO_2}$  and MAP (measured at 15 and 30 minutes and at 1, 2, 4, and 6 hours) were compared using nonparametric rank tests; changes in the total number of doses of surfactant required were analyzed using Kaplan-Meier techniques; and the median durations of oxygen dependence and mechanical ventilation were analyzed with nonparametric tests.

#### SAMPLE SIZE

The sample size of 100 subjects in each treatment group provided statistical power of 80% for the 95% CI on the difference in adjusted means for  $F_{IO_2}$  AUC<sub>0-6</sub> from the analysis of variance to fall within an interval of -20% to 20% of the reference mean if

the difference between means was no more than 15%, given a type I error rate of 0.05.

#### LONG-TERM OUTCOMES

These were compared with chi-square tests. Any differences observed in these outcomes at the  $p < 0.05$  level in both the entire population and in infants born at  $\leq 32$  weeks gestation were considered significant.

## RESULTS

The study enrolled 301 infants from January 2000 to May 2001 at 20 centers in the United States. Eight infants were randomized but not treated with surfactant because of unexpected improvement in their respiratory status prior to initial dosing of surfactant; these eight patients were not included in the analyses (Table 1).

The remaining 293 subjects who were treated with surfactant comprised the entire study population, and all of the analyses were performed on this population. Three violations of entry criteria were recorded. One infant was born at 36 weeks gestational age, a second infant had an Apgar score of  $< 3$  at 5 minutes of age, and a third infant was ventilated

with high frequency prior to treatment with the first dose of surfactant. These three subjects were randomized, and treated, and are included in the final analyses. Ninety-six infants were assigned to and received poractant alfa 100 mg/kg. Ninety-nine infants were assigned to and received poractant alfa 200 mg/kg, and 98 infants were assigned to receive beractant 100 mg/kg for the initial dose; inadvertently, one infant assigned to each of these doses received the other surfactant at the same dose instead. These two infants were counted in the analyses as actually treated.

The characteristics of the study population are given in Table 1. There were no differences in birth weight or gestational age among the study groups. Distribution within the three birth weight strata was equivalent for each of the three treatment groups. Mean gestational age, gender, race, and partial or complete course of antenatal steroid exposure with betamethasone or dexamethasone were similar among the three groups. More male subjects were treated overall but there were no differences among the treatment groups. Proportions of infants born  $\leq 32$  weeks gestational age were also similar among the three groups. Baseline  $FIO_2$  and mean airway pressure were similar among the three groups. Mean age at first dose of surfactant administration was 3 hours in all groups.

**Table 1 Population Characteristics of the Three Treatment Groups for All 293 Infants**

Characteristic	Poractant Alfa 100 mg/kg (n = 96)	Poractant Alfa 200 mg/kg (n = 99)	Beractant 100 mg/kg (n = 98)
Birth weight (g)*	1148 (265)	1151 (259)	1187 (273)
Gestational age (wk)*	28.8 (2.0)	28.7 (2.0)	28.7 (2.0)
Gestational age ( $\leq 32$ wk)	85 (89%)	95 (96%)	90 (92%)
Male	56 (58%)	61 (62%)	56 (57%)
Race, white	42 (44%)	41 (41%)	43 (44%)
Antenatal steroids	79 (82%)	75 (76%)	83 (85%)
Inborn	79 (82%)	85 (86%)	80 (82%)
Birth weight groups (g)			
750–1150	52 (54%)	51 (52%)	44 (45%)
1151–1450	29 (30%)	30 (30%)	33 (34%)
1451–1750	15 (16%)	18 (18%)	21 (21%)
Age at first dose (h) <sup>†</sup>	2.5 (1.9–3.7)	2.7 (1.9–3.6)	2.5 (1.7–4.2)

\*Mean (standard deviation).

<sup>†</sup>Median (interquartile range).

All other data are n (%).

