An Open Label Comparison of Calfactant and Poractant Alfa
Administration Traits and Impact on Neonatal Intensive Care
Unit Resources

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INFORMATION FOR THE HEALTH CARE PROFESSIONAL

Administration traits or endpoints (e.g., faster reduction in FiO_2, reflux and bradycardia rates or oxygen desaturation) have not been proven to impact key clinical outcomes such as mortality or BPD due to respiratory distress syndrome (RDS).

Clinical studies have not established that lower surfactant dose volumes result in superior safety or efficacy based on clinically relevant endpoints and there have been no prospective, randomized clinical trials comparing CUROSURF® (poractant alfa) to calfactant intratracheal suspension.

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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.

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 700-2000 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 accompanying full prescribing information.

Clinical Investigation

An Open Label Comparison of Calfactant and Poractant Alfa Administration Traits and Impact on Neonatal Intensive Care Unit Resources

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OBJECTIVE To compare calfactant (CA) and poractant alfa (PA) administration traits, short-term clinical responses, and resource use in the neonatal respiratory distress syndrome (RDS) setting.

METHODS An open label series of 277 (213 PA and 64 CA) infants was evaluated for 445 administrations. Registered respiratory therapists collected patient, surfactant administration, and post-administration clinical data. Economic analysis involved labor costs of surfactant administration and usage, wastage, and product average wholesale price. Analysis utilized the Mann-Whitney rank sum test for differences in administration time and either the chi-square or Fisher's exact test for categorical variables.

RESULTS PA had a statistically lower bedside administration time than CA (3.8 minutes vs. 5.3 minutes; P = .006) and a higher percentage of doses administered in less than five minutes (58.9% vs. 4.3%; P < .001). Doses administered per patient were similar (1.67 vs. 1.72). PA and CA were similar in time to recovery (81.4% vs. 74.3%), percent desaturation (24.8% vs. 26.7%), and bradycardia (3.8% vs. 8.5%). Reflux was significantly higher (13.2% vs. 3.5%; P < .001) with CA. Economic analyses found total administration costs per dose were $2.21 for PA and $3.08 for CA. Mean wastage costs were $141.21 for PA and $337.34 for CA (P < .001).

CONCLUSIONS PA appeared to utilize fewer neonatal intensive care unit resources than CA due to reduced administration time and less wastage of drug product. Future studies should more closely evaluate time, resource, wastage, and post-administrative clinical effects to fully assess the impact of surfactant products in this setting.

KEYWORDS calfactant, pharmacoeconomics, poractant alfa, respiratory distress syndrome, surfactant

INTRODUCTION

Treatment with pulmonary surfactant significantly reduces the morbidity and mortality associated with neonatal respiratory distress syndrome (RDS)[1,2] by reducing air-liquid surface tension in the alveoli and preventing

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ABBREVIATIONS AWP, average wholesale price; CA, calfactant; NICU, neonatal intensive care unit; PA, poractant alfa; PL, phospholipids; RDS, respiratory distress syndrome; RRT, registered respiratory therapist

collapse.[3,4] Among the treatment modalities utilized in the RDS setting, pulmonary surfactants demonstrate the best clinical and economic outcomes.[5] To date, natural surfactants show greater clinical benefits in treating RDS than synthetic agents, including faster onset,[5-10] fewer cases of pneumothorax,[5-11] reduced dependence on supplemental oxygen and positive-pressure ventilation,[5-11] and a lower mortality rate [relative risk 0.87 (95% CI, 0.76-0.98)].[8] Natural surfactants may benefit from the presence of proteins not contained within currently available synthetic surfactants: surfactant-associated proteins B and C, which increase phospholipid (PL) stability and enhance PL interaction with the air-liquid interface.[5,7]

Three natural surfactants are currently available in the United States: poractant alfa (PA; Curosurf, DEY, LP, Napa, CA), beractant (BA; Survanta, Ross Laboratories, St. Louis, MO), and calfactant (CA; Infasurf, Forest Laboratories, St. Louis, MO). PA and BA are compared in several published clinical trials that demonstrate relative advantages of PA when compared to BA in infant oxygenation,[12-14] ventilatory requirements,[12-14] need for redosing,[13] incidence of complications such as patent ductus arteriosus,[12] and mortality up to 36 weeks postconceptional age in infants born at ≤ 32 weeks gestation.[13] CA and BA are also compared in published clinical trials. Bloom et al. demonstrated a modest benefit in oxygen requirement with a longer sustained effect with CA compared to BA.[15] However, to date, no studies directly compare PA to CA.

