Evaluating Surfactants for Formulary

Insights for pharmacy during a class review
RESPIRATORY DISTRESS SYNDROME (RDS) AND SURFACTANT REPLACEMENT THERAPY

Premature birth: a significant concern
Thirty-five percent of all infant deaths are related to preterm birth, and a significant cause of morbidity and mortality among preterm infants is RDS.1 In a recent study of infants born extremely preterm (less than 28 weeks gestational age), 93% developed RDS; therefore, it is important to have an effective protocol for the management of RDS in the NICU.2

Although controversies still exist regarding the best way to treat RDS in neonates, the goal is to maximize survival and minimize adverse events. And while many components will likely comprise RDS in neonates, the goal is to maximize survival and minimize adverse events. And while many components will likely comprise

Surfactant replacement therapy
Primary surfactant deficiency in premature infants can result in atelectasis and poor lung compliance, contributing to RDS. Surfactant replacement therapy, which is intended to replace the endogenous surfactant the patient is not producing in sufficient quantities, plays an important role in treating RDS.3 In a study evaluating premature infants born between 2000 and 2009 at Vermont Oxford Network hospitals, a majority (65.7%) of those weighing 501 g to 1500 g were treated with surfactant.4

Surfactants vary in composition and dose5-7
For two drugs to meet the FDA's definition of pharmaceutical equivalence, they must meet three criteria:6 7

• contain the same active ingredient(s)
• are of the same dosage form and route of administration
• are identical in strength or concentration

Clinical studies have demonstrated the importance of SP-B, SP-C and phospholipids, but they have not established the quantity required for optimal surfactant efficacy. Furthermore, clinical studies have not definitively proven that lower volume results in superior efficacy or safety based on clinically relevant endpoints.

Please see important safety information on page 8.

ALIGNING SURFACTANT SELECTION AND NICU PROTOCOLS

Individualizing care
Clinicians today have many choices regarding ventilation modes (eg, mechanical ventilation [MV], nCPAP, NPPV, HFV, NAVA) and must select not only which mode is right for which patient, but also if and when to incorporate surfactant. Because infants with RDS can differ in disease severity, age, and comorbidities, treatment protocols should account for individualization of care.8

For example, rapid extubation after surfactant administration may not be achievable or desirable in the most premature infants. Ultimately, it is up to the clinician to decide when each patient is stable enough to be extubated or transitioned to less invasive ventilation.

Recent recommendations support less invasive RDS treatment protocols9
Improvements in prenatal care, such as increased use of antenatal corticosteroids, have reduced the need for conventional intubation and subsequent mechanical ventilation for many infants. Post-delivery treatment protocols have also evolved. This has made less invasive ventilation a viable option for initial stabilization in many infants.10 In line with these advances, the use of surfactant has also evolved.

In 2014, the American Academy of Pediatrics published specific recommendations regarding the management of infants in need of respiratory support.11

Teamwork and communication between neonatologists and pharmacists
Management of RDS is complex, and the care delivered in the first hour of life can affect outcomes. For this reason, teamwork and communication are critical in optimizing neonatal care.12

This teamwork begins as early as the planning phase, when protocols are developed, which may be when your team selects a surfactant.

Close partnership among neonatologists, nurses, respiratory therapists, and pharmacists is essential to ensure the surfactant chosen fits with RDS protocols.

Stakeholders to consult
Consultation and collaboration with all stakeholders can help to identify and weigh how different considerations may impact patient treatment goals. Some individuals to consider consulting include:

• NICU Medical Director
• Staff Neonatologists
• NICU Nurse Manager
• Director of Respiratory Services (RRT)
• NICU Clinical Pharmacist
• Hospital Director of Pharmacy

The ASHP identified lack of medical staff involvement in a drug evaluation as a “common pitfall.”13 Open communication, early and often, can help keep everyone on the same page, minimize delays, and ensure buy-in to the final consensus.

Table 1: Differences in Surfactant Dosage8-10

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Initial Volume (mg/mL)</th>
<th>Initial Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poractant</td>
<td>76</td>
<td>200</td>
</tr>
<tr>
<td>Beractant</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Curosurf</td>
<td>5.0-11.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

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

Safety Information
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.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proposed protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>CPAP immediately after birth with subsequent selective surfactant administration may be considered as an alternative to routine intubation</td>
</tr>
</tbody>
</table>

Adapted from Committee on Fetus and Newborn. Respiratory Support in Preterm Infants at Birth. Pediatrics. 2014.
CONSIDERATIONS IN SURFACTANT SELECTION

Clinical and pharmacy considerations

The natural surfactants currently approved by the FDA have been studied in clinical trials, and a wealth of information is available. Across these trials, many factors were evaluated, and some of these factors may be relevant to your analysis when reviewing the surfactant class.

In preparing the analysis supporting a formulary decision, the frames of reference adopted are important. For example, evaluating the different options in a drug class against just 1 or 2 criteria may not capture all of the related concerns spanning the course of treatment. The considerations presented here are a selection of factors that were considered in a number of trials, analyses, and recommendations; however, this is not a comprehensive list. There may be additional points relevant to your NICU and you are encouraged to include them in your analysis.

