PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**CUROSURF®**

poractant alfa

Suspension, 80 mg surfactant/mL, Intratracheal

Lung Surfactant (Porcine)

Manufacturer:
Chiesi Farmaceutici, S.p.A.
26/A Via Palermo
Parma 43122
Italy

Imported and Distributed by:
Methapharm Inc.
81 Sinclair Boulevard
Brantford, ON, N3S 7X6

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RECENT MAJOR LABEL CHANGES

Indications, Pediatrics (1.0)	06/2021
Serious Warnings and Precautions (3.0)	06/2021
Dosage and Administration, Dosing Considerations (4.1)	06/2021
Dosage and Administration, Administration (4.3)	06/2021
Warnings and Precautions, General (8.0)	06/2021
Warnings and Precautions, Immune (8.0)	06/2021
Warnings and Precautions, Ophthalmologic (8.0)	06/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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, 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.

1.1 Pediatrics

Pediatrics: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Curosurf in premature infants have been established.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Curosurf is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

No specific contraindications have been identified.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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, 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 WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests section below).**
- **Administration of Curosurf may cause bradycardia, hypotension, endotracheal tube blockage, apnea, airway obstruction, and oxygen desaturation. Stop administration and take appropriate measures to alleviate such conditions. Dosing may proceed after the patient is stable (see WARNINGS AND PRECAUTIONS).**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- FOR INTRATRACHEAL ADMINISTRATION ONLY.
- For infants requiring mechanical ventilation, Curosurf is administered intratracheally by instillation through a 5 French end-hole catheter, and briefly disconnecting the endotracheal tube from the ventilator (see **4.3 Administration** using conventional administration methods). 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.
- In spontaneously breathing preterm infants Curosurf may be administered through the Less Invasive Surfactant Administration (LISA) technique using a thin catheter (see **4.3 Administration** using LISA method).
- Curosurf should be administered by or under the supervision of clinicians experienced in intubation, ventilation management and general care of premature infants.
- 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, hypotension, endotracheal tube blockage, apnea, airway obstruction, and oxygen desaturation have occurred during the dosing procedure of Curosurf by endotracheal tube or thin tube (LISA technique). 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.
- 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.

4.2 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).

Table 1 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

4.3 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.

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. See STORAGE, STABILITY AND DISPOSAL, and SPECIAL HANDLING INSTRUCTIONS.

Use with conventional administration

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.

Application with Less Invasive Surfactant Administration (LISA) method

In spontaneously breathing preterm infants, Curosurf can be administered through the LISA technique using a thin catheter. Continuous Positive Airways Pressure (CPAP) ventilator support can be continued throughout administration by this method. CPAP is a non-invasive respiratory support option and a means to avoid harmful effects of positive pressure ventilation (PPV).

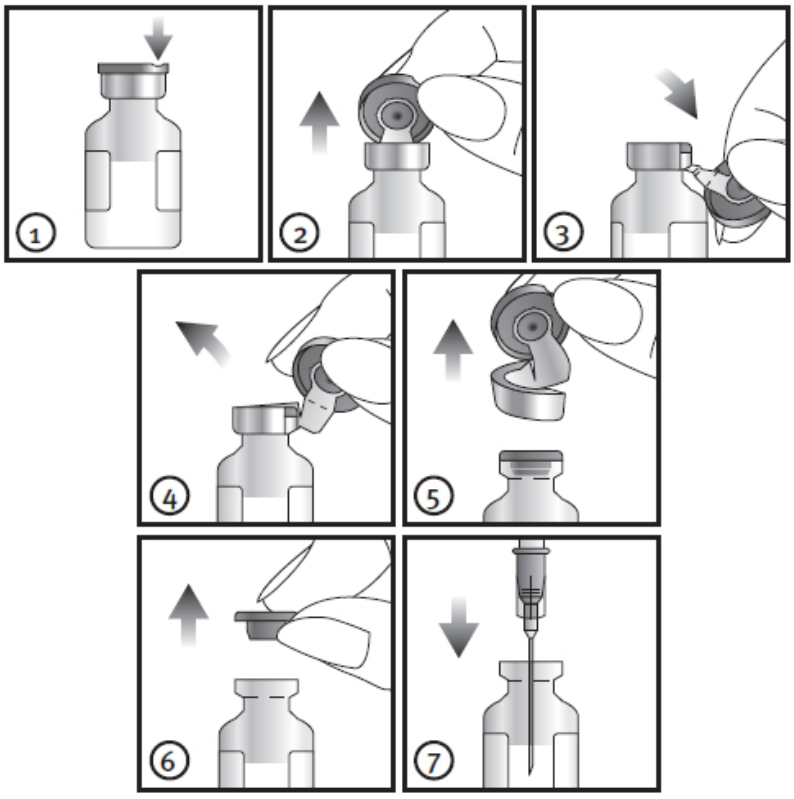
The other standard methods for Curosurf instillation, including Intubate SURfactant Extubate (INSURE), require intubation and PPV for its distribution. Instead, LISA is performed during spontaneous breathing with CPAP.