In the neonatal intensive care unit (NICU), time is often critical, particularly when treating RDS in very low birth weight preterm infants. Health care professionals in this setting place significant importance on medications that afford easy preparation and quick administration and exert a rapid onset of action. Surfactant therapies that best meet these criteria and exhibit a lower incidence of adverse effects may reduce health care resource consumption and enhance outcomes. Additionally, in an era of heightened emphasis on cost efficiency,[16-18] economic differences that result from differences in vial size and product wastage could also play a role in determining a product's place on a health system's formulary. At the time of this evaluation, there are no published surfactant studies that focus primarily on practical administrative measures such as these.

This pilot evaluation was conceived to provide important preliminary information about differences that may exist between PA and CA as a prelude to further investigation. The primary objective was to compare the technical administration traits of PA and CA in treating premature neonates with RDS in the NICU setting. Secondary objectives included comparing their impact on short-term clinical effects and resources utilized.

METHODS

In order to observe potential differences in the technical aspects of administration between PA and CA, very low birth weight preterm infants were enrolled in a sequential, non-randomized, open label study at the Pennsylvania Hospital NICU of the University of Pennsylvania Health System from October 2001 to May 2004. PA was used exclusively from October 2001 to August 2003 and CA was used exclusively from September 2003 to May 2004. PA was resumed for routine use after the completion of the study. Approval was obtained from the institutional review board as a nonconsent study because of the observational nature of the evaluation.

All infants who were intubated and required surfactant therapy for RDS during the investigational period were included in the study. There were no exclusions for any concomitant conditions or disease states, as these variables were not expected to affect the administration of surfactant therapy. Consistent with product labeling, PA was dosed at 2.5 mL/kg initially, then at 1.25 mL/kg for additional doses.[19] CA was dosed at 3 mL/kg for all doses.[20] Each dose was administered intratracheally by a registered respiratory therapist (RRT) in two aliquots, according to manufacturer dosing recommendations.[19,20]

The Pennsylvania Hospital NICU is a 45-bed Level III unit. There is a dedicated RRT staff of at least one RRT at all times. The RRTs have from 8 to 26 years of experience, and all are highly skilled in administering various surfactant products. Because of the RRT familiarity with different surfactant products, the study design did not include a "learning

curve" when changing surfactant products. The same RRT staff was present for both phases of the study.

RRTs administered the surfactant following the same standard dosing procedures. Both surfactants were administered with the same ancillary supplies and equipment. At the time of surfactant administration, the RRTs recorded temporal, clinical, and pharmaceutical data in a standard data collection table. Patient information included gender, gestational age, and birth weight. After administration, the infants were observed for five to fifteen minutes to record the incidence of any short-term clinical effects. The RRTs documented their own time and clinical descriptions; because this was an observational study, formal time and motion studies with objective third party observers were not done. Infants were administered additional doses of surfactant if they remained intubated and were still receiving supplemental oxygen ($FiO_2 \geq 0.30$) more than twelve hours after the previous dose, at the discretion of the attending neonatologists. All infants did not receive a repeat dose if FiO_2 was ≥ 0.30, but there were no changes in attending staff or repeat dosing strategies during the study.

The primary outcome measures of the study were the time of drug administration to the infant, and the following short-term clinical effects: time to recovery; number of surfactant doses administered; reflux up the endotracheal tube or into the pharynx; oxygen desaturation, defined as pulse oximetry < 90%; and bradycardia, defined as heart rate <100 beats per minute during administration. Secondary outcome measures included the number of vials used for each administration and unused product remaining within the single-dose vials (which was discarded after one use, per manufacturer recommendations).[19,20]

Statistical differences in administration time between the PA and CA groups were tested using the Mann-Whitney rank sum test. Administration time was further categorized into < 5 minute and ≥ 5 minute intervals. Recovery times were also subsequently categorized into < 1 minute and 1-5 minute intervals. Categorized variables including the clinical outcome observations of desaturation, reflux, and bradycardia were tested using either the chi-square or Fisher's exact test. Statistical significance

Table 1. Study population

	PA	CA
Number of patients	213	64
Mean # doses per infant	1.67	1.72
Birth weight (g)*	1410 ± 676	1649 ± 875
Gestational age (wks)*	29.4 ± 3.5	30.2 ± 4.2

CA, calfactant; PA, poractant alfa
* mean ± SD

was defined as P < .05.

