# AUSTRALIAN PRODUCT INFORMATION - CUROSURF® (PORACTANT ALFA) SUSPENSION

## 1 NAME OF THE MEDICINE

poractant alfa

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CUROSURF (poractant alfa) Intratracheal Suspension is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal or intrabronchial administration. It is an extract of natural porcine lung surfactant consisting of 99% polar lipids (mainly phospholipids) and about 1% hydrophobic low molecular weight proteins (surfactant associated proteins SP-B and SP-C). It is suspended in 0.9% sodium chloride solution.

Each millilitre of surfactant mixture contains 80 mg of total phospholipids (including 54 mg of phosphatidylcholine of which 30.5 mg is dipalmitoyl phosphatidylcholine) and 1 mg of protein including 0.3 mg of SP-B.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

## 3 PHARMACEUTICAL FORM

Suspension for intratracheal administration.

CUROSURF is a white to creamy white suspension of poractant alfa.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants and for prophylactic use in infants at risk of RDS.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

The clinician administering CUROSURF must be experienced in neonatal intensive care, including endotracheal intubation, mechanical ventilation and cardiorespiratory and oxygen monitoring.

CUROSURF is administered intratracheally by instillation through a 5 French end-hole catheter and briefly disconnecting the endotracheal tube from the ventilator. Alternatively, CUROSURF may be administered through the secondary lumen of a dual lumen endotracheal tube without interrupting mechanical ventilation, or in the delivery room through temporary placement of an ET tube followed by CPAP.

Before administering CUROSURF, ensure 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 stabilise before proceeding with dosing.

**Rescue Treatment**

The initial recommended dose is 2.5 mL/kg birth weight (200 mg /kg). Treatment should commence as soon as possible after diagnosing RDS. Up to two repeat doses of 1.25 mL/kg birth weight (100 mg/kg) each may be administered, at approximately 12 hour intervals, in infants who remain intubated and in whom RDS is considered responsible for their persisting or deteriorating respiratory status. The maximum recommended total dose (sum of the initial and two repeat doses) is 5 mL/kg (400 mg/kg).

**Prophylaxis**

A single dose of 100-200 mg/kg should be administered as soon as possible after birth (preferably within 15 minutes). Further doses of 100 mg/kg can be given 6-12 hours after the first dose and then 12 hours later in infants who have persistent signs of RDS and remain ventilator- dependent (maximum total dose: 300-400 mg/kg).

Doses may be determined from the CUROSURF dosing chart shown in Table 1.

**Table 1**

| CUROSURF DOSING CHART | | | | | |
|---|---|---|---|---|---|
| **WEIGHT (grams)** | **INITIAL DOSE 2.5 ml/kg** | **REPEAT DOSE 1.25 mL/kg** | **WEIGHT (grams)** | **INITIAL DOSE 2.5 mL/kg** | **REPEAT DOSE 1.25 mL/kg** |
| | **EACH DOSE (mL)** | | | **EACH DOSE (mL)** | |
| 600-650 | 1.60 | 0.80 | 1301-1350 | 3.30 | 1.65 |
| 651-700 | 1.70 | 0.85 | 1351-1400 | 3.50 | 1.75 |
| 701-750 | 1.80 | 0.90 | 1401-1450 | 3.60 | 1.80 |
| 751-800 | 2.00 | 1.00 | 1451-1500 | 3.70 | 1.85 |
| 801-850 | 2.10 | 1.05 | 1501-1550 | 3.80 | 1.90 |
| 851-900 | 2.20 | 1.10 | 1551-1600 | 4.00 | 2.00 |
| 901-950 | 2.30 | 1.15 | 1601-1650 | 4.10 | 2.05 |
| 951-1000 | 2.50 | 1.25 | 1651-1700 | 4.20 | 2.10 |
| 1001-1050 | 2.60 | 1.30 | 1701-1750 | 4.30 | 2.15 |
| 1051-1100 | 2.70 | 1.35 | 1751-1800 | 4.50 | 2.25 |
| 1101-1150 | 2.80 | 1.40 | 1801-1850 | 4.60 | 2.30 |
| 1151-1200 | 3.00 | 1.50 | 1851-1900 | 4.70 | 2.35 |
| 1201-1250 | 3.10 | 1.55 | 1901-1950 | 4.80 | 2.40 |
| 1251-1300 | 3.20 | 1.60 | 1951-2000 | 5.00 | 2.50 |

***For endotracheal tube instillation using a 5 French end-hole catheter***

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. Immediately before CUROSURF administration, the infant's ventilator settings should be changed to a rate of 40-60 breaths/minute, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain SaO2 >92%. Keep the infant in a neutral position (head and body in alignment without inclination). Briefly disconnect the endotracheal tube from the ventilator.

