PRODUCT MONOGRAPH

Pr CUROSURF®

(poractant alfa)

80 mg surfactant/mL Suspension

Lung Surfactant (Porcine)

Chiesi Farmaceutici, S.p.A.
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Parma 43122
Italy

Imported and Distributed by:
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Date of Approval:
February 20, 2017

Submission Control No: 166405

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Product Monograph

CUROSURF®

(poractant alfa)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non medicinal Ingredients
Intratracheal (Endotracheopulmonary instillation)	Suspension, 80 mg surfactant (extract)/mL	There are no clinically relevant non medicinal ingredients in CUROSURF. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

CUROSURF® (poractant alfa) Suspension for Intratracheal Use is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural porcine lung extract consisting of 99% polar lipids (mainly phospholipids) and approximately 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). It is suspended in 0.9% sodium chloride solution, resulting in a composition that provides 80 mg/mL of surfactant (extract) that includes 76 mg of phospholipids and approximately 1 mg/mL of protein, of which 0.45 mg is SP-B. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine. The pH may be adjusted with sodium bicarbonate to a pH of 6.2 (5.5-6.5). CUROSURF contains no preservatives.

INDICATIONS AND CLINICAL USE

CUROSURF (poractant alfa) is indicated:

- for the treatment of Respiratory Distress Syndrome (RDS) in premature infants.

To treat premature infants requiring mechanical ventilation with clinical signs of surfactant deficiency and/or RDS confirmed by x-ray, the first dose of CUROSURF has to be administered as soon as possible, preferably within 6 hours of birth. Based on the results of clinical trials (see **Clinical Trials**) best results are obtained when CUROSURF is administered early in the course of RDS in infants with gestational age < 30 weeks or birth weight < 1500 g.

CUROSURF should only be administered by those trained and experienced in the care and resuscitation of preterm infants. The infant's general conditions should be stabilized. Infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified in response to respiratory changes. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

No specific contraindications have been identified.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **CUROSURF is intended for Intratracheal use only (see Dosage and Administration).**
- **CUROSURF should only be administered by those trained and experienced in the care and resuscitation of preterm infants. Prior to administering CUROSURF, the infant's general conditions should be stabilized (see Indications and Clinical Use, Warnings and Precautions: General and Monitoring and Laboratory Tests sections below).**
- **The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance; therefore frequent clinical and laboratory assessments are needed to determine modifications to oxygen concentration and ventilator settings (see Monitoring and Laboratory Tests section below).**
- **Transient adverse effects seen with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. Stop administration and take appropriate measures to alleviate condition. After the patient is stable, dosing may proceed with appropriate monitoring (see General section below).**

General

CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

Prior to starting treatment with CUROSURF the infant's general conditions should be stabilized. Correction of acidosis, hypotension, anaemia, hypoglycemia and hypothermia is also recommended.

During administration of CUROSURF, transient episodes of hypotension may occur. 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. Administration of CUROSURF to preterm infants with severe hypotension has not been studied.

Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the probability of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

Infants born following prolonged rupture of membranes (> 3 weeks) may not demonstrate an optimal response.

Surfactant administration can be expected to reduce the severity of RDS but will not eliminate entirely the mortality and morbidity associated with prematurity, as preterm babies may have other complications.

In cases of unsatisfactory response to treatment with CUROSURF or rapid relapse, it is advisable to consider the possibility of other complications of immaturity such as patent ductus arteriosus or other lung diseases such as pneumonia before the administration of the next dose.

There is no information available on the effects of administering initial doses of CUROSURF other than 1.25 mL/kg (100 mg/kg) or 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 starting more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies for RDS, e.g., high-frequency ventilation.

The administration of CUROSURF to preterm infants with severe hypotension has not been studied.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with CUROSURF, or other surfactants.

Mutagenicity studies of CUROSURF have not indicated any mutagenic potential for the compound.

Immune

Antigenicity studies in animals have shown that CUROSURF does not provoke an acute anaphylactic reaction after repeat sensitization by the intratracheal route and does not induce the formation of specific antibodies after sensitization by the subcutaneous route.

Infants treated with surfactant should be carefully monitored with respect to signs of infection. At the earliest signs of infection the infant should immediately be given appropriate antibiotic therapy.

The results of the animal studies are in agreement with the outcome from the clinical trials in which CUROSURF did not increase either the antibody response or the degree of appearance of immune complexes when compared to the conventional therapy in control infants ("sham" treatment, i.e. disconnection from respirator and manual ventilation for 2 minutes).

Neurologic

After administration of CUROSURF a transient depression of cerebro-electrical activity lasting from 2 to 10 minutes has been recorded. This has been observed in one study and its impact is not clear.

Intracranial haemorrhage: During post-marketing experience uncommon episodes of intracranial haemorrhage have been observed. These have been related to reduction in mean arterial blood pressure and early peaks in arterial oxygenation (PaO_2). Avoidance of high PaO_2 peaks by ventilator adjustment immediately after instillation of CUROSURF are suggested.

Respiratory

During administration of CUROSURF, transient episodes of bradycardia, endotracheal tube blockage or reduced oxygen saturation may occur. 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.

During treatment with CUROSURF, hyperoxia, cyanosis and reflux through the endotracheal tube may also occur. In the event of reflux, administration should be stopped and, if necessary, peak inspiratory pressure on the ventilator should be increased until clearing of the endotracheal tube occurs.

After administration of CUROSURF pulmonary compliance (chest expansion) and oxygenation can improve rapidly, thus requiring prompt adjustment of ventilator settings [see Monitoring and Laboratory Tests].