Doses are the same as indicated for the other modalities. 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).

A small diameter (4-5F) semi-rigid catheter with a mark at 1.5 cm above the tip is placed into the trachea of infants on CPAP. The catheter is placed with this mark at the level of the vocal cord with direct visualization by laryngoscopy. Curosurf is instilled by a single bolus over **0.5 - 3 minutes**. Do not administer rapidly as reflux may occur. After Curosurf instillation, the catheter is immediately removed.

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.



4.4 Missed Dose

Not applicable.

5 OVERDOSAGE

There is no experience with over-dosage (deliberate or accidental) following the administration of Curosurf in clinical trials or post-market setting. In the event of over-dosage, 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the lot number/expiry date of the product supplied.

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intratracheal	Suspension 80 mg surfactant*/mL Suspension	• Sodium bicarbonate • Sodium chloride • Water for injection
*Individual constituents of pig lung surfactant: phosphatidylchloline, dipalmitoylphosphatidylcholine, acidic phospholipids, surfactant proteins (SP-B & SP-C), Free fatty acids, triglycerides and cholesterol		

Curosurf 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.

7 DESCRIPTION

Curosurf 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.

8 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

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 bradycardia, hypotension, endotracheal tube blockage, apnea, airway obstruction, and oxygen desaturation 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 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. The most common complication reported in the Curosurf group in clinical trials 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).

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

Preterm newborns have relatively high incidences of cerebral haemorrhages, cerebral ischemia, 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).

Preterm newborns 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.

Carcinogenesis and Mutagenesis
Carcinogenicity studies have not been performed with Curosurf, or other surfactants.

Mutagenicity studies of Curosurf have not indicated an increase in mutagenic potential.

Immune
In antigenicity studies in animals, Curosurf did not provoke an acute anaphylactic reaction after repeat sensitization by the intratracheal route and did not induce the formation of specific antibodies after sensitization by the subcutaneous route.

In clinical studies, Curosurf did not increase the antibody response or the degree of appearance of immune complexes compared to “sham” treatment (i.e., disconnection from respirator and manual ventilation for 2 minutes).

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.

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.

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, 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 recommended.

Ophthalmologic
The relation of ROP to the LISA procedure is unlikely, but possible. Desaturation, which may occur during the procedure, may trigger to some extent ROP during the neonatal transition after birth. The majority of events in clinical trials were non-serious, mild or moderate and resolved by the end of the study. Exceptions were: laser therapy (which was serious and with unknown outcome), intestinal perforation (which was serious and severe) and aphonia (which had not yet resolved by the end of the study).

Respiratory
During administration of Curosurf, transient episodes of bradycardia, endotracheal tube blockage, apnea, airway obstruction, 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 WARNINGS AND PRECAUTIONS, 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 PaO_2 or oxygen saturation is also advisable.

Sexual Health
Reproduction
Studies to assess the effects of Curosurf (or other surfactants) on reproductive function have not been conducted.

8.1 Special Populations

8.1.1 Pregnant Women

Curosurf is not indicated for pregnant women.

8.1.2 Breast-feeding

Curosurf is not indicated during breast-feeding.

8.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of

Curosurf in premature infants have been established.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

The safety profile for conventional administration of Curosurf is derived from six randomized, multicenter, controlled trials including four rescue studies (EURO I, EURO III, EURO IV, EURO VI) and two prevention studies (50.00/CT/02/90 and 50.01/CT/04/93). 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 haemorrhage has been reported both in clinical trials with Curosurf and in post-marketing adverse drug reaction (ADR) reports in infants who had received Curosurf.