Insert the pre-cut 5 French catheter into the endotracheal tube and instil the first aliquot (1.25 mL/kg birth weight) of CUROSURF. The infant should be positioned such that either the right or left side is 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. When the infant is stable, reposition the infant such that the other side is dependent and administer the remaining aliquot using the same procedures. Do not suction airways for 1 hour after surfactant instillation unless signs of significant airway obstruction occur.

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

***For endotracheal instillation using the secondary lumen of a dual lumen 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). Do not attach 5 French end-hole catheter. Keep the infant in a neutral position (head and body in alignment without inclination). Administer CUROSURF through the proximal end of the secondary lumen of the endotracheal tube as a single dose, given over 1 minute and without interrupting mechanical ventilation.

After completion of this dosing procedure, ventilatory management may require transient increases in $FiO_2$, ventilatory rate or PIP.

***For endotracheal instillation using the INtubation SURfactant Extubation (INSURE) treatment protocol***

There is a third option of administration through an endotracheal tube in the delivery room before mechanical ventilation has been started. In this case a bagging technique is used to distribute the surfactant through the lungs. Extubation to Continuous Positive Airway Pressure (CPAP) is an option either in the delivery room or later after admission to the neonatal unit.

**Directions for use**

CUROSURF should be inspected visually for discolouration prior to administration. The colour of CUROSURF is white to creamy white. CUROSURF should be stored in a refrigerator at +2 to +8 ºC. Before use, the vial should be slowly warmed to room temperature and gently turned upside-down in order to obtain a uniform suspension. DO NOT SHAKE.

Unopened, unused vials of CUROSURF that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Do not warm to room temperature and return to refrigerated storage more than once. Protect from light. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

## 4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

No specific contraindications are yet known.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Prophylaxis with surfactant should only be performed where adequate delivery room facilities are available and according to the following recommendations:

- prophylaxis (within 15 min of birth) should be given to almost all babies under 27 weeks' gestation;
- prophylaxis should be considered for babies over 26 weeks but < 30 weeks' gestation if intubation is required in the delivery suite or if the mother has not received prenatal corticosteroids;
- when prenatal corticosteroids were administered, surfactant should be administered only if RDS develops;
- considering the other risk factors prophylaxis should also be considered in preterm infants when any of the following are present: perinatal asphyxia, maternal diabetes, multiple pregnancies, male sex family history of RDS and caesarean section

In all other preterm neonates it is recommended that surfactant be administered using early rescue or selective approaches.

**Before administration of CUROSURF**

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

**During administration of CUROSURF**

In the event of reflux, administration of CUROSURF should be stopped and, if necessary, peak inspiratory pressure on the ventilator should be increased until clearing of the endotracheal tube occurs.

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

However, aspiration of tracheal secretions is not recommended for at least 6 hours after administration, with the exception of life-threatening conditions.

The administration of exogenous surfactants, including CUROSURF, can rapidly affect oxygenation and lung compliance. Therefore infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes.

In the event of occurrence of episodes of bradycardia, hypotension, endotracheal tube blockage and oxygen desaturation (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) administration of CUROSURF should be stopped and appropriate measures to normalise heart rate should be considered and undertaken. After stabilisation, the infant can still be treated with appropriate monitoring of vital signs.

**After administration of CUROSURF**

After administration of CUROSURF pulmonary compliance (chest expansion) and oxygenation can improve rapidly, thus requiring prompt adjustment of ventilator settings.

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 recommended.

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 analysis, continuous monitoring of transcutaneous $PaO_2$ or oxygen saturation is also advisable.

Nasal continuous positive airway pressure (nCPAP) can be used to continue the treatment, but only in units equipped to perform this technique.

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.

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.

Apnoea and sepsis may occur as consequences of the immaturity of the infants.

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 foetal circulation despite the provision of intensive care. These infants are also at high risk of developing infections such as pneumonia and bacteraemia (or septicaemia). Seizures may also occur in the perinatal period. 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.

Infants born following very prolonged rupture of the membranes (greater than 3 weeks) may have some degree of pulmonary hypoplasia and may not show an optimal response to exogenous surfactant.