The improvement of alveolar gas exchange can result in a rapid increase of arterial oxygen concentration: therefore a rapid adjustment of the inspired oxygen concentration should be made to avoid hyperoxia. In order to maintain proper blood oxygenation values, in addition to periodic blood gas analyses, continuous monitoring of transcutaneous PaO2 or oxygen saturation is also advisable.

Sexual Function/Reproduction

Studies to assess the effects of CUROSURF (or other surfactants) on reproductive function have not been conducted since clinical use will be limited to short-term administration in newborns.

Monitoring and Laboratory Tests

After administration of exogenous surfactants, including CUROSURF, pulmonary compliance (chest expansion) and oxygenation can improve rapidly, thus requiring prompt adjustment of ventilator settings. Infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilator support can be modified to respond to respiratory changes. The improvement of alveolar gas exchange can result in a rapid increase of arterial oxygen concentration: therefore a rapid adjustment of the inspired oxygen concentration should be made to avoid hyperoxia. In order to maintain proper blood oxygenation values, in addition to periodic hemo-gas analysis, continuous monitoring of transcutaneous PaO_2 or oxygen saturation is also advisable. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions generally seen with CUROSURF are bradycardia and hypotension; other events reported were endotracheal tube blockage and oxygen desaturation (see **Dosage and Administration** section on how to minimize these events). Pulmonary hemmorhage is a known complication of premature birth and very low birth-weight and has been reported both in clinical trials with CUROSURF and in post-marketing adverse drug reactions (ADR) reports in infants who have received CUROSURF.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions generally seen with CUROSURF (poractant alfa) are bradycardia and hypotension; other events reported were endotracheal tube blockage and oxygen desaturation (see Dosage and Administration section on how to minimize these events).

There were no deaths observed due to the administration of CUROSURF.

The following table is based on a single study in which infants were treated (rescue) with CUROSURF vs. “Sham” treatment (Table 1).

TABLE 1

	Percentage and Number (n/N) of Patients [a]	
	CUROSURF (200 mg/kg)	**Sham [b]**
Number of infants studied	77	69
Acquired Pneumonia	14% (11/77)	20% (14/69)
Bronchopulmonary Dysplasia [c]	16% (12/77)	26% (18/69)
Intracranial Hemorrhage [d]	47% (36/77)	55% (38/69)
Patent Ductus Arteriosus	60% (46/77)	46% (32/69)
Pneumothorax #	18% (14/77)	35% (24/69)
Pulmonary Interstitial Emphysema #	23% (18/77)	39% (27/69)

a Not all complications were assessed for each patient; therefore, denominators reflect the total number of patients assessed for a specific complication
b Sham treated patients received manual ventilation only with no surfactant instilled.
Chi Square Test; Statistically significant (<0.05) difference between treatment groups.
c Grades III - IV.
d Grades I - IV.

In EURO 1, the incidence of pneumothorax (p=0.0398) and pulmonary interstitial emphysema (p=0.0155) were significantly lower in CUROSURF treated patients than in "sham" treated patients.

No significant differences were observed between treatment groups for any other complications. The most common complication reported in the CUROSURF group was **patent ductus arteriosus**, which was reported at a higher rate than in the sham group. This is not an unexpected finding, since the direction of blood flow through the ductus arteriosus is controlled largely by the degree of pulmonary vascular resistance in infants with RDS.

In most infants with RDS, pulmonary vascular resistance decreases as recovery from RDS begins, leading to the clinical appearance of pulmonary congestion from increased left-to-right blood flow. Because surfactant therapy results in a significant decrease in pulmonary vascular resistance, the left-to-right shunting of blood through the ductus may be more pronounced and thus diagnosed more frequently in infants who receive surfactant therapy for diagnosed RDS (i.e., "rescue" group).

The occurrence of complications associated with prematurity was also evaluated in all the controlled trials (Studies 1 through 6) combined. The rates of these complications in the controlled trials for infants who received rescue or prevention treatment with CUROSURF and were randomized, are in Table 2 (pooled data from six trials).

TABLE 2

	Percentage and Number (n/N) of Patients[a]	
	CUROSURF Rescue	**CUROSURF Prophylaxis**
Number of Infants studied	2785	283
Acquired Pneumonia	16.1 (425/2641)	6.9% (9/131)
Acquired Septicemia	21.3% (581/2722)	15.8% (23/146)
Bronchopulmonary Dysplasia	32.6%[b] (758/2326)	22.0% (58/264)
Intracranial Hemorrhage	29.2% (566/1941)	52.0% (143/275)
Patent Ductus Arteriosus	38.7% (1058/2737)	21.2% (31/146)
Pneumothorax	12.9% (359/2780)	5.8% (16/277)
Pulmonary Hemorrhage	6.5% (138/2139)	1.5% (2/131)
Pulmonary Interstitial Emphysema	21.4% (139/650)	10.5% (29/277)
Recurrent Apnea	26.7% (558/2092)	NA
Retinopathy of Prematurity	14.6% (346/2370)	8.6% (21/245)

NA Not assessed

a Not all complications were assessed for each patient; therefore, denominators reflect the total number of patients assessed for a specific complication.

b The majority of patients with bronchopulmonary dysplasia in the rescue group were from study 6, in which bronchopulmonary dysplasia was defined as requirement for oxygen supplementation at 28 days (no radiographic evidence required).