The Non-INvasive Surfactant APPlication (NINSAPP) study compared surfactant administration via LISA technique to conventional endotracheal intubation (referred to as “conventional administration”). A total of 4 adverse reactions were reported in both the LISA and the conventional administration control groups in 4 (4.0%) and 4 (3.7%) patients, respectively. Adverse reactions reported in >1 patient in any treatment group were: pulmonary haemorrhage (in 2 [2.0%] and 2 [1.8%] patients in the LISA and control groups, respectively) and pneumothorax (in 1 [1.0%] and 2 [1.8%] patients in the LISA and control groups, respectively). All these reactions were serious, either moderate or severe in intensity and resolved by the end of the study.

9.2 Clinical Trial Adverse Reactions

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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Use with conventional administration

The six randomized, multicenter, controlled trials of Curosurf included four rescue studies and two prevention studies conducted in approximately 3,400 infants. In the four rescue trials (EURO I, EURO III, EURO IV, EURO VI), patients were required to be diagnosed with RDS to be eligible for the study, whereas in the two prophylaxis trials (50.00/CT/02/90 and 50.01/CT/04/93), patients were randomized if they were within specific gestational age limits (24 to 30 weeks and 25 to 31 weeks, respectively).

EURO I is the only study in which patients were randomised to receive either Curosurf or a “sham” treatment. In the “sham” treatment, patients were disconnected from the respirator for 2 minutes and manually ventilated using the same protocol as for patients treated with Curosurf except that no material was instilled into the airways.

Most common (≥ 10% of patients in either treatment group) complications associated with prematurity by treatment in a randomised study (EURO I) in which Curosurf was compared to placebo (“sham”) treatment are reported in Table 3.

Table 3 EURO I TRIAL: MOST COMMON COMPLICATIONS ASSOCIATED WITH PREMATURITY (≥ 10% of patients for each treatment group)*

	Percentage and Number (n/N) of Patients [a]	
	Curosurf (200 mg/kg)	**Sham [b]**
Number of infants randomized	78	66
Patients with at least one complication[a]	89% (69/78)	91% (60/66)
Acquired Pneumonia	17% (13/78)	21% (14/66)
Acquired Septicemia	14% (11/77)	18% (12/66)
Bronchopulmonary Dysplasia [c]	19% (15/78)	22% (15/66)
Intracranial Haemorrhage [d]	51% (40/78)	64% (42/66)
Patent Ductus Arteriosus	60% (47/78)	48% (32/66)
Pneumothorax	21% (16/78)	36% (24/66)
Pulmonary Interstitial Emphysema	21% (16/78)	38% (25/66)

* At the time of the trial, adverse event reporting conventions allowed for collection of quantitative data related only to prematurity-related complications. Adverse events other than those listed above may have occurred in ≥10% of patients.

a Not all complications were assessed (as present or not present) 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.

c Grades III - IV.

d Grades I - IV.

The occurrence of complications associated with prematurity was also evaluated in all the controlled trials (Studies 50.00/CT/02/90, 50.01/CT/04/93, EURO I, EURO III, EURO IV, EURO VI) 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 4 (pooled data from six trials).

Table 4 MOST COMMON COMPLICATIONS ASSOCIATED WITH PREMATURITY (≥ 10% of patients for each treatment group, Studies 50.00/CT/02/90, 50.01/CT/04/93, EURO I, EURO III, EURO IV, EURO VI)*

	Percentage and Number (n/N) of Patients[a]	
	Curosurf Rescue	**Curosurf Prophylaxis**
Number of Infants randomized	2792	269
Patients with at least one complication	78.8% (2200/2792)	73.2% (197/269)
Acquired Pneumonia	16.0% (427/2673)	6.9% (9/131)
Acquired Septicemia	21.3% (575/2705)	15.8% (23/146)
Bronchopulmonary Dysplasia	33.0%[b] (771/2334)	21.6% (55/255)
Intracranial Haemorrhage (All Grades)	29.8% (584/1958)	50.6% (134/265)
Other morbid conditions (e.g., surgery)	20.4 (432/2119)	NA
Patent Ductus Arteriosus	38.8% (1053/2717)	21.2% (31/146)
Pneumothorax	13.0% (363/2789)	5.6% (15/266)
Pulmonary Interstitial	20.7% (137/662)	10.2% (27/266)
Emphysema	26.7% (558/2092)	NA
Recurrent Apnea	14.6% (349/2387)	8.9% (21/237)
Retinopathy of Prematurity		

