DESCRIPTION

CUROSURF® (poractant alfa) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It 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). It is suspended in 0.9% sodium chloride solution. The pH is adjusted as required with sodium bicarbonate to a pH of 6.2 (5.5 - 6.5). CUROSURF contains no preservatives.

CUROSURF is a white to creamy white suspension of poractant alfa. Each milliliter of surfactant mixture contains 80 mg of total phospholipids (including 54 mg of phosphatidylcholine of which 30.5 mg is dipalmitoyl phosphatidylcholine) and 1.0 mg of protein including 0.3 mg of SP-B.

CLINICAL PHARMACOLOGY

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.

Activity

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

In vivo - In several pharmacodynamic studies, CUROSURF improved lung compliance, pulmonary gas exchange, or survival in premature rabbits.

Pharmacokinetics

CUROSURF is administered directly to the target organ, the lung, where biophysical effects occur at the alveolar surface. No human pharmacokinetic studies to characterize the absorption, biotransformation, or excretion of CUROSURF have been performed. Non-clinical studies have been performed to evaluate the disposition of phospholipids present in CUROSURF.

Animal Metabolism

In both adult and newborn rabbits, approximately 50% of the radiolabeled component was rapidly removed from the alveoli in the first three hours after single intratracheal administration of CUROSURF-^{14}C-DPPC (dipalmitoylphosphatidylcholine). Over a 24-hour period, approximately 45% of the labeled DPPC was cleared from the lungs of adult rabbits compared to approximately 20% in newborn rabbits. In newborn rabbits, CUROSURF-^{14}C-DPPC passed from the alveolar space into the lung parenchyma and then was secreted again into the alveoli, whereas in adult rabbits, most of the DPPC was not recycled. The half-life in the lung appeared to be about 25 hours in adult rabbits and 67 hours in newborn rabbits.

The concentration of ^{14}C-DPPC in alveolar macrophages was ≤ 2% of that in the lung in newborn and adult rabbits. Of the total ^{14}C-DPPC recovered in newborn rabbits, <0.6% was found in the serum, liver, kidneys, and brain respectively at 48 hours.

No information is available about the metabolic fate of the surfactant-associated proteins in CUROSURF.

CLINICAL STUDIES

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

In Study 1, infants 700-2000g 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 1.

TABLE 1

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, infants 700-2000g 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 2.5mL/kg (200mg/kg). In the multiple-dose arm, the initial dose of CUROSURF was 2.5mL/kg (200mg/kg) and subsequent doses of CUROSURF were 1.25mL/g (100mg/kg). The results from Study 2 are shown below in Table 2.

TABLE 2

EFFICACY PARAMETER	SINGLE-DOSE CUROSURF n=184 %	MULTIPLE-DOSE CUROSURF n=173 %	P-VALUE
MORTALITY at 28 DAYS (ALL CAUSES)	21	13	0.048
BPD	18	18	N.S.
PNEUMOTHORAX	17	9	0.03
PULMONARY INTERSTITIAL EMPHYSEMA	27	22	N.S.

N.S.: not statistically significant

ACUTE CLINICAL EFFECTS
As with other surfactants, marked improvements in oxygenation may occur within minutes of the administration of CUROSURF.

INDICATION AND USAGE
CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

WARNINGS
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 pre-term infants.

TRANSIENT ADVERSE EFFECTS SEEN WITH THE 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

PRECAUTIONS
General
Correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia is recommended prior to CUROSURF administration.

Surfactant administration can be expected to reduce the severity of RDS but will not eliminate the mortality and morbidity associated with other complications of prematurity.

Sufficient information is not available 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess potential carcinogenic and reproductive effects of CUROSURF, or other surfactants, have not been conducted.

Mutagenicity studies of CUROSURF, which included the Ames test, gene mutation assay in Chinese hamster V75 cells, chromosomal aberration assay in Chinese hamster ovarian cells, unscheduled DNA synthesis in HELA S3 cells, and in vivo mouse nuclear test, were negative.

ADVERSE REACTIONS
Transient adverse effects seen with the administration of CUROSURF include bradycardia,

hypotension, endotracheal tube blockage, and oxygen desaturation.

The rates of common complications of prematurity observed in Study 1 are shown below in Table 3.

TABLE 3

COMPLICATIONS OF PREMATURITY	CUROSURF 2.5 mL/kg (200 mg/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.

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.

FOLLOW-UP EVALUATIONS

Seventy-six infants (45 treated with CUROSURF) were evaluated at 1 year of age and 73 infants (44 treated with CUROSURF) at 2 years of age. 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.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY.