The rates of individual complications associated with prematurity in the rescue and prophylaxis groups were similar to or less than those observed in either the Curosurf or "sham" groups in Study EURO I, with the exception of bronchopulmonary dysplasia. The relatively high rate of bronchopulmonary dysplasia in the rescue group in the integrated analysis is probably due to the lack of stringency in the definition of bronchopulmonary dysplasia in EURO VI (i.e., requirement for supplemental oxygen at 28 days without radiographic evidence, from which the majority of patients in the rescue group were drawn, compared to EURO I (i.e., requirement for oxygen supplementation and/or radiographic evidence).

Complications reported in the largest controlled rescue study (EURO VI) with CUROSURF (2,168 randomized patients) were assessed for possible or probable relationship to CUROSURF; assessment resulted in possible or probable relationship in less than 2% of patients for any complication, including pulmonary hemorrhage, tube blockage, patent ductus arteriosus, pneumothorax, hypotension, intracranial hemorrhage, bradycardia, and ventilator setting deterioration.

Follow-up Evaluations: Data from follow-up evaluations at 1 year of age (76 patients, 45 treated with CUROSURF) and at 2 years of age (73 patients, 44 treated with CUROSURF) of infants treated in one single dose study (EURO I), showed no significant differences between treatment groups for weight, length, occipitofrontal circumference, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment, or auditory impairment. No significant difference was observed between groups for developmental quotient, derived using the Griffiths Mental Developmental Scales, in 16 patients (10 treated with CUROSURF and 6 controls) followed up at 5.5 years corrected age.

Histological lung examination of the 44 patients from in EURO I who died (18 patients in the CUROSURF group and 26 patients in the "Sham" group) showed a significant difference between groups for the occurrence of pulmonary interstitial emphysema which was found in 9 patients in the "sham" group and in no patients in the CUROSURF group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Infections and infestations: Septic shock (Uncommon, ≥1/1,000 to <1/100)

Nervous System Disorders: Haemorrhage intracranial (Uncommon ≥1/1,000 to <1/100)

Respiratory, thoracic and mediastinal disorders: Pneumothorax (Uncommon ≥1/1,000 to <1/100), Bronchopulmonary dysplasia, Pulmonary haemorrhage (Rare ≥1/10,000 to <1/1,000)

Abnormal Hematologic and Clinical Chemistry Findings

No clinically significant hematologic and chemistry findings associated with the administration of CUROSURF were reported in clinical trials.

After administration of CUROSURF, pulmonary compliance (chest expansion) and oxygenation can improve rapidly, thus requiring prompt adjustment of ventilator settings. Assisted ventilation should not be abruptly stopped so as not to increase the risk of apnoea. Infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilator support can be modified to respond to respiratory changes. See Monitoring and Laboratory Tests and Dosage and Administration for further information.

Post-Market Adverse Drug Reactions

Undesirable side effects collected during post-marketing experience are listed in the table below according to System Organ Class (showed with the MedDRA Preferred Term) and to the following frequency: very common (≥ 1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

TABLE 3

System organ Class	Adverse Reaction	Frequency
Infections and Infestations	Sepsis	Uncommon
Nervous system disorders	Haemorrhage intracranial	Uncommon
Cardiac disorders	Bradycardia	Rare
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchopulmonary dysplasia	Rare
	Pulmonary haemorrhage	Rare
	Pneumothorax	Uncommon
	Hyperoxia	Not known
	Cyanosis neonatal	Not known
	Apnoea	Not known
Investigations	Oxygen saturation decreased	Rare
	Electroencephalogram abnormal	Not known
Injury, poisoning and procedural complications	Endotracheal intubation complication	Not known

Apnoea and sepsis neonatal may occur as a consequence of the immaturity of the infants.

The occurrence of intracranial haemorrhages after CUROSURF instillation has been related to reduction in mean arterial blood pressure and early peaks in arterial oxygenation (PaO_2). Avoidance of high PaO_2 peaks by ventilator adjustment immediately after instillation is suggested.

Preterm newborns have relatively high incidences of cerebral haemorrhages and cerebral ischemia, reported as periventricular leukomalacia and haemodynamic anomalies such as patent ductus arteriosus and persistence of fetal circulation despite the provision of intensive care. These infants are also at high risk of developing infections such as pneumonia and bacteraemia (e.g. septicaemia).

During administration through endotracheal tube, reflux of the surfactant into the endotracheal tube can occur (see sections Warning and Precautions).

Preterm babies also commonly develop haematological and electrolyte disorders which may be worsened by severe illness and mechanical ventilation. To complete the picture of complications of prematurity, the following disorders directly related to illness severity and use of mechanical ventilation, necessary for reoxygenation, may occur: pneumothorax, interstitial pulmonary emphysema and pulmonary haemorrhage. Finally, the prolonged use of high concentrations of oxygen and mechanical ventilation are associated with the development of bronchopulmonary dysplasia and retinopathy of prematurity.

DRUG INTERACTIONS

Overview

No known drug interactions have been identified.

Post-market surveillance reports did not include any safety issues or events indicative of drug interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

FOR INTRATRACHEAL ADMINISTRATION ONLY.

CUROSURF is administered intratracheally by instillation through a 5 French end-hole catheter, and briefly disconnecting the endotracheal tube from the ventilator.

CUROSURF should be administered by or under the supervision of clinicians experienced in intubation, ventilation 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. The infant should be allowed to stabilize before proceeding with dosing.