* At the time of the trial(s), adverse event reporting conventions allowed for collection of quantitative data related only to prematurity-related complications. Adverse events other than those listed above may have occurred in ≥10% of patients.

NA Not assessed

a Not all complications were assessed (as present or not present) 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 EURO VI, in which bronchopulmonary dysplasia was defined as requirement for supplemental oxygen at 28 days (no radiographic evidence required).

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 differences between treatment groups for weight, length, occipitofrontal circumference, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment, or auditory impairment. No 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 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 Invasive Surfactant Administration with a Thin Catheter (LISA) Technique

The **N**on-**IN**vasive **S**urfactant **APP**lication (**NINSAPP**) study compared surfactant administration via LISA technique to conventional endotracheal intubation.

Preterm infants of gestational age <27 and ≥23 weeks, with surfactant deficiency syndrome were enrolled in the study. In the LISA group, Curosurf, at a dose of at least 100 mg/kg, was administered via endotracheal thin catheter while continuing CPAP. In the control group patients were treated through the conventional approach consisting of intubation, surfactant (Curosurf, at

least 100 mg/kg) administration and mechanical ventilation. Table 5 summarizes adverse events reported during surfactant administration.

Table 5 Adverse events during surfactant administration occurring more frequently in infants treated with Curosurf than in infants with the control treatment – NINSAPP Study (Safety population)

System Organ Class/ Preferred term	**LISA group N = 101**	**Conventional administration group N = 109**
	Number of patients (%)	Number of patients (%)
Cardiac disorders		
Bradycardia	12 (11.9%)	3 (2.8%)
Investigations		
Oxygen desaturation	58 (57.4%)	29 (26.6%)
Nervous system disorders		
Froth at the mouth	22 (21.8%)	3 (2.8%)
Respiratory, thoracic and mediastinal disorders		
Apnoea	22 (21.8%)	14 (12.8%)
Coughing	8 (7.9%)	1 (0.9%)
Choking	7 (6.9%)	2 (1.8%)
Sneezing	5 (5.0%)	0 (0.0%)

Table 6 Treatment-Emergent Adverse Events occurring in ≥1% of infants treated with Curosurf and occurring more frequently than in infants with the control treatment - NINSAPP Study (Safety Population)

System Organ Class/ Preferred Term	LISA group N = 101	Conventional Administration group N = 109
	Number of patients (%)	Number of patients (%)
Cardiac disorders		
Cardio-respiratory distress	2 (2.0%)	1 (0.9%)
Cardiomyopathy	1 (1.0%)	0 (0.0%)
Pulmonary valve stenosis	1 (1.0%)	0 (0.0%)
Congenital, familial and genetic disorders		
Atrial septal defect	1 (1.0%)	0 (0.0%)
Endocrine disorders		
Hyperparathyroidism secondary	1 (1.0%)	0 (0.0%)
Eye disorders		
Eyelid oedema	1 (1.0%)	0 (0.0%)
Ocular hyperaemia	1 (1.0%)	0 (0.0%)
Gastrointestinal disorders		
Intestinal perforation	12 (11.9%)	10 (9.2%)
Necrotising colitis	13 (12.9%)	6 (5.5%)
Meconium ileus	3 (3.0%)	1 (0.9%)
Ascites	1 (1.0%)	0 (0.0%)
Duodenal perforation	1 (1.0%)	0 (0.0%)
Meconium plug syndrome	1 (1.0%)	0 (0.0%)
General disorders and administration site conditions		