As the analysis is being prepared, a good source of information is PubMed.gov, a portal maintained by the National Institutes of Health, which can be found at http://www.pubmed.gov. This database will help identify newly published studies to ensure that any analysis includes the latest research. The ASHP recommends consideration of clinical studies—including meta-analyses, randomized clinical trials, case reports, and association consensus statements—in evaluating all formulary decisions. The following studies may help you evaluate the impact of different surfactant doses and compositions.


Safety Information

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

Please see important safety information on page 6.

SURFACANT CONSIDERATIONS*

<table>
<thead>
<tr>
<th>SURFACANT CONSIDERATIONS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (surfactant administered in mg/kg per dose)15</td>
</tr>
<tr>
<td>Redosing rate (patients requiring more than 1 dose)13,24</td>
</tr>
<tr>
<td>Onset of action (reduction in FiO2)15,17,18</td>
</tr>
<tr>
<td>Volume/Viscosity14,15</td>
</tr>
<tr>
<td>Time needed for staff to administer4</td>
</tr>
<tr>
<td>Rate of complications during administration (eg, ET tube blockage)17,20</td>
</tr>
<tr>
<td>Rate of reflux3</td>
</tr>
<tr>
<td>Incidence of adverse events13,20</td>
</tr>
<tr>
<td>Duration of MV and days on oxygen11</td>
</tr>
<tr>
<td>Compatibility with less invasive ventilation13</td>
</tr>
<tr>
<td>Pharmacoeconomic assessments21</td>
</tr>
<tr>
<td>Ability to facilitate desired protocol goals3</td>
</tr>
<tr>
<td>Administration/storage11</td>
</tr>
<tr>
<td>Body of clinical evidence available21</td>
</tr>
</tbody>
</table>

*This is not a comprehensive list, and some factors included in this list may not be relevant to all hospitals.

RESOURCES AND FURTHER INFORMATION

Comparative trials and analyses to consider

The ASHP recommends consideration of clinical studies—including meta-analyses, randomized clinical trials, case reports, and association consensus statements—in evaluating all formulary decisions. The following studies may help you evaluate the impact of different surfactant doses and compositions.


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

EVALUATION AND EXPERIENCE PROCESS

In-house trial periods can provide customized data

Peer-reviewed, head-to-head trials published in reputable journals are usually considered to have a high Level of Evidence and provide valuable information about different drug options being considered. However, they may not include all the needed data, or reflect a particular organization. The ASHP notes that a medication-use evaluation (MUE) should be used for medications being considered for formulary. Designing a MUE to evaluate the surfactant choice being considered, with data-collection requirements developed in conjunction with all stakeholders, will provide local data that may be unavailable anywhere else.

One resource when planning a MUE is the ASHP Guidelines on Medication-Use Evaluation, which includes detailed steps for a suggested process flow.

“Consideration of patient care and unbiased reviews of the biomedical literature are the cornerstone principles of formulary decision making.”

— ASHP Guidelines, Am J Health-Syst Pharm. 2008:17
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CUROSURF® (PORACTANT ALFA)
INTRATRACHEAL SUSPENSION

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 FiO2 ≥ 0.60 are as follows for CUROSURF 2.5 mL/kg (200 mg/kg) 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%).

REFERENCES

Please see accompanying full prescribing information.

7
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):
  o Two divided aliquots after briefly disconnecting endotracheal tube from ventilator; or
  o 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*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Important Administration Instructions
  2.2 Recommended Dosage
  2.3 Preparation of the CUROSURF Suspension
  2.4 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Acute Changes in Oxygenation and Lung Compliance
  5.2 Administration-Related Adverse Reactions
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Immunogenicity
  6.3 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use
10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
  14.1 Rescue Treatment of Respiratory Distress Syndrome
16 HOW SUPPLIED/STORAGE AND HANDLING

*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 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

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

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 $\text{SaO}_2 > 92\%$.
   - 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 $\text{PaO}_2$ of about 55 mmHg, $\text{PaCO}_2$ 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 $\text{FiO}_2$, 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 $\text{FiO}_2 \geq 0.60$ (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

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

*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.
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.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess potential carciogenic 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.

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 FiO₂ ≥ 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Single Dose CUROSURF</th>
<th>Control n=67</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 28 Days (All Causes)</td>
<td>31%</td>
<td>48%</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia*</td>
<td>18%</td>
<td>22%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>21%</td>
<td>36%</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>Pulmonary Interstitial Emphysema</td>
<td>215%</td>
<td>38%</td>
<td>≤ 0.05</td>
</tr>
</tbody>
</table>

*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 FiO₂ ≥ 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Single Dose CUROSURF Rate (%)</th>
<th>Multiple Dose CUROSURF Rate (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 28 Days (All Causes)</td>
<td>21%</td>
<td>13%</td>
<td>0.048</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia*</td>
<td>18%</td>
<td>18%</td>
<td>N.S.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>17%</td>
<td>9%</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulmonary Interstitial Emphysema</td>
<td>27%</td>
<td>22%</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

*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)].