Marked improvements in oxygenation may occur within minutes of administration of CUROSURF. Therefore, frequent and careful clinical observation and arterial or transcutaneous monitoring of systemic oxygenation are essential to avoid hyperoxia, which could cause an increased incidence of intracranial haemorrhage. If oxygen saturation is in excess of 95 %, FiO_2 should be promptly reduced until it reaches 90 - 95 % and, if necessary, peak ventilator inspiratory pressure reduced. Failure to reduce ventilatory inspiratory pressure rapidly can result in lung distension and fatal pulmonary air leaks. Assisted ventilation should not be abruptly stopped so as not to increase the risk of apnoea.

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.

Recommended Dose and Dosage Adjustment

The initial dose of CUROSURF is 2.5 mL/kg (200 mg/kg) birth weight. This dose may be determined from the CUROSURF dosing chart below. This dose is administered into each main bronchus via a feeding tube to ensure proper distribution (and not into the lower trachea).

Repeated doses
Up to two repeat doses of 1.25 mL/kg (100 mg/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 (300-400 mg/kg).

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 initial entry.

Table 4 - CUROSURF Dosing Chart					
Weight (grams)	EACH DOSE (mL)		Weight (grams)	EACH DOSE (mL)	
	INITIAL DOSE 2.5 mL/kg	REPEAT DOSE 1.25 mL/kg		INITIAL DOSE 2.5 mL/kg	REPEAT DOSE 1.25 mL/kg
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

Administration

CUROSURF should be inspected visually for discoloration prior to administration. The color of CUROSURF is white to creamy white. A slight color change, towards yellow, may occur on aging without denoting product degradation. CUROSURF should be stored in a refrigerator at +2 to +8°C.

Before use, the vial should be slowly warmed to room temperature (by holding it in an incubator for about one hour or in a thermostated bath for about three minutes), and gently turned upside-down, in order to obtain a uniform suspension. DO NOT SHAKE.

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.

Slowly withdraw the entire contents of the vial of CUROSURF into a 3 or 5 mL plastic syringe through a large-gauge needle (e.g., at least 20-gauge).

Attach the pre-cut 8-cm 5 end-hole 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. The catheter should not protrude from the endotracheal tube.

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.

Immediately before CUROSURF administration, the infant's ventilator settings should be changed to a rate of 40-60 breaths/minute, inspiratory time 0.5 seconds and supplemental oxygen sufficient to maintain SaO_2 > 92%, for this initial dose only. The infant is kept in a neutral position (head and body in alignment without inclination). Briefly disconnect the endotracheal tube from the ventilator. The pre-cut 5 French catheter is inserted into the endotracheal tube and the CUROSURF is given in a bolus dose over 2 to 3 seconds. The infant should be positioned such that either the right or left side is dependent for this aliquot. 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. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

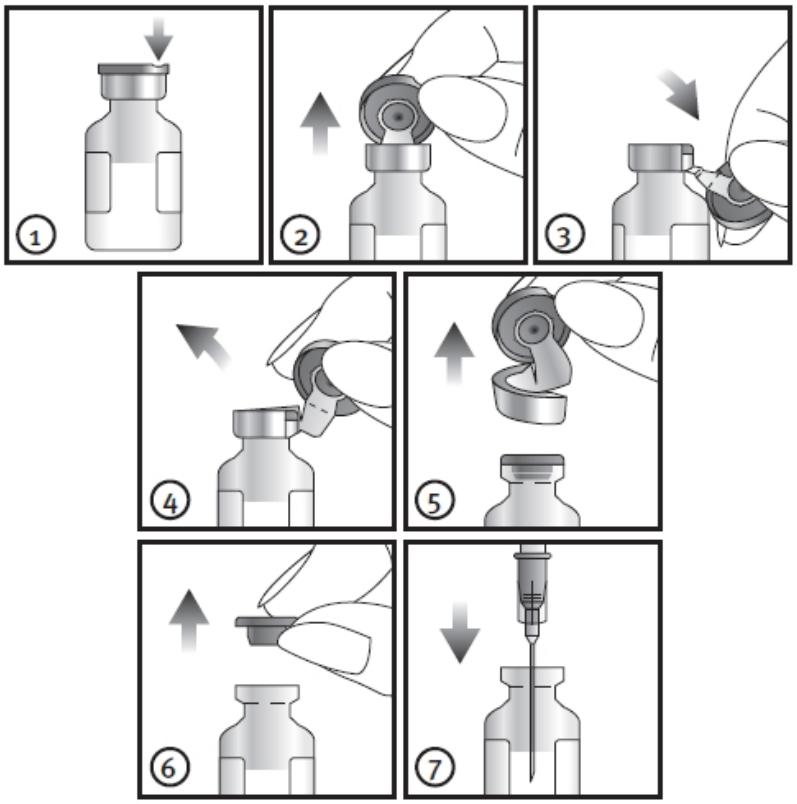
After completion of the dosing procedure, resume usual ventilator management and clinical care. Immediately after dosing, it is recommended that the FiO_2 be adjusted to maintain an SaO_2 of 92-97%. In clinical trials, ventilator management was modified to maintain a PaO_2 of about 55 mHG, $PaCO_2$ of 35-45, and pH > 7.3.

Instructions for Use

1) *Locate the notch (FLIP UP) on the coloured plastic cap.*
2) *Lift the notch and pull upwards.*
3) *Pull the plastic cap with the aluminium portion downwards.*

4 and 5) Remove the whole ring by pulling off the aluminium wrapper.

6 and 7) Remove the rubber cap to extract content.



OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been no reports of over-dosage (deliberate or accidental) following the administration of CUROSURF in clinical trials or post-market setting. In the event of accidental over-dosage, 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. Based on animal data, over-dosage might result in acute airway obstruction.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CUROSURF (poractant alfa) aqueous suspension for intratracheal administration compensates for the deficiency of surfactant in Respiratory Distress Syndrome (RDS) and restores surface activity to the lungs of the premature newborn.

CUROSURF, is a pulmonary surfactant prepared from porcine lungs, consisting of a combination of phospholipids and apoproteins. Administered intratracheally, CUROSURF distributes rapidly throughout the alveolar spaces reducing surface tension at the air-liquid interface during ventilation and stabilizing the alveoli against collapse at resting transpulmonary pressures. This activity is brought about by the major component of the phospholipid fraction, dipalmitoylphosphatidylcholine (DPPC) and it is facilitated by the interaction with the surfactant specific apoproteins, which improve the spreading and adsorption of DPPC at the alveolar surface. Treatment administration as soon as possible after birth may provide a more uniform distribution of surfactant.

Pharmacodynamics

In clinical studies of premature infants with RDS, CUROSURF-treated infants showed a rapid and significant decreased need for supplemental oxygen, a rapid and significant increase in arterial/alveolar oxygen pressure ratio (a/A PO_2) and in lung compliance. The improvement in oxygenation was reflected by a nearly three-fold increase in the ventilation/perfusion ratio (PaO_2/FiO_2) within one hour of treatment.

In a study (EURO I -see **Clinical Trials**) comparing premature rescue-infants treated with a single dose of CUROSURF (200 mg/kg) to premature infants who received a "sham" treatment, statistically significantly lower incidences of pulmonary interstitial emphysema, pneumothorax and a significantly higher incidence of survival without bronchopulmonary dysplasia (BPD) were reported in the CUROSURF group.

In prophylaxis studies of premature infants at risk of developing RDS, single or multiple doses of CUROSURF (100 mg/kg - 200 mg/kg) reduced mortality and the incidence of BPD and increased survival without BPD at 28 days.

Pharmacokinetics

CUROSURF is administered directly into the trachea. The metabolic disposition of CUROSURF in humans has not been studied. No information is available about the metabolic fate of the surfactant-associated proteins in CUROSURF.

STORAGE AND STABILITY

CUROSURF is available in ready-to-use vials that should be stored in a refrigerator at +2 to +8°C. Do not use past the expiry date on the label. Vials are for single use only and all unused drug should be discarded. Protect from light. 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CUROSURF (poractant alfa) Suspension for Intratracheal Administration is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL or 3 mL. Each milliliter contains 80 mg of surfactant (extract) (120 mg surfactant (extract)/1.5 mL or 240 mg surfactant (extract)/3 mL) suspended in 0.9% sodium chloride solution. One vial per carton.

Table 5 - Composition of CUROSURF (Poractant alfa) intratracheal suspension:

Component	For 1 mL
Sodium Chloride Injection	0.88 mL
Pig Lung Surfactant	80 mg
Individual constituents: • Total phospholipids - phosphatidylchloline - dipalmitoylphosphatidylcholine • Acidic phospholipids • Total surfactant proteins (SP-B & SP-C) • Free fatty acids • Triglycerides • Cholesterol	 76 mg 55 mg 30 mg 6.4 mg 1 mg 0.55 mg 0.1 mg 0.02 mg
Sodium Bicarbonate Injection	pH adjustment agent

[1] Average values of 13 lots tested.
[2] Calculated from total phosphorus content.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Poractant alfa

Chemical name: none

Structural Formula: N/A

Structure and molecular mass:

Phospholipids

phosphatidylcholine (PC) or lecithin (1,2-diacyl-sn-glycero-3-phosphorylcholine)
phosphatidylglycerol (PG) (1,2-diacyl-sn-glycero-3-phosphoryl-1'-sn-glycerol)
phosphatidylinositol (PI) (1,2-diacyl-sn-glycero-3-phosphoryl-1'-inositol)
phosphatidylserine (PS) (1,2-diacyl-sn-glycero-3-phosphorylserine)
phosphatidylethanolamine (PE) (1,2-diacyl-sn-glycero-3-phosphorylethanolamine)
sphingomyelin (SM) (sphingosine ceramide of phosphorylcholine)
lysophosphatidylcholine (LPC)

The phospholipid component is present as a mixture of phospholipids with variable "R" substituents and therefore the overall molecular weight is not defined.

Low molecular weight hydrophobic proteins

Surfactant protein SP-B MW: 8.7 kDa
Surfactant protein SP-C MW: 3.7 kDa

Physicochemical properties:

White to creamy white suspension.

CUROSURF® (poractant alfa) Suspension for Intratracheal Use is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural porcine lung extract consisting of 99% polar lipids (mainly phospholipids) and approximately 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). It is suspended in 0.9% sodium chloride solution, resulting in a composition that provides 80 mg/mL of surfactant (extract) that includes 76 mg of phospholipids and including approximately 1 mg/mL of protein, of which 0.45 mg is SP-B. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine. The pH may be adjusted with sodium bicarbonate to a pH of 6.2 (5.5 – 6.5). CUROSURF contains no preservatives.

CLINICAL TRIALS

CUROSURF has been studied in controlled clinical trials (Rescue studies and Prophylaxis versus Rescue studies) in 3400 patients. The pivotal clinical trials are listed below.