Oedema peripheral	2 (2.0%)	0 (0.0%)
Catheter site extravasation	1 (1.0%)	0 (0.0%)
Multi-organ failure	1 (1.0%)	0 (0.0%)
Pain	1 (1.0%)	0 (0.0%)
Peripheral swelling	1 (1.0%)	0 (0.0%)
Vessel puncture site haemorrhage	1 (1.0%)	0 (0.0%)
Infections and infestations		
Sepsis neonatal	15 (14.9%)	14 (12.8%)
Conjunctivitis	5 (5.0%)	0 (0.0%)
Rash pustular	3 (3.0%)	0 (0.0%)
Gastroenteritis clostridial	2 (2.0%)	0 (0.0%)
Cytomegalovirus infection	1 (1.0%)	0 (0.0%)
Gastroenteritis astroviral	1 (1.0%)	0 (0.0%)
Respiratory syncytial virus bronchiolitis	1 (1.0%)	0 (0.0%)
Injury, poisoning and procedural complications		
Face injury	2 (2.0%)	1 (0.9%)
Anastomotic complication	1 (1.0%)	0 (0.0%)
Contusion	1 (1.0%)	0 (0.0%)
Investigations		
Norovirus test positive	1 (1.0%)	0 (0.0%)
Metabolism and nutrition disorders		
Hyperglycaemia	1 (1.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Haemangioma	5 (5.0%)	2 (1.8%)
Nervous system disorders		
Cerebral ventricle dilatation	2 (2.0%)	0 (0.0%)
Cerebellar haemorrhage	1 (1.0%)	0 (0.0%)
Cerebral infarction	1 (1.0%)	0 (0.0%)
Seizure	1 (1.0%)	0 (0.0%)
Renal and urinary disorders		
Acute kidney injury	1 (1.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort	6 (5.9%)	1 (0.9%)
Neonatal respiratory distress syndrome	2 (2.0%)	0 (0.0%)
Increased viscosity of nasal secretion	1 (1.0%)	0 (0.0%)
Throat irritation	1 (1.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders		
Erythema	3 (3.0%)	2 (1.8%)
Skin lesion	2 (2.0%)	1 (0.9%)
Skin erosion	1 (1.0%)	0 (0.0%)
Surgical and medical procedures		
Intestinal resection	1 (1.0%)	0 (0.0%)
Laser therapy	1 (1.0%)	0 (0.0%)
Skin operation	1 (1.0%)	0 (0.0%)
Vascular disorders		

Haematoma	4 (4.0%)	3 (2.8%)
Haemorrhagic infarction	2 (2.0%)	1 (0.9%)
Hypertension	1 (1.0%)	0 (0.0%)
Hypotension	1 (1.0%)	0 (0.0%)
Hypovolaemic shock	1 (1.0%)	0 (0.0%)
Thrombophlebitis	1 (1.0%)	0 (0.0%)

Table 7 Procedure-related Adverse Events – NINSAPP Study (Safety Population)

SOC, PT	**LISA group N = 101**		**Conventional administration group N = 109**	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Any AE related to the procedure	**4 (4.0%)**	**5**	**8 (7.3%)**	**8**
Eye disorders	**1 (1.0%)**	**1**	**0 (0.0%)**	**0**
ROP	1 (1.0%)	1	0 (0.0%)	0
Gastrointestinal disorders	**0 (0.0%)**	**0**	**1 (0.9%)**	**1**
Intestinal perforation	0 (0.0%)	0	1 (0.9%)	1
Injury, poisoning and procedural complications	**0 (0.0%)**	**0**	**1 (0.9%)**	**1**
Endotracheal intubation complication	0 (0.0%)	0	1 (0.9%)	1
Nervous system disorders	**0 (0.0%)**	**0**	**1 (0.9%)**	**1**
Aphonia	0 (0.0%)	0	1 (0.9%)	1
Respiratory, thoracic and mediastinal disorders	**3 (3.0%)**	**3**	**5 (4.6%)**	**5**
Pulmonary haemorrhage	2 (2.0%)	2	1 (0.9%)	1
Pneumothorax	0 (0.0%)	0	2 (1.8%)	2
Haemoptysis	0 (0.0%)	0	1 (0.9%)	1
Neonatal respiratory distress syndrome[a]	1 (1.0%)	1	0 (0.0%)	0
Stridor	0 (0.0%)	0	1 (0.9%)	1
Surgical and medical procedures	**1 (1.0%)**	**1**	**0 (0.0%)**	**0**
Laser therapy	1 (1.0%)	1	0 (0.0%)	0

[a] Reported as: one-side surfactant application

9.3 Less Common Clinical Trial Adverse Reactions

Infections and infestations: Septic shock
Nervous System Disorders: Haemorrhage intracranial

Respiratory, thoracic and mediastinal disorders: Pneumothorax, Bronchopulmonary dysplasia, Pulmonary haemorrhage

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION for further information.