A pharmacoeconomic analysis was also conducted to determine the costs associated with each therapy. The cost of surfactant administration was determined by multiplying the RRT wage ($35/hour for Philadelphia area; $0.58/minute)[21] by the time spent by the RRT. The cost of wasted drug was determined by subtracting the amount of the surfactant dose given from the amount of surfactant in the vial dispensed, then multiplying by the per-mL cost for each product, which was determined using average wholesale price (AWP 2005). For PA, AWP was $327.60 for a 1.5-mL vial and $641.34 for a 3-mL vial.[22] For CA, AWP was $732.12 for a 6-mL vial.[22] For patients receiving PA who required both 3-mL vials and 1.5-mL vials, the cost per mL of the 1.5-mL vial was used to calculate wastage costs.

RESULTS

A total of 277 patients were evaluated: 213 in the PA group and 64 in the CA group. The patient data and dosing characteristics have been summarized in Table 1. The average gestational age of the study population was 29.4 ± 3.5 weeks in the PA group and 30.2 ± 4.2 weeks in the CA group. Average birth weight was 1410 ± 676 grams for the PA group and 1649 ± 875 grams for the CA cohort. Infants in the PA group received a mean of 1.67 doses per patient. Infants in the CA group received a mean of 1.72 doses per patient.

With respect to time-in-motion observations, there was a significant difference in average surfactant administration time between groups for the 141 administrations for which time was recorded (95 PA, 46 CA) (Figure 1). Mean surfactant administration time per dose of PA was 3.8 minutes, compared to 5.3 minutes for CA (P = .006). Furthermore, there was a signifi-
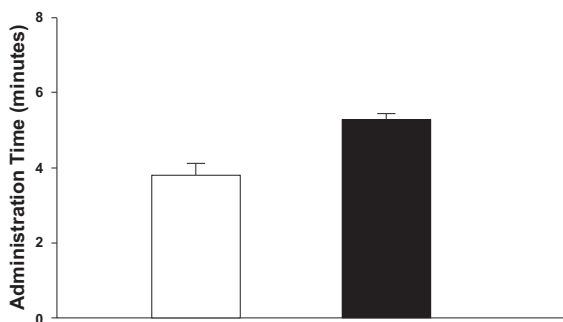
Figure 1. Mean surfactant administration time (mean ± SEM).
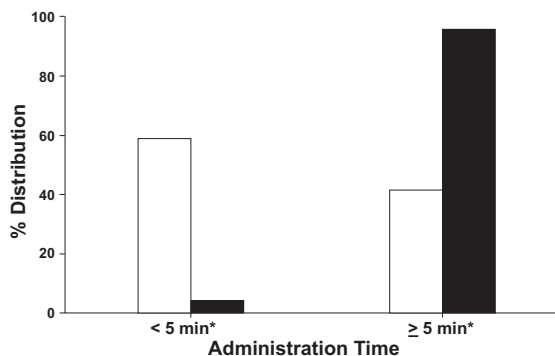□ = poractant alfa; ■ = calfactant.
P = .006

Figure 2. Distribution of surfactant administration time.
□ = poractant alfa; ■ = calfactant.
**P < .001*

cant difference in the percentage of doses that were administered in less than five minutes (Figure 2). In the PA treatment group, 58.9% of the surfactant doses were administered in less than five minutes, whereas only 4.3% of CA doses were administered in that time (P < .001). There was no difference in preparation time for the two surfactant products.