50.00/CT/02/90:
Randomized, controlled, multicenter trial of CUROSURF prophylaxis versus rescue treatment with 136 infants in the prophylaxis arm and 132 infants in the rescue arm; administration of 200 mg/kg doses (see Bibliography reference 20)

50.01/CT/04/93:
Randomized, controlled, multicenter trial of CUROSURF prophylaxis versus rescue treatment with 134 infants in the prophylaxis arm and 122 infants in the rescue arm; administration of 100 mg/kg doses(see Bibliography reference 21)

EURO I:
Randomized, controlled, multicenter trial of CUROSURF rescue versus "sham" treatment with 77 infants in the rescue arm and 69 infants in the "sham" arm; administration of 200 mg/kg doses of CUROSURF (see Bibliography reference 3)

EURO III:
Randomized, controlled, multicenter trial of CUROSURF early treatment versus late treatment with 86 infants in the early arm and 96 infants in the late/control arm; administration of 200 mg/kg doses (see Bibliography reference 2)

EURO IV:
Randomized, controlled, multicenter trial of CUROSURF single dose versus multiple doses with 176 infants in the single dose arm and 167 infants in the multiple doses arm; administration of 200 mg/kg initial dose followed by 100 mg/kg doses (see Bibliography reference 16)

EURO VI:
Randomized, controlled, multicenter trial of CUROSURF high dose versus low dose with 1069 infants in the low dose arm and 1099 infants in the high dose arm; administration of 100 mg/kg doses for low dose and 200 mg/kg initial dose followed by 100 mg/kg doses for high dose group (see Bibliography reference 6).

The results of two Pivotal studies (EURO I and 50.01/CT/04/93) are summarized below:

Table 6 - Efficacy Assessment - EURO I

Treatment Group*:	CUROSURF N = 77 (%)	Sham N = 69 (%)
Number of Doses:	single dose (200 mg/kg)	single dose "sham"
Mortality at 28 days	24 (31) [a]	35 (51)
BPD (Grade III-IV) at 28 days	12 (16)	18 (26)

* Birth Weight Range: 700 - 2000 g
a = $p<0.05$

Table 7 - Efficacy Assessment - Prophylaxis 50.01/CT/04/93

Gestational Age (GA)		25 - 28 weeks		29 - 31 weeks	
Treatment*		Prophylaxis N = 49 (%)	Rescue N = 63 (%)	Prophylaxis N = 85 (%)	Rescue N = 59 (%)
Survival at 28 days	Yes	41 (84)	49 (78)	78 (92)	50 (85)
	No	8 (16)	14 (22)	7 (8)	9 (15)
Survival at 42 weeks GA	Yes	40 (82)	45 (71)	76 (89)	48 (81)
	No	9 (18)	18 (29)	9 (11)	11 (19)
Survival without BPD at 28 days		16 (33)	21 (33)	65 (76)	35 (59)
Death or BPD at 28 days		33 (67)	42 (67)	20 (24)	24 (41)

* up to 4 doses (100/mg/kg/dose)

DETAILED PHARMACOLOGY

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

In vivo - In several pharmacodynamic studies using ventilated or non-ventilated premature rabbits, poractant alfa improved lung mechanics.

Static pressure-volume recordings showed a dramatic enhancement of lung expansion in premature newborn rabbits following poractant alfa administration and good stability during deflation of the lungs.

Under conditions of standardized tidal volume (10 mL/kg) ventilation, high values for lung-thorax compliance were also associated with an improvement in alveolar gas exchange. Histological examination showed the poractant alfa treated animals to have a nearly uniform alveolar expansion pattern with well-aerated terminal air spaces and well preserved epithelium in conducting airways.

Poractant alfa administered as a single intratracheal dose of 160 mg/kg (2.0 mg/mL) to 14 immature newborn rabbits, while an additional 17 animals served as untreated controls, resulted in a significantly increased lung-thorax compliance in animals who received poractant alfa relative to controls ($p<0.01$). The amount of total protein in the lung lavage fluid was also reduced in animals who received poractant alfa relative to controls (2.5 mg/mL vs. 10 mg/mL, $p<0.05$), indicating reduced lung permeability; this is important since vascular-to-alveolar protein leakage is known to be a factor in the inactivation of pulmonary surfactant.

Animal Metabolism

Poractant alfa is administered directly to the target organ, the lung, where biophysical effects occur at the alveolar surface.

In both adult and newborn rabbits, approximately 50% of the radio labeled component was rapidly removed from the alveoli in the first three hours after single intratracheal administration of 200 mg/kg poractant alfa-^{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 animals.

In newborn rabbits, poractant alfa-^{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 *in toto* appears to be about 25 hours in adult rabbits and 67 hours in newborn rabbits.

Very little DPPC was found in alveolar macrophages at any time for both young and adult animals and very small amounts (0.33% to 0.52% of the total DPPC recovered) were found in the serum, liver, kidneys and brain of young animals at 48 hours.

No information is available about the metabolic fate of the surfactant associated proteins in poractant alfa. The metabolic disposition of poractant alfa in humans has not been studied.

TOXICOLOGY

Acute Toxicity Studies:
Acute toxicity studies performed in different animal species by intraperitoneal and intratracheal routes did not elicit signs of lung or systemic toxicity, nor mortality. The acute toxicity studies are summarized in **Table 8.**

Subacute Toxicity Studies:
The subacute intratracheal toxicity study in the dog, rabbit and rat (14 days) showed no clinical effects or hematological changes, nor macroscopic variations. Moreover, poractant alfa did not reveal any evidence of direct toxicity in the rat by intraperitoneal route (4 weeks). The subacute toxicity studies are summarized in **Table 9.**

Carcinogenicity Studies:
Carcinogenicity studies have not been performed with poractant alfa.