9.5 Post-Market Adverse Reactions

Undesirable side effects collected during post-marketing experience which are not described above are listed in the table below according to System Organ Class.

Table 8 Post-Market Adverse Events by System Organ Class

System organ Class	Adverse Reaction
Respiratory, thoracic and mediastinal disorders	Hyperoxia
	Cyanosis neonatal
Investigations	Oxygen saturation decreased
	Electroencephalogram abnormal

10 DRUG INTERACTIONS

10.1 Overview

No known drug interactions have been identified.

Post-market surveillance reports did not include events indicative of drug interactions.

10.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

10.3 Drug-Food Interactions

Interactions with food have not been established.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Curosurf 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.

11.2 Pharmacodynamics

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

In vivo - In pharmacodynamic studies using ventilated or non-ventilated premature rabbits, poractant alfa improved lung mechanics. Static pressure-volume recordings showed 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 increased lung-thorax compliance in animals who received poractant alfa relative to controls. 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), 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.

11.3 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.

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 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.

12 STORAGE, STABILITY AND DISPOSAL

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 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.

13 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Poractant alfa

Chemical name: none

Molecular formula 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

Structural formula: N/A

Physicochemical properties: White to creamy white suspension.

Product Characteristics

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.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

Table 9 Summary of patient demographics for clinical trials in respiratory distress syndrome in premature infants

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean Gestational Age	Sex
50.00/CT/02/90	Randomized, controlled, multicenter trial of Curosurf prophylaxis versus rescue treatment	Intratracheal 200 mg/kg	Prophylaxis arm = 136 infants Rescue arm = 132 infants	Prophylaxis arm = 27.5 weeks Rescue arm = 27.4 weeks	Prophylaxis arm = 71M/65F Rescue arm = 62M/70F
50.01/CT/04/93	Randomized, controlled, multicenter trial of Curosurf prophylaxis versus rescue treatment	Intratracheal 100 mg/kg	Prophylaxis arm = 134 infants Rescue arm = 122 infants	Prophylaxis arm = 28.9 weeks Rescue arm = 28.3 weeks	Prophylaxis arm = 75M/59F Rescue arm = 63M/59F
EURO I	Randomized, controlled, multicenter trial of Curosurf rescue versus “sham” treatment	Intratracheal 200 mg/kg	Rescue arm = 77 infants “Sham” arm = 69 infants	Rescue arm = 28.8 weeks “Sham” arm = 28.4 weeks	Rescue arm = 50 M/27F “Sham” arm = 40M/29F
EURO III	Randomized, controlled, multicenter trial of Curosurf early treatment versus late treatment	Intratracheal 200 mg/kg	Early arm = 86 infants Late/control arm = 96 infants	Early arm = 29.9 weeks Late/control arm = 29.7 weeks	Early arm = 47M/39F Late/control arm = 57M/39F

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean Gestational Age	Sex
EURO IV	Randomized, controlled, multicenter trial of Curosurf single dose versus multiple doses	Intratracheal 200 mg/kg initial dose followed by 100 mg/kg doses	Single dose arm =176 infants Multiple doses arm = 167 infants	Single dose arm =29.2 weeks Multiple doses arm = 28.9 weeks	Single dose arm =99M/77F Multiple doses arm = 91M/76F
EURO VI	Randomized, controlled, multicenter trial of Curosurf high dose versus low dose	Intratracheal Low dose arm = 100 mg/kg doses High dose arm = 200 mg/kg initial dose followed by 100 mg/kg doses	Low dose arm = 1069 infants High dose arm = 1099 infants	Low dose arm = 29.4 weeks High dose arm = 29.3 weeks	Low dose arm = 619M/450F High dose arm = 629M/470F
NINSAPP Study	Randomised, prospective, multicentre, single-dose, controlled parallel-group trial of non-invasive Curosurf application during CPAP assisted spontaneous breathing versus conventional therapy of respiratory distress syndrome in extremely preterm neonates	Intratracheal 164.1 ± 52.0 mg/kg 2.0 ± 1.6 minutes, 162.8 ± 52.2 mg/kg, 1.8 ± 1.2 minutes	LISA arm = 107 preterm neonates Conventional administration arm = 104 preterm neonates	LISA arm: 25.3 weeks Conventional administration arm: 25.2 weeks	LISA arm: 63M/44F Conventional administration arm: 52M/ 52F