Clinical observations were also made during the initial five- to fifteen-minute period after surfactant administration to gauge tolerability (Figure 3). A significant difference in the incidence of reflux between the two treatment groups was observed (PA 3.5% vs. CA 13.2%; P < .001). There was also a trend toward fewer episodes of bradycardia with PA (PA 3.8% vs. CA 8.5%; P = .05). In addition, a lower incidence of desaturation was observed with this surfactant, although the difference was not significant. In terms of time for recovery after administration (Figure 4), PA showed a greater percentage of patients with a recovery time of less than one minute, although it was not significant (PA 81.4% vs. CA 74.3%).

In addition to clinical observations, economic factors were also considered. Since preparation time was not significantly different between surfactants, costs were only calculated for administration time of each dose (Figure 5). Administration costs per dose were $2.21 for the PA group and $3.08 for the CA group. A significant difference in cost due to drug wastage between the groups was also noted (Figure 6). Mean wastage cost per dose in the PA group was $141.21, while mean wastage cost in the CA group was $337.34 (P < .001). This resulted in a cost savings of $196.13 per dose delivered.

DISCUSSION

This exploratory study was the first to compare CA and PA. The goal was to evaluate the technical aspects of administration with initial short-term clinical observations and economic implications of two surfactant products. Observations indicated that PA was associated with a shorter average administration time compared to CA, fewer incidences of reflux, and trends favoring time to recovery, incidence of desaturation, and bradycardia. PA appeared to offer a cost savings compared to CA based on cost of administration and drug wastage.

Several valuable observations can be made based on this analysis. A significantly shorter surfactant administration time is observed with PA, and this disparity may be due partly to the higher PL concentration in that surfactant: PA contains 99% PL, at a concentration of 80 mg PL/mL, whereas CA consists of 95% PL at a concentration of 35 mg PL/mL.[19,20] The higher PL concentration in PA allows for a smaller volume and facilitates more rapid administration. The percentage of doses administered within five minutes is greater in infants receiving PA than with CA. This difference in administration time can be clinically significant for both the RRT providing care in a stressful environment and the distressed, physiologically labile infant receiving ventilatory support. The higher PL concentration also affords administration of a more potent dose (200 mg/kg). Ramanathan et al.[13] reports that administration of a larger initial dose of PA (200 mg/kg) results in a significantly greater percentage of infants who are successfully treated with only one dose compared to a smaller PA dose of 100 mg/kg
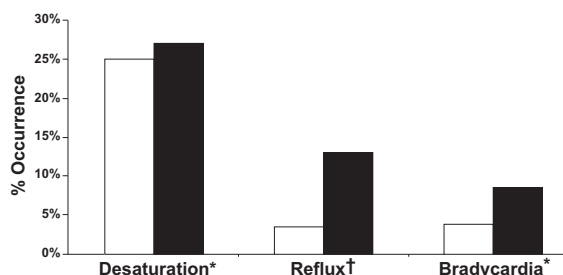
Figure 3. Clinical observations after administration.
□ = poractant alfa; ■ = calfactant.
* P = .05
† P < .001

Figure 4. Time for recovery after administration.
□ = poractant alfa; ■ = calfactant.
* P > .05

(73% vs. 59%; P < .002). Fewer instances of redosing indicate faster clinical resolution of RDS, which results in reduced resource utilization and increased cost savings. Another factor that may play a role in the observed difference in administration time is the viscosity of the products. A less viscous surfactant may be reasonably expected to have a quicker administration time, as well as other desirable administrative or clinical effects.[23]

The differences in PL concentration that result in a corresponding lower dosage volume associated with PA may also account for the reduced adverse effects seen with PA in this study. The significantly lower percentage of infants who refluxed surfactant into the endotracheal tube or pharynx with PA is likely due to the larger volume of surfactant administered with CA and possibly also a difference in viscosity. These differences, although slight, may be clinically important. Reflux may contribute to obstruction of the endotracheal tube or tracheobronchial tree, which may predispose the neonate to development of distended terminal airways, pulmonary interstitial emphysema or pneumothorax,[24] decreased arterial saturation, and bradycardia.[7] Furthermore, reflux disrupts the administration of pulmonary surfactant, delaying the time it takes the drug to reach its site of action. This adverse effect may result in drug loss, greater resource utilization, and discomfort to the infant. Such maldistribution of surfactant may also impede the neonate's recovery from RDS. Indeed, infants appear to experience a quicker recovery time with PA (Figure 4). With less reflux, the delivery of care is effectively coupled with greater tolerance and ease of administration.