Mutagenicity Studies:
Poractant alfa did not show any evidence of mutagenic or clastogenic activity.

Reproduction and Teratology Studies:
Reproduction studies have not been performed with poracant alfa.

Special Studies:

Poractant alfa by the parenteral route in the guinea pig neither elicits active anaphylactic reactions, nor stimulates the production of antibodies detectable by passive cutaneous anaphylactic reaction. No anaphylactic reaction was observed by intratracheal route. Furthermore, there is no evidence of dermal sensitizing potential (Magnusson and Kligman test).

Table 8: Acute Toxicity Studies with Poractant Alfa

Species	Strain	Pretest Conditions[1]	No. Per group (M/F)	Age	Dose volume (mL/ kg)	Route	Dose (mg/kg)	Findings: 15 day observation
Mouse	CD-1 (ICR) BR	l/d	5/5	Adult	25	IP	2000	No deaths; piloerection (24 hr), hypoactivity (2 hr.); no abnormal findings at necropsy.
Mouse	Swiss	fd; l/d	5/5	5-6 weeks	25 6.25 12.5 25	IP	0 500 1000 2000	No deaths; transient, dose-dependent hypoactivity; piloerection (3 hr) for doses ≥1000 mg/kg; no abnormal findings at necropsy.
Rat	Sprague-Dawley	l/d	5/5	4-5 weeks	0 0 2.5	IT[2]	0[3] 0[4] 200	No deaths; symptoms of suffocation immediately after dosing (due to large volume administered); inflammation of the trachea noted at necropsy in both treated and "sham" control animals.
Rat	Sprague-Dawley (CD)	l/d	5/5	Adult	25	IP	2000	No deaths; reduced consistency of feces (1hr), piloerection (3 hr); no abnormal finding at necropsy.
Rat	Sprague-Dawley	fd; l/d	5/5	6-7 weeks	25 25	IP	0 2000	No deaths; hypoactivity (2-3 hr); no abnormal findings at necropsy.
Guinea pig	Dunkin-Hartley	l/d	5/5	Adult	0 2.5	IT[2]	0[4] 200	No deaths; no transient symptoms of suffocation (30-60 min); inflammation of the trachea noted at necropsy in both treated and control animals.
Rabbit	New Zealand white (HY/CR)	l/d	5/5	Juvenile	0 2.5	IT	0[5] 200	No deaths; no symptoms correlated with treatment; at necropsy, minimal lymphocytic infiltration and mild to moderated congestion of lungs and trachea in both treated and control animals.

Species	Strain	Pretest Conditions[1]	No. Per group (M/F)	Age	Dose volume (mL/ kg)	Route	Dose (mg/kg)	Findings: 15 day observation
Dog	Beagle	fd	3/3	13 weeks	0 2.5	IT	0[6] 200	No deaths; transient respiratory insufficiency requiring oxygen administration (attributed to the large volume administered), somnolence and ataxia on the day of treatment due to administration of general anesthesia.

[1] fd=food deprived; l/d= 12-hour light/12-hour dark cycle
[2] Via chronically implanted catheter
[3] No treatment; no catheter implanted
[4] Sham treatment; implantation of catheter which was filled with air and saline solution
[5] Serum for IgG was previously heated at 56°C for 2 hours
[6] Sham treatment; insertion of endotracheal tube; no liquid intubated.

Table 9: Repeated Dose Toxicity Studies with Poractant Alfa

Species	Strain	No. Per group (M/F)	Age	Route	Dose[7] (mg/kg)	Dose volume (mL/kg)	Duration	Findings
Rat	Sprague-Dawley	8/8	4-4.5 weeks	IT[8]	0[9] 0[10] 200	0 0 2.5	14 days	Deaths: 5 treated and 4 sham control animals due to pneumonia or suffocation following drug administration. Histopathology: Higher frequency of alveolar phagocytic cells in treated animals.
Rat	Sprague-Dawley (CD)	20/20 (0, 600 mg/kg) 10/10 (200, 350 mg/kg)	38-40 days	IP	0 200 350 600	7.5 2.5 4.4 7.5	4 weeks [11] +4 week recovery	Deaths: 2 males in the high-dose group accidentally during study procedures. Clinical signs: injection site inflammation. Histopathology: increased liver weight in mid and high-dose females; minimal to moderate centrilobular hepatocytic vacuolation in high-dose males with partial regression at the end of the recovery period.

Species	Strain	No. Per group (M/F)	Age	Route	Dose[7] (mg/kg)	Dose volume (mL/kg)	Duration	Findings
Rabbit	New Zealand white	5/5	not given	IT	0[12] 100	0 1.25	14 days	Deaths: 3 treated animals due to suffocation during drug administration and 1 control following intubation. Clinical signs: Sneezing during drug administration and abnormal respiratory sounds. Histopathology: Increased frequency and degree of alveolar macrophage aggregation and increased incidence of alveolar edema and pneumonia in treated vs. Control animals.
Dog	Beagle	4/4	19-21 weeks	IT	0[13] 50[14]	0 0.625	14 days	Deaths: 1 treated animal (200 mg/kg) due to suffocation during drug administration. Clinical signs: Transient tachypnea, coughing following drug administration Histopathology: No treatment-related changes.