Curosurf has been studied in controlled clinical trials (Rescue studies and Prophylaxis versus Rescue studies) in around 3600 patients.

15.2 Study Results

EURO I study:

In a study (EURO I) comparing premature rescue-infants treated with a single dose of Curosurf (200 mg/kg) to premature infants who received a "sham" treatment in which patients were

disconnected from the respirator for 2 minutes and manually ventilated using the same protocol as for patients treated with Curosurf except that no material was instilled into the airways. A higher incidence of survival without bronchopulmonary dysplasia (BPD) was reported in the Curosurf group.

The results of three Pivotal studies (EURO I, 50.01/CT/04/93 and the NINSAPP Study) are summarized below:

Table 10 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)	35 (51)
BPD (Grade III-IV) at 28 days	12 (16)	18 (26)

* Birth Weight Range: 700 - 2000 g

50.01/CT/04/93 study:

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.

Table 11 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)

Non-INvasive Surfactant APPlication (NINSAPP) study:

A clinical study, NINSAPP, compared the administration of Curosurf with the LISA technique and the standard of care (intubation, administration and mechanical ventilation) in spontaneously-breathing preterm newborns with RDS and gestational age between 23 and 27 weeks. The primary endpoint of the study was survival without bronchopulmonary dysplasia (BPD) at 36 gestational weeks. The efficacy was assessed using a non-inferiority design with a margin of -5% for the difference in the proportion in survival without BPD (LISA - Control). The study met its

primary endpoint; the 95% confidence interval for the difference in proportions was above the -5% non-inferiority margin. Results are presented in Table 12 below.

Table 12 Efficacy Assessment – Non INvasive Surfactant APPlication (NINSAPP) Study

Treatment Group	LISA group N = 107	Conventional administration group N = 104
Survival without BPD	72 (67.3%)	61 (58.7%)
Difference between proportion: LISA - Control (95% CI)	8.604 (-4.045, 21.253)*	
Survival without BPD by GA,		
GA: 23-24^{+6} weeks	21 (51.2%)	19 (47.5%)
GA: 25-26^{+6} weeks	51 (77.3%)	42 (65.6%)

Death	10 (9.3%)	12 (11.5%)
BPD	25 (23.4%)	31 (29.8%)
Survival without major complications (IVH Grade ≥II, PVL, ROP requiring surgery)	64 (59.8%)	43 (41.3%)
NEC requiring surgery	9 (8.4%)	4 (3.8%)
Need for Intubation and MV within 96 hrs of surfactant administration	56 (52.3%)	102 (98.1%)

* The NI margin was pre-defined in the study protocol and set to 5%
IVH=Intraventricular Hemorrhage; PVL=Periventricular Leukomalacia, ROP=Retinopathy of Prematurity, NEC=Necrotizing Enterocolitis, MV=Mechanical Ventilation

16 NON-CLINICAL TOXICOLOGY

General Toxicology
Acute Toxicity Studies:
Endotracheal administration of CUROSURF (200 mg/kg) to healthy, i.e. non-surfactant-deficient rats, guinea pigs, dogs and rabbits, produced isolated respiratory symptoms, which can be attributed to excessive volume loading of the respiratory tract by the liquid.

Intra-peritoneal administration up to 2000 mg/kg of CUROSURF caused pilo-erection and hypo-activity in mice and rats.

Subacute Toxicity Studies:
Sub-acute intra-tracheal toxicity study in dogs, rabbits and rats (14 days) showed neither clinical effects or haematological changes, nor macroscopic variations related to the CUROSURF administration. Only respiratory findings attributable to the excessive volume administered into lungs were seen.