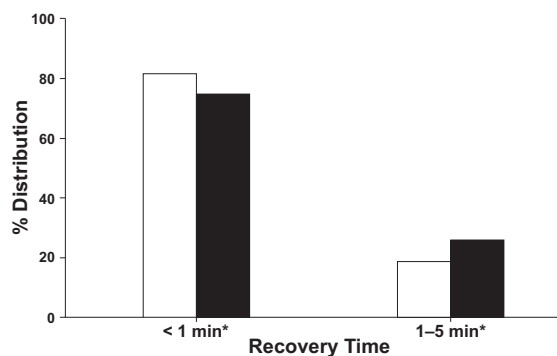Furthermore, larger volumes of surfactant may be associated with transient hypercapnia and a decrease in oxygenation. When administering surfactant to very low birth weight neonates, the transient hypercapnia that is associated with the administration of the surfactant appears to have an impact on cerebral blood flow and its autoregulation.[25,26] It would be desirable to minimize the fluctuation in $PaCO_2$ that has been shown to be associated with the administration of surfactants. Additionally, less volume could cause less of a surface-active effect with respect to the disturbance of ventilation for the brief period of time that the surfactant is being administered and then distributed in the lungs. Thus, a smaller volume may have an impact on these parameters, and its effects should be evaluated in controlled clinical trials.

Differences in composition and viscosity may have other consequences as well. Rudiger et al. observe that preterm infants who develop bronchopulmonary dysplasia have a significantly lower percentage of several compounds, including polyunsaturated fatty acid-containing phospholipids and plasmalogen, a minor surfactant lipid, in their lungs.[27] These compounds contribute to lower surfactant viscosity at low surface tension levels.[28] PA contains a relatively high proportion of these components compared to other available surfactants, although CA's relative concentration is not available to compare directly to PA's.[28] A direct viscosity comparison between PA and CA should be considered for future research.

Other favorable short-term clinical trends associated with PA include time to recovery, percentage of infants experiencing oxygen desaturation, and bradycardic events. Oxygen desaturation and bradycardia are undesir-
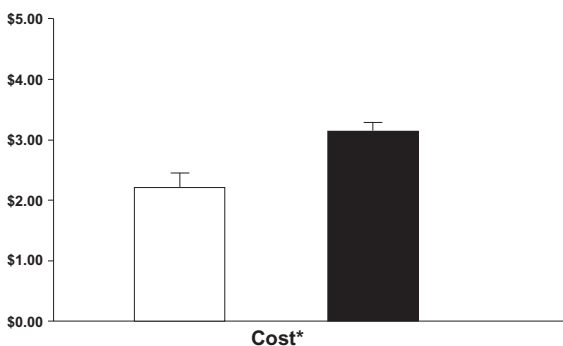
Figure 5. Total administration cost per dose (total mean cost ± SEM).
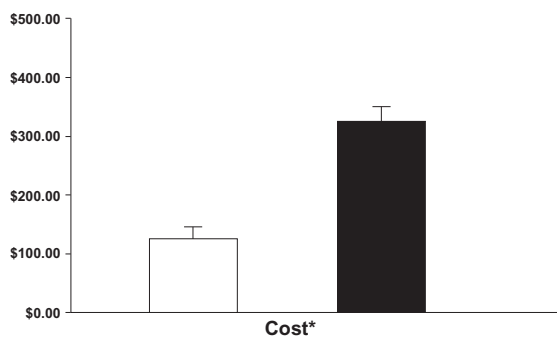□ = poractant alfa; ■ = calfactant.
* P > .05

Figure 6. Mean wastage cost per dose (mean wastage cost ± SEM).
□ = poractant alfa; ■ = calfactant.
* P < .001

able side effects because they impair oxygen delivery, incur further NICU intervention and resource utilization, and place unwarranted stress on the infant. Although not directly statistically comparable, the rate of bradycardia associated with PA in this analysis (3.8%; Figure 3) is lower than the 5.2% rate of bradycardia observed in a postmarketing study of more than 900 preterm infants by Lamboley-Gilmert et al.[29] The rate of transient desaturation (15.7%) in their analysis is lower than the rate of desaturation observed in the present analysis (25%; Figure 3), but this may be due in part to the fact that Lamboley-Gilmert and colleagues defined desaturation as the decrease of oxygen saturation below 85%, whereas in this study, desaturation was defined as less than 90%.