M = Male; F Female; IT = lntratracheal; IP = Intraperitoneal

[7] Administered once daily

[8] Via chronically implanted catheter

[9] No treatment: no catheter implanted

[10] Sham treatment: implantation of catheter which is filled with air and saline solution

[11] 0 and 600 mg/kg groups: 15 animals per sex sacrificed at the end of treatment; 5 animals per sex sacrificed after the recovery period
200 and 350 mg/kg groups: 1 0 animals per sex sacrificed at the end of treatment

[12] Sham treatment: insertion of endotracheal tube; no liquid intubated.

[13] Test group: 50% v/v dilution, Freund's Complete Adjuvant in water

[14] The dose of Curosurf was reduced from 200 mg/kg after the first animal dosed had to be sacrificed due to severe respiratory distress and the second animal dosed with 100 mg/kg also developed respiratory distress.

Undiluted Curosurf (80 mg/mL)
50% v/v dilution Curosurf

Control group: 50% v/v dilution, Freund's Complete Adjuvant in water
Saline
50% v/v dilution, Freund's Complete Adjuvant in saline

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PART III: CONSUMER INFORMATION

CUROSURF
poractant alfa

This leaflet is part III of a three-part "Product Monograph" published when CUROSURF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CUROSURF. Contact your doctor or nurse if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Curosurf is used to treat Respiratory Distress Syndrome (RDS) in newborn babies.

Your baby may have other problems as well as RDS which may need other treatments.

What it does:
Most babies are born with a substance in their lungs known as 'surfactant'. This substance lines the lungs and stops them from sticking together and so makes normal breathing possible. Some babies, however, particularly premature babies, do not have enough of this surfactant when they are born, which causes RDS. Curosurf is a natural surfactant, which works in the same way as your baby's own surfactant would have done and, therefore, will help your baby to breathe normally until your baby produces his or her own surfactant.

When it should not be used:
Curosurf should not be used if your baby has an allergy to pig proteins or the other ingredients in this product or components of the container. There are no other known contraindications to this product.

What the medicinal ingredient is:
The active substance is a mixture of fats and proteins which come from a pig lung called poractant alfa.

What the important nonmedicinal ingredients are:
The other ingredients are sodium chloride, sodium bicarbonate and water for injection. This product contains less than 1 mmol sodium (23 mg) per vial.

What dosage forms it comes in:
It is a sterile suspension and is supplied in a single use 5 mL glass vial containing either 1.5 mL (120 mg) or 3 mL (240 mg) of phospholipid fraction from pig lung. Each mL of sterile suspension contains 80mg of phospholipid fractions from pig lungs.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Curosurf should only be given to your baby by trained doctors and nurses with experience in treating premature babies.**
- **Giving surfactants such as Curosurf to babies with Respiratory Distress Syndrome can have a very quick effect on their lungs. Your baby will need to stay in the hospital. The doctor or nurse will need to carefully observe your baby and make adjustments to medications and equipment as needed to help your baby until your baby's breathing becomes normal.**

BEFORE your doctor uses CUROSURF he or she will consider:

- Any allergies to this drug or its ingredients or components of the container (Contraindications).

INTERACTIONS WITH THIS MEDICATION

There are no known drug interactions with this medication.

PROPER USE OF THIS MEDICATION

Usual dose:
The doctor or nurse will give Curosurf to your baby. They will warm the Curosurf liquid to room temperature, and then using a syringe they will give it to your baby through tubes into the baby's windpipe. They may disconnect your baby from the ventilator for a few minutes to do this.

Your doctor will decide the right dose for your baby, depending on your baby's weight. If your baby is being given Curosurf to prevent Respiratory Distress Syndrome (RDS) it is important that Curosurf is given as soon as possible after RDS has been diagnosed. The initial dose is 2.5 mL/kg of birth weight. If your baby needs another dose of Curosurf, up to two repeat doses of 1.25 mL/kg of birth weight each may be given every 12 hours.

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 initial entry.

Overdose:
There have been no reported overdoses of Curosurf; however, if your baby is overdosed your doctor will decide on the best course of treatment.

Missed Dose:
Not applicable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines can cause side effects although not everybody gets them. Possible side effects are listed below according to their frequency. If you are not sure what the side effects below are ask your doctor to explain them to you.

Uncommon (affecting less than 1 in 100 people)

- Infection
- Bleeding in the brain
- Air in the chest cavity caused by lesions in the lungs.

Rare (affecting less than 1 in 1000 people)

- Slower heart rate
- Low blood pressure
- Chronic lung disease
- Decrease in oxygen around the body

The following side effects have also been reported:

- Decreased amount of oxygen in the body
- Blue colour of the skin or gums, caused by too little oxygen
- Stopping of breathing
- Complication with placement of the tubes into the lungs
- Abnormal reading of the brain activity

If you think any of the above side effects become serious, contact your doctor immediately.

This is not a complete list of side effects. For any unexpected effects while taking CUROSURF, contact your doctor or nurse.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store in a refrigerator at 2°C to 8°C, protected from light. Do not shake. However, before it is given to your baby it will be warmed to room temperature.

Unopened unused vials of Curosurf that have warmed to room temperature can be returned to the refrigerator within 24 hours for future use. Do not warm to room temperature and return to refrigerated storage more than once.

Do not use Curosurf after the expiry date that is on the label. The expiry date refers to the last day of that month.

Use each vial once, and then throw away what is left over. The hospital will make sure that any unused Curosurf is disposed of safely.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the importer/distributor, Methapharm Inc.
at: 1-800-287-7686 ext. 7804

This leaflet was prepared by Chiesi Farmaceutici, S.p.A

Last revised: 03 February 2017

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