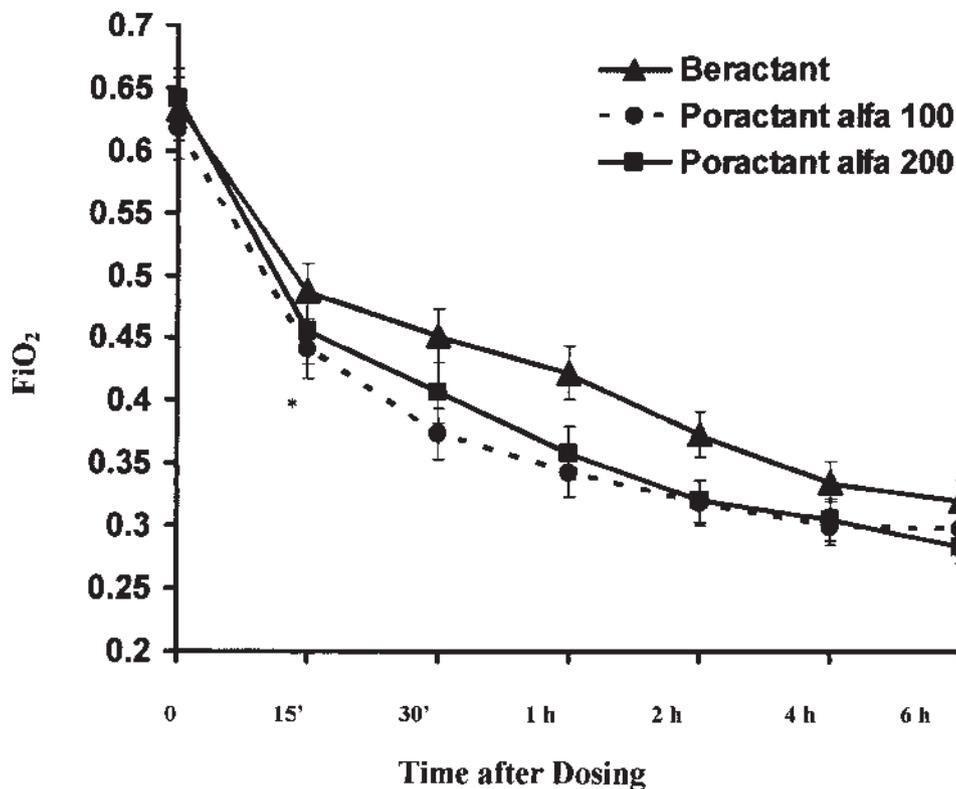
### Primary Outcome

Mean  $FiO_2$  (Fig. 1) for 100 and 200 mg/kg poractant alfa groups were significantly lower than that for the beractant group at all time points until 6 hours ( $p < 0.05$ ). There was no significant difference between the mean  $FiO_2$  in infants treated with 100 or 200 mg/kg of poractant alfa. The primary outcome,  $FiO_2$  AUC<sub>0-6</sub>, was significantly lower for both poractant alfa 100 mg/kg (1.956  $FiO_2$  hours;  $p < 0.001$ ) and poractant alfa 200 mg/kg (1.989  $FiO_2$  hours;  $p < 0.005$ ) compared with the beractant treatment group (2.237  $FiO_2$  hours). This result remained significant after adjusting for birth weight, age at treatment, study site, or early onset sepsis. Forty-five infants in the poractant alfa 100 mg/kg group, 47 infants in the poractant alfa 200 mg/kg group, and 50 infants in the beractant 100 mg/kg group were treated with surfactant within 2.5 hours of birth. Earlier treatment enhanced the differences in mean

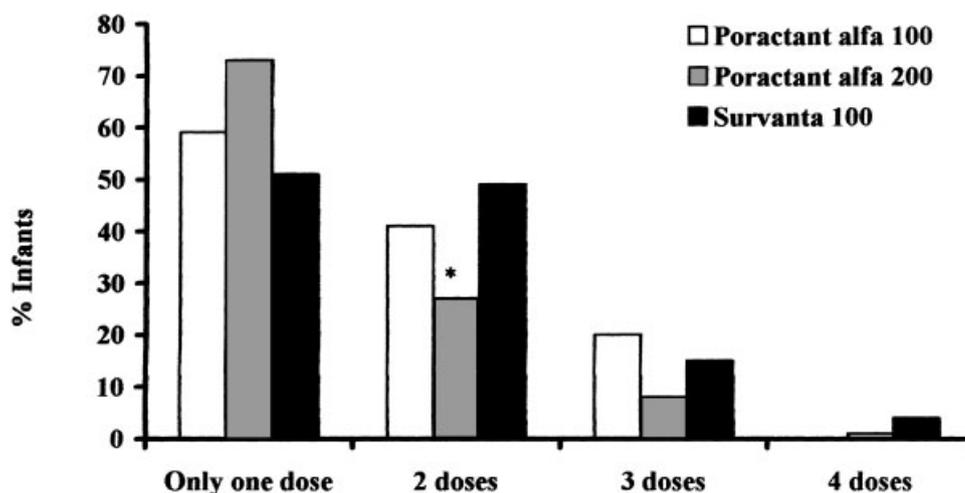
$FiO_2$  AUC<sub>0-6</sub> between the poractant alfa and beractant treated groups.  $FiO_2$  AUC<sub>0-6</sub> was significantly lower in infants treated with either initial dose of poractant alfa within 2.5 hours of birth compared with beractant ( $p < 0.02$ ; data not shown).