Financial benefits may be observed when considering administration time and drug wastage. The key driver to savings in this analysis was less waste of PA, resulting in a significant mean cost-savings per dose of $196.13. Marsh et al.[30] performed a similar study comparing the vial sizes, drug waste, and cost savings of PA and BA and also found that vial size was a key cost driver.

The difference in administration cost per patient (Figure 5) is likely a conservative estimate of cost savings. In the level three NICU that served as this study's setting, specialized RRTs are responsible for administering surfactant to the infants. However, in some hospitals or in certain circumstances, neonatologists or neonatal nurse practitioners may be required to directly administer the surfactant therapy. Applying neonatologist or specialty nurse wage

data would increase the economic disparities. Additionally, there is a less tangible opportunity cost associated with taking a physician away from practice to perform the technical task of surfactant administration.

The endpoints explored herein reflect important aspects of surfactant therapy that should be considered in future studies. Future assessments of surfactants should take into account the impact of preparation and administration time, recovery time, and product wastage. It would also be valuable to examine other factors, such as rates and costs of redosing and re-intubation, as well as preparation and administration time that takes into account all aspects of the drug delivery process, such as delivery time of the drug to the unit from the pharmacy or an automated dispensing machine. A study of this nature would allow an examination of the relative time span between the physician order and drug administration. Other areas of interest for investigation that may affect surfactant administration include analyses considering gestational age, weight, or disease severity. Furthermore, this study was not designed or powered to analyze long-term clinical differences between PA and CA, such as mortality or chronic lung disease. Due to the lack of comparative studies between these two surfactants, an investigation of this manner would be useful and relevant, albeit difficult, as it has been estimated that measurement of a statistically significant reduction in mortality would require a sample size of more than several thousand patients.[31]

Due to the nature of the study design, this exploratory analysis has several limitations that

must be acknowledged. The primary limitation is the use of a sequential, non-randomized, open label design, which invites the possibility of change in clinical practice over the time period of the study, as well as potential bias of the clinicians in favor of either drug. Due to the observational design and less of design control, the surfactants were used exclusively for different lengths of time, which results in an unequal amount of data between treatment groups. It would be ideal for future studies to be randomized, double-blind, and involve parallel-treatment groups over the same length of time. Another limitation is the use of AWP to determine costs because institutional costs vary based upon individual contracts; the actual institution costs for this analysis were unavailable throughout the entire study period. Since this analysis was conducted at a single institution, the results may not accurately reflect other regions that may have different policies or practices.

Furthermore, power to determine significant statistical differences between the short-term clinical outcomes was not determined *a priori*. Therefore, in this study, a type II error may have occurred if the number of infants enrolled was not sufficient to detect a significant difference.

Several potential variables associated with the study design and its limited control merit mention. As the study involved surfactant administration by different RRTs over a period of years, there may be variability between the individual RRT administration times and techniques. It is also possible that as an individual RRT becomes more adept with surfactant administration, the time required for drug administration decreases. Although it would be difficult to eliminate this variable entirely, it might be minimized by conducting a trial with parallel treatment groups that measures the consistency of RRT administration times. Another potential variable involves the re-use of partially used vials. Although the manufacturers state that the surfactant vials are for single-use,[19,20] some institutions draw up multiple doses from the same vial. Because the manufacturer's recommendations were followed in this study, the results might differ from those in institutions that utilize vials for multiple doses; they may have different economic results, as they would likely incur less overall wastage. Yet another variable that may affect drug wastage and cost is the availability of a smaller CA vial. At the time of the study, CA was only available as a 6-mL vial. A 3-mL vial has since become available. A sensitivity analysis was performed to determine the impact of this new size, as well as several other variables.