Slight to moderate reversible centrilobular hepatocyte vacuolisation and vacuolar degeneration occurred in the liver of rats after intra-peritoneal administration of CUROSURF at the dose of 600

mg/kg/day for 4 weeks. This is a condition that is expected after intra-peritoneal administration of high doses of lipids. Acute inflammation and fibrosis occurred at the injection site at 600 mg/kg. No local or systemic treatment related effects were seen up to a 350 mg/kg dose.

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

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

Reproductive and Developmental Toxicology:
Reproduction studies have not been performed with poractant alfa.

Special Toxicology:
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).

Juvenile Toxicology:
Juvenile toxicity studies have not been performed with poractant alfa.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]CUROSURF®
poractant alfa suspension

This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Curosurf**.

Serious Warnings and Precautions

- **Curosurf should only be given to your baby by trained healthcare professional(s) 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 healthcare professional(s) 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.**

What is Curosurf used for?

- Curosurf is used to treat Respiratory Distress Syndrome (RDS) in newborn premature babies.
- Your baby may have other problems as well as RDS which may need other treatments.

How does Curosurf work?

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.

What are the ingredients in Curosurf?

Medicinal ingredients: The active substance is a mixture of fats and proteins which come from a pig lung called poractant alfa.

Non-medicinal ingredients: The other ingredients are sodium bicarbonate, sodium chloride and water for injection. This product contains less than 1 mmol sodium (23 mg) per vial.

Curosurf comes in the following dosage forms:

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.

Do not use Curosurf if:

- Your baby has any allergies to Curosurf or any other ingredients in this product or components of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional about Curosurf. Before using Curosurf, the healthcare professional(s) will check that the baby's general conditions are stabilized, by adjusting, for example, acid blood pH (acidosis), low blood pressure (hypotension), red blood cell decrease (anaemia), blood sugar levels (hypoglycaemia), low body temperature (hypothermia).

Other warnings you should know about:

- If your baby gets an infection, antibiotics may be given to treat the infection.
- After administration of Curosurf a momentary lowering (transient depression) of the electrical activity of the brain (cerebro-electrical activity), lasting from 2 to 10 minutes has been recorded.

The following may interact with Curosurf:

There are no known drug interactions with this medication.

How to take Curosurf:

The healthcare professional(s) 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 or catheter into the baby's windpipe. They may disconnect your baby from the ventilator for a few minutes to do this.

Your healthcare professional(s) 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.

Usual dose:

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.

Overdose:

There have been no reported overdoses of Curosurf; however, if your baby is overdosed your healthcare professional(s) will decide on the best course of treatment.

Missed Dose:

Not applicable.

What are possible side effects from using Curosurf?

These are not all the possible side effects your baby may feel when taking Curosurf. If your baby experiences any side effects not listed here, contact your healthcare professional.

During the administration of Curosurf with a thin catheter, some temporary side effects have been seen: slow heart rate, stopping of breathing, decreased amount of oxygen in the body, froth at the mouth, coughing, choking, and sneezing. Furthermore, necrotizing enterocolitis (severe infection and inflammation of the GI tract) and focal intestinal perforation (localized rupture of the intestinal wall) are signals possibly linked to the LISA method used by your healthcare professional to give the drug to your baby.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Infection		X	
Bleeding in the brain		X	
Air in the chest cavity caused by lesions in the lungs.		X	
RARE			
Slower heart rate		X	
Low blood pressure		X	
Chronic lung disease		X	
Decrease in oxygen around the body		X	
NOT KNOWN			
Decreased amount of oxygen in the body		X	
Blue colour of the skin or gums, caused by too little oxygen		X	
Stopping of breathing		X	
Complication with placement of the tubes into the lungs		X	
Abnormal reading of the brain activity		X	

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Reporting Suspected Side Effects

For the general public: Should you experience a side effect following immunization, please report it to your healthcare professional(s).

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and Chiesi Farmaceutici, S.p.A. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory (http://www.phac-aspc.gc.ca/im/aefi-essi-form-eng.php) and send it to your local Health Unit.

Storage:
Keep out of 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.

If you want more information about Curosurf:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the Canadian distributor's website www.methapharm.com or by calling Methapharm at 1-866-701-4636

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