### Secondary Outcomes

Seventy infants (73%) were successfully treated with only one dose of 200 mg/kg poractant alfa (Fig. 2) compared with 58 (59%) in the poractant alfa 100 mg/kg group and 50 (51%) in the beractant group ( $p < 0.002$ ). Overall, 36% of infants received two or more doses of surfactant in the poractant alfa 200 mg/kg group compared with 68% in the beractant group ( $p = 0.002$ ). There was no difference in changes in mean airway pressure during the 6 hours after the first dose of surfactant in the three groups.



**Figure 1**  $FiO_2$  versus time curves for the three treatment groups in all 293 infants. The mean and standard error are plotted. \* =  $p < 0.05$  at all posttreatment time points in the poractant alfa groups compared with beractant.



**Figure 2** Percent of infants receiving one or more doses of surfactant in the three groups (n = 293). \* =  $p < 0.002$  poractant alfa 200 mg/kg versus beractant 100 mg/kg group.

The incidences of air leaks, patent ductus arteriosus, necrotizing enterocolitis, pulmonary hemorrhage, need for rescue high-frequency ventilation,  $\geq$  grade III intraventricular hemorrhage, duration of mechanical ventilation, and oxygen requirement at 28 days were not different among

the three groups for the entire cohort of 293 infants or the 270 infants born  $\leq 32$  weeks gestation (Table 2). Infants who are alive and receiving supplemental oxygen at 36 weeks postconceptional age among those  $\leq 32$  weeks were also similar among the groups (Table 2).

**Table 2** Outcomes by Groups as Randomized and for the Subgroup  $\leq 32$  wk

Outcome	Poractant Alfa 100 mg/kg (n = 96)	Poractant Alfa 200 mg/kg (n = 99)	Beractant 100 mg/kg (n = 98)
Pneumothorax	6 (6%)	3 (3%)	5 (5%)
Pulmonary hemorrhage	6 (6%)	6 (6%)	5 (5%)
PDA	36 (38%)	44 (44%)	45 (46%)
NEC	4 (4%)	5 (5%)	5 (5%)
IVH grade III-IV	9 (9%)	8 (8%)	9 (9%)
Oxygen at 28 d	48 (50%)	49 (49%)	49 (50%)
<b>Infants <math>\leq 32</math> wk</b>	<b>(n = 85)</b>	<b>(n = 95)</b>	<b>(n = 90)</b>
Pneumothorax	5 (6%)	3 (3%)	5 (6%)
Pulmonary hemorrhage	6 (7%)	6 (6%)	4 (4%)
PDA	36 (42%)	43 (45%)	39 (43%)
NEC	5 (6%)	8 (8%)	7 (8%)
IVH grade III-IV	8 (9%)	7 (7%)	8 (9%)
Duration of MV (d)*	16 (20)	14 (17)	16 (20)
Supplemental O <sub>2</sub> (d)*	40 (21)	37 (23)	39 (23)
Alive and on oxygen at 36 wk PCA	30 (35%)	36 (38%)	33 (37%)

Numbers (percent).

\*Mean (standard deviation).

PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; MV, mechanical ventilation; PCA, postconceptional age.

**MORTALITY AT 28 DAYS**

The neonatal mortality rate at 28 days for the 200 mg/kg poractant alfa group was 3% (3 of 99) compared with 6% (6 of 96) and 8% (8 of 98) in the 100 mg/kg poractant alfa and beractant groups, respectively (Table 3); these differences were not significant.

**MORTALITY AT 36 WEEKS**

Mortality at 36 weeks postconceptional age for infants born  $\leq 32$  weeks gestation was 3% (3 of 95) in the 200 mg/kg poractant alfa group compared with 11% (9 of 85 and 10 of 90) each in the 100 mg/kg poractant alfa and beractant treated infants (Table 3); these differences were significant for the 200 mg/kg poractant alfa group compared with both the beractant group ( $p=0.034$ ) and the 100 mg/kg poractant alfa group ( $p=0.046$ ). The odds ratios for death at 36 weeks postconceptional age in the 200 mg/kg poractant alfa group versus the beractant group and the 100 mg/kg poractant alfa group were 0.26 (95% CI, 0.07 to 0.98;  $p < 0.05$ ) and 0.28 (95% CI, 0.07 to 1.05), respectively (Table 3).