Variables tested included the acquisition cost of the products, a new vial size for CA, and labor costs. The first variable examined for the sensitivity analyses was the AWP cost of the products. Holding the cost of PA constant, it was determined that the AWP cost of the 6-mL vial of CA would have had to be $303 for the wastage costs to be equal. This was less than half the actual AWP price. It was also determined that the AWP cost of the 6-mL vial of CA would have had to be $360 for the cost difference to no longer be statistically significant. With the recent introduction of a 3-mL vial for CA,[20] it was next decided to go back and replace the use of 6-mL vials with 3-mL vials where appropriate and recalculate the cost difference. The mean wastage cost dropped to $169.47, which was not statistically different from the PA mean wastage cost of $141.21.

Finally, sensitivity analyses were performed around the use of other health care professionals instead of administration by only RRTs. At the time of writing, the median neonatologist salary in the Philadelphia area was $200,207 per year.[32] Assuming a 40-hour workweek, this would average $96.25/hr ($1.60/min), nearly three times the RRT rate. If administration were performed by only neonatologists, the mean cost would have been $6.08 for PA and $8.48 for CA. A median salary in the Philadelphia area for neonatal nurse practitioners was $85,094,[32] which translates into $0.68/min. The total cost for neonatal nurse practitioners to administer PA would have been $2.58, and $3.60 for CA.

Ideally, a large, randomized, controlled trial comparing parallel treatment groups over an equal length of time would firmly define the differences between these products, although it would be difficult to carry one out with adequate sample size and power. The results obtained in this analysis should aid in future study direction regarding hypothesis generation, endpoints, and study design, and introduce a new perspective on variables to be con-

sidered when selecting a surfactant for clinical application. Evaluation of existing surfactants and new formulations in this manner as they become available would assist the clinician in assessing the costs and benefits of individual surfactant preparations.

This pilot study was an exploratory evaluation to determine how PA and CA compared with respect to their technical aspects of administration, short-term clinical observations, and the implications of any differences observed. These observations come with some limitations, based primarily on the study design, but the results imply that there may be areas of difference between PA and CA in drug administration time and short-term clinical outcomes.

CONCLUSIONS

The results of this initial pilot evaluation indicate that PA appears to involve less time for administration than CA with significantly fewer instances of reflux. Furthermore, the trends appear to favor PA with respect to time to recovery, percent desaturation, and bradycardia, and PA consumes significantly less staff time and administration costs. PA is associated with less product waste based on unused surfactant remaining in vials during the dates of the study. Considering the limitations of this evaluation, the results of this exploratory investigation suggest that there may be differences in administration time and, thus, cost between PA and CA, as well as differences in the incidence of short-term clinical observations. Prospective, randomized controlled trials are needed to further establish potential differences that exist between these surfactant products' technical, clinical, and financial outcomes.

REFERENCES

1. Schwartz RM, Luby AM, Scanlon JW, Kellogg RJ. Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500 g. N Engl J Med 1994;330:1476-80.

2. Sinn JK, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: Systemic review of randomized controlled trials. J Paediatr Child Health 2002;38:597-600.

3. Ishisaka DY. Exogenous surfactant use in neonates. Ann Pharmacother 1996;30:389-98.

4. Merrill JD, Ballard RA. Pulmonary surfactant for neonatal respiratory disorders. Current Opin Pediatr 2003;15:149-54.

5. Gal P, Ransom JL. Acute respiratory distress syndrome. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York: McGraw-Hill; 2005:557-75.

6. Halliday HL. Natural vs synthetic surfactants in neonatal respiratory distress syndrome. Drugs 1996;51:226-37.

7. Nguyen TN, Cunsolo SM, Gal P, Ranson JL. Infasurf and Curosurf: Theoretical and practical considerations with new surfactants. J Pediatr Pharmacol Ther 2003;8:97-114.

8. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No.: CD000144. DOI: 10.1002/14651858.CD000144.

9. Suresh GK, Soll RF. Lung surfactants for neonatal respiratory distress syndrome: Animal-derived or synthetic agents? Pediatr Drugs 2002;4:485-92.

10. Vermont-Oxford Neonatal Network. A multicenter, randomized trial comparing synthetic surfactant with modified bovine surfactant extract in the treatment of neonatal respiratory distress syndrome. Pediatrics 1996;97:1-6.