CUROSURF should be administered by, or under the supervision of, clinicians experienced in intubation, ventilatory management, and general care of premature infants.

Marked improvements in oxygenation and lung compliance may occur within minutes of administration of CUROSURF. Therefore, the infant should receive frequent clinical and laboratory assessments such that oxygen and ventilator support can be modified to respond to respiratory status changes.

Dosage
The initial dose of CUROSURF is 2.5 mL per kg birth weight. Up to 2 subsequent doses of 1.25 mL/kg birth weight can be administered at 12-hour intervals if needed (i.e., in infants who remain intubated and require mechanical ventilation and supplemental oxygen). Dosages may be determined from the following CUROSURF dosing chart for a range of birth weights.

TABLE 4

CUROSURF DOSING CHART

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

Directions for Use
CUROSURF should be inspected visually for discoloration prior to administration. The color of CUROSURF is white to creamy white. CUROSURF should be stored in a refrigerator at +2 to +8°C (36-46°F). Before use, the vial should be slowly warmed to room temperature and gently turned upside-down, in order to obtain a uniform suspension. DO NOT SHAKE.

Unopened, unused vials of CUROSURF 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. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

General
CUROSURF is administered intratracheally by instillation through a 5 French end-hole catheter (cut to a standard length of 8 cm) inserted into the infant's endotracheal tube, with the tip positioned distally in the endotracheal tube. The catheter tip should not extend beyond the distal tip of the endotracheal tube. Each dose of CUROSURF should be administered as two aliquots, with each aliquot administered into one of the two main bronchi by positioning the infant with either the right or left side dependent.

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. The infant should be allowed to stabilize before proceeding with dosing.

Initial Dose
The initial recommended dose of CUROSURF is 2.5 mL/kg birth weight. This dose may be determined from the CUROSURF dosing chart (see table 4 above).

Slowly withdraw the entire contents of the vial of CUROSURF into a 3 or 5mL plastic syringe through a large-gauge needle (e.g., at least 20 gauge). Attach the pre-cut 8-cm 5 French catheter to the syringe. Fill the catheter with CUROSURF. Discard excess CUROSURF through the catheter so that only the total dose to be given remains in the syringe.

Immediately before CUROSURF administration, the infant's ventilator settings should be changed to a rate of 40-60 breaths/minute, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain SaO_2>92%. Keep the infant in a neutral position (head and body in alignment without inclination). Briefly disconnect the endotracheal tube from the ventilator. Insert the pre-cut 5 French catheter into the endotracheal tube and instill the first aliquot (1.25 mL/kg birth weight) of CUROSURF. The infant should be positioned such that either the right or left side is dependant for this aliquot. After the first aliquot of surfactant 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. When the infant is stable, reposition the infant such that the other side is dependant and administer the remaining aliquot using the same procedures. After instillation of the second aliquot, remove the catheter without flushing. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

After completion of the dosing procedure, resume usual ventilator management and clinical care. In the clinical trials, ventilator management was modified to maintain a PaO_2 of about 55mmHg, $PaCO_2$ of 35-45, and pH >7.3.

Repeat doses
Up to two repeat doses of 1.25 mL/kg birth weight (each) may be administered, using the same technique described for the initial dose. Repeat doses should 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 dose (sum of the initial and up to two repeat doses) is 5 mL/kg.

Dosing Precautions
Transient episodes of bradycardia, decreased oxygen saturation, reflux of the surfactant into the endotracheal tube, and airway obstruction have occurred during the dosing procedure of CUROSURF. These events require interrupting the administration of CUROSURF and taking the appropriate measures to alleviate the condition. After stabilization, dosing may resume with appropriate monitoring.

How supplied
CUROSURF® (poractant alfa) Intratracheal Suspension (NDC Numbers: 49502-125-01 [1.5 mL]; 49502-125-03 [3 mL]) is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension. One

vial per carton.

Store CUROSURF Intratracheal Suspension in a refrigerator at +2 to +8°C (36-46°F). Unopened vials of CUROSURF may be warmed to room temperature for up to 24 hours prior to use. CUROSURF should not be warmed to room temperature and returned to the refrigerator more than once. PROTECT FROM LIGHT. Do not shake. Vials are for single use only. After opening the vial discard the unused portion of the drug.

Rx Only.

Manufactured for:
Dey, LP
2751 Napa Valley Corporate Drive
Napa, CA 94558

By:
Chiesi Farmaceutici, S.p.A.
26/A Via Palermo & 9(
Via San Leonardo
Parma, Italy 43100