**DISCUSSION**

This study was designed and powered to assess differences in  $FI_{O_2}$  AUC<sub>0-6</sub> over the first 6 hours among the three groups. Treatments with poractant

alfa 100 and 200 mg/kg were associated with faster weaning of supplemental oxygen compared with beractant. Differences in  $FI_{O_2}$  AUC<sub>0-6</sub> between infants treated with poractant alfa and those treated with beractant were also larger with earlier treatment. The mean  $FI_{O_2}$  AUC<sub>0-6</sub> was significantly smaller for infants treated with either 100 or 200 mg/kg of poractant alfa within 2.5 hours of birth compared with infants treated with beractant.

Exposure to oxygen, even for brief periods of time in term newborns, has been shown to result in an increased oxidative stress that lasts for at least a month.<sup>17</sup> Alveolar macrophages from premature lungs behave differently when exposed to oxygen, with a significant increase in the production of proinflammatory cytokines than those from term or adult lungs.<sup>18</sup> Preterm infants who develop chronic lung disease have elevated levels of proinflammatory cytokines in their lungs, and expression of these cytokines is controlled by nuclear factor kappa B (NF- $\kappa$ B). Bourbia et al<sup>19</sup> recently demonstrated that in preterm infants, activation of NF- $\kappa$ B from tracheal aspirate is directly related to inspired oxygen concentration. Under expression of bone morphogenetic protein-4 (BMP-4), a signaling molecule, has been shown to perturb normal lung development. Sebald et al<sup>20</sup> demonstrated that NF- $\kappa$ B mediates BMP-4 suppression, demonstrating a potential functional linkage between oxygen-induced proinflammatory mediators and lung injury. Faster weaning of oxygen may potentially decrease subclinical forms of

**Table 3 Comparison of Mortality at 28 Days for the Groups as Randomized and for Mortality at 36 wk Postconceptional Age (PCA) for Infants Born at  $\leq 32$  wk Gestation**

Mortality	Treatment Groups			P200 versus P100 OR (95% g CI)	P100 versus B100 OR (95% CI)	P200 versus B100 OR (95% CI)
	P100	P200	B100			
Mortality at day 28 (n)	96	99	98			
n (%)	6 (6)	3 (3)	8 (8)	0.47 (0.11 to 1.93)	0.75 (0.25 to 2.25)	0.35 (0.09 to 1.37)
p values from chi-square test*				0.28	0.61	0.11
Mortality at 36 wk PCA (n)	85	95	90			
n (%)	9 (11)	3 (3)	10 (11)	0.28 (0.07 to 1.05)	0.95 (0.36 to 2.46)	0.26 (0.07 to 0.98)*
p values from chi-square test†				0.05	0.91	0.03

\* $p < 0.05$ .

†p values for category variables from a chi-square test.

OR, odds ratio; CI, confidence interval; P100, poractant alfa 100 mg/kg; P200, poractant alfa 200mg/kg; B100, beractant 100 mg/kg.

lung injury in preterm infants. However, this has not been demonstrated in any clinical trials, including a trial of poractant alfa.<sup>21</sup>

Initial treatment with 200 mg/kg poractant alfa (but not 100 mg/kg poractant alfa) also was associated with significantly less need for additional doses of surfactant. This may have been due to the larger initial dose of poractant alfa (200 mg/kg) compared with beractant (100 mg/kg), which was also shown in a trial using different doses of poractant alfa.<sup>21</sup>

Apart from dose, there are three major differences between poractant alfa and beractant that might account for the more rapid improvements in need for oxygen. First, poractant alfa contains a higher proportion of polar lipids compared with beractant as a result of the liquid-gel chromatography stage of preparation.<sup>22</sup> Second, the amount of surfactant protein B (SP-B) is also reported to be higher in poractant alfa (2 to 3.7 mg SP-B/mM phospholipids) compared with beractant (1.3 mg SP-B/mM phospholipids).<sup>23</sup> Third, beractant contains more SP-C compared with poractant alfa. Although the relative amounts of SP-B and SP-C vary among different natural surfactant preparations, SP-B contributes significantly to the actions of surfactant. Activity of beractant has been shown to be improved by supplementing it with SP-B.<sup>24,25</sup> The combination of larger amounts of polar lipids and SP-B may have accounted for the faster response seen with poractant alfa compared with beractant.