11. Halliday HL. History of surfactant from 1980. Biol Neonate 2005;87:317-22.

12. Malloy CA, Nicoski P, Muraskas JK. A randomized trial comparing beractant and poractant treatment in neonatal respiratory distress syndrome. Acta Paediatr 2005;94:779-84.

13. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K, et al. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol 2004;21:109-19.

14. Speer CP, Gefeller O, Groneck P, Laufkotter E, Roll C, Hanssler L, et al. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child 1995;72:F8-13.

15. Bloom BT, Kattwinkel J, Hall RT, Delmore PM, Egan EA, Trout JR, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (beractant) in the treatment and prevention of respiratory distress syndrome. Pediatrics 1997;100:31-38.

16. Baumer AM, Clark AM, Witmer DR, Geize SB, Vermeulen LC, Deffenbaugh JH. National survey of the impact of drug shortages in acute care hospitals. Am J Health Syst Pharm 2004;61:2015-2022.

17. Becker C. A dose of higher costs. With drug manufacturers being hit with new fees from distributors, providers and GPOs face new pricing pressures. Mod Healthc 2004;34:4-7.

18. Hoffman JM, Shah ND, Vermeulen LC, Hunkler RJ, Hontz KM. Projecting future drug expenditures – 2005. Am J Health Syst Pharm 2005;62:149-67.

19. Curosurf [prescribing information]. Napa, CA: DEY, L.P.; 2002.

20. Infasurf [prescribing information]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2003.

21. Salary.com™ Job Salaries & Compensation Survey Software [homepage on the Internet]. Needham, MA: Salary.com. Available at: http://www.salary.com/. Accessed June 9, 2005.

22. 2005 Drug Topics Red Book, 109th ed. Montvale, NJ. Thomson PDR; 2005.

23. King DM, Wang Z, Palmer HJ, Holm BA, Notter RH. Bulk shear viscosities of endogenous and exogenous lung surfactants. Am J Physiol Lung Cell Mol Physiol 2002;282:L277-284.

24. Hentschel R, Jorch G. Acute side effects of surfactant treatment. J Perinat Med 2002;30:143-148.

25. Gunkel JH, Banks PLC. Surfactant therapy and intracranial hemorrhage: Review of the literature and results of new analyses. Pediatrics 1993;92:775-786.

26. Kaiser JR, Gauss CH, Williams DK. Surfactant administration acutely affects cerebral and systemic hemodynamics and gas exchange in very-low-birth-weight infants. J Pediatr 2004;144:809-814.

27. Rudiger M, von Baehr A, Haupt R, Wauer RR, Rustow B. Preterm infants with high polyunsaturated fatty acid and plasmalogen content in tracheal aspirates develop bronchopulmonary dysplasia less often. Crit Care Med 2000;28:1572-1577.

28. Rudiger M, Tolle A, Meier W, Rustow B. Naturally derived commercial surfactants differ in composition of surfactant lipids and in surface viscosity. Am J Physiol Lung Cell Mol Physiol 2005;288:L379-383.

29. Lamboley-Gilmert G, Lacaze-Masmonteil T, Neonatologists of the Curosurf postmarketing French study. The short-term outcome of a large cohort of very preterm infants treated with poractant alfa (Curosurf) for respiratory distress syndrome: A postmarketing phase IV study. Pediatr Drugs 2003;5:639-645.

30. Marsh W, Smeeding J, York JM, Ramanathan R, Sekar K. A cost minimization comparison of two surfactants—beractant and poractant alfa—based upon prospectively designed, comparative clinical trial data. J Pediatr Pharmacol Ther 2004;9:117-125.

31. Tarnow-Mordi WO, Soll RF. Artificial versus natural surfactant—can we base clinical practice on a firm scientific footing? Eur J Pediatr 1994;153 Suppl 2:S17-S21.

32. Salary.com Job Salaries & Compensation Survey Software [homepage on the Internet]. Needham, MA: Salary.com. Available at: http://www.salary.com/. Accessed November 17, 2005.

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: 12/2014

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:
    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 $SaO_2 > 92\%$.
    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_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 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

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