Administration of poractant alfa at 12-hour intervals might have biased the number of doses given in favor of fewer doses for poractant alfa. However, it is unlikely that this alone accounts for the differences observed in the number of doses required because infants treated initially with poractant alfa 200 mg/kg also required fewer additional doses than the patients who received 100 mg/kg poractant alfa initially.<sup>21</sup>

In infants with moderate to severe RDS treated with nasal continuous positive airway pressure, a single dose of poractant alfa at 200 mg/kg significantly reduced the need for subsequent

mechanical ventilation.<sup>26</sup> Clinical practice is evolving toward early extubation to noninvasive forms of ventilation to minimize lung injury. In this study, 73% of infants treated with poractant alfa 200 mg/kg initially required only one dose of surfactant. We speculate that a rapidly acting, low-volume and effective surfactant would permit clinicians to extubate infants earlier, thus removing the possibility of subsequent intratracheal dosing as well as minimizing the potential for lung injury from continued mechanical ventilation.

In addition to faster weaning of oxygen and fewer doses required in the 200 mg/kg poractant alfa group, a third important finding of this study was a significant reduction in mortality among infants born at  $\leq 32$  weeks gestation randomized to 200 mg/kg poractant alfa initially in comparison with those randomized to either beractant or 100 mg/kg poractant alfa initially. We were surprised to find this difference in mortality with our relatively small sample size. A previous smaller study comparing these surfactants also showed a difference in mortality favoring poractant alfa but this was not significant.<sup>10</sup> A meta-analysis of both trials (this and Speer et al<sup>10</sup>) shows an odds ratio for neonatal mortality of 0.31 (95% CI, 0.010 to 0.98; unpublished observations). The results make us believe that these differences in mortality are real. Causes of death included severe grades of intraventricular hemorrhage and/or multiple organ failure. There were no differences in death due to respiratory failure among the three groups, which is surprising. Perhaps larger doses of a more effective surfactant exert their benefit in other ways than preventing acute respiratory failure by moderating disease severity and reducing long-term complications. It should be noted however, that this study was not powered to evaluate mortality as a primary outcome.

Other larger trials comparing various natural surfactants in the treatment of RDS have only shown differences in the short-term outcomes of RDS, and no differences in mortality or long-term outcomes. This may have been due to several factors, including differences in the natural surfactants

compared, sample sizes used, inclusion criteria, timing of surfactant administration, and differences in study populations or in definitions in late outcomes.

In conclusion, our data indicate that infants <35 weeks gestation treated with an initial dose of 200 mg/kg are weaned from supplemental oxygen more rapidly during the first 6 hours after dosing, that significantly fewer infants require additional doses if the 200 mg/kg initial dose of poractant alfa is used, and that infants  $\leq$ 32 weeks treated with an initial dose of 200 mg/kg poractant alfa have a survival advantage.

#### ACKNOWLEDGMENTS

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#### NOTES

Presented in part at the Pediatric Academic Societies' Annual Meeting in Baltimore, M.D., May 4 to 7, 2002.

## APPENDIX 1

### Participating Principal Investigators and Hospitals

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## 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](http://www.fda.gov/medwatch).

Revised: 12/2014

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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 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:**
  - a) Position the infant in a neutral position (head and body in alignment without inclination), with either the right or left side dependent.
  - b) 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<sub>2</sub> > 92%.
  - c) Briefly disconnect the endotracheal tube from the ventilator.
  - d) Insert the pre-cut 5 French catheter into the endotracheal tube and instill the first aliquot of CUROSURF suspension.
  - e) 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:**
  - a) When the infant is stable, reposition the infant such that the other side is dependent.
  - b) 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<sub>2</sub> of about 55 mmHg, PaCO<sub>2</sub> 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<sub>2</sub>, 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<sub>2</sub> ≥ 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**

	<b>CUROSURF 2.5 mL/kg n=78</b>	<b>CONTROL* n=66</b>
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  $\leq 4\text{mN/m}$  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  $\text{FiO}_2 \geq 0.60$  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%	$\leq 0.05$
Bronchopulmonary Dysplasia*	18%	22%	N.S.
Pneumothorax	21%	36%	$\leq 0.05$
Pulmonary Interstitial Emphysema	21%	38%	$\leq 0.05$

\*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  $\text{FiO}_2 \geq 0.60$  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



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