Surfactant administration can be expected to reduce the severity of RDS but cannot be expected to eliminate entirely the mortality and morbidity associated with preterm birth, as preterm infants may present other complications associated with their immaturity.

There is no information available on effects of initial doses other than 100 or 200 mg/kg, dosing more frequently than every 12 hours, or administration of CUROSURF starting more than 15 hours after diagnosing RDS.

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

When CUROSURF was administered with the LISA technique, an increase in frequency of bradycardia, apnoea and reduced oxygen saturation was reported. These events were generally of brief duration, without consequences during administration and easily managed. When these events became serious, the surfactant treatment was stopped and the complications were treated.

**Use in the elderly**

No data available.

**Paediatric use**

Refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

**Effects on laboratory tests**

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Not known.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

No data available.

**Use in pregnancy**

No data available.

**Use in lactation**

No data available.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Clinical Trial Experience**

Transient adverse effects seen with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage and oxygen desaturation.

The rates of common complications of prematurity observed in Study 1 are shown in Table 2.

**Table 2**

| **COMPLICATIONS OF PREMATURITY** | | |
|---|---|---|
| | **CUROSURF 2.5 mL/kg (200 mg/kg) n = 77 %** | **CONTROL* n = 69 %** |
| Acquired pneumonia | 14 | 20 |
| Bronchopulmonary dysplasia | 16 | 26 |
| Intracerebral haemorrhage (all grades) | 47 | 55 |
| Patent ductus arteriosus (required treatment) | 53 | 47 |
| Pneumothorax | 18 | 35 |
| Pulmonary interstitial emphysema | 23 | 38 |

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

***Less Invasive Surfactant Administration with a thin catheter (LISA) technique***

In clinical trials, some transient and mild adverse events, without consequences during administration, were more frequent in the LISA groups than in the standard treatment control groups; in particular: oxygen desaturation (57.4% LISA group vs. 26.6% standard group), apnoea (21.8% vs. 12.8%), bradycardia (11.9% vs. 2.8%), froth at the mouth (21.8 vs. 2.8%), coughing (7.9% vs. 0.9%), choking (6.9% vs. 1.8 %) and sneezing (5% vs. 0). This difference between the two groups could be justified by the less frequent use of sedation in the LISA groups vs. standard of care. The majority of these events were easily managed.

During a spontaneous comparative clinical trial (Study 3) there was an increased incidence of cases of necrotizing enterocolitis requiring surgery (8.4% in the group with LISA method and 3.8% in the group with standard administration-intubation/MV) and

focal intestinal perforation requiring surgery (11.2% in the LISA group and 10.6% in the standard group) in the LISA group, with no statistically significant difference between groups. These events could be either complications of prematurity or consequences of treatments used in these preterm babies.

***Follow up Evaluations***

Seventy-six infants (45 treated with CUROSURF) were evaluated at 1 year of age and 73 infants (44 treated with CUROSURF) at 2 years of age. Data from follow-up evaluations for weight and length, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment or auditory impairment was similar between treatment groups. In 33 survivors (17 treated and 16 controls) at one year, the mean of the developmental quotient (derived using the Griffiths Mental Developmental Scales) was similar between groups.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

There have been no reports of overdosage following the administration of CUROSURF. In the event of accidental overdosage, and only if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, as much of the suspension as possible should be aspirated and the infant should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

Endogenous pulmonary surfactant reduces surface tension at the air-liquid interface of the alveoli during ventilation and stabilises the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in preterm infants results in Respiratory Distress Syndrome (RDS) characterised by poor lung expansion, inadequate gas exchange, and a gradual collapse of the lungs (atelectasis). CUROSURF compensates for the deficiency of surfactant and restores surface activity to the lungs of these infants.

***Activity***

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

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

In pharmacodynamic studies in premature infants, CUROSURF treatment produced improved arterial oxygen concentration within 5 minutes of administration, with increases in the ratios of a/A $PO_2$ and $PaO_2/FiO_2$. Improved oxygenation allowed reductions in the concentration of inspired oxygen ($FiO_2$) within 1 hour, and reductions in ventilator settings (peak insufflation pressure and mean airway pressure). Treatment was also associated with increased chest wall movements, improved lung compliance and decreased inspiratory resistance.

## Clinical trials

### *Activity*

Large international open and controlled clinical trials have documented the therapeutic effects of CUROSURF in infants with RDS and preterm infants at risk for RDS. Preterm newborn infants treated with a single dose of CUROSURF (1.25-2.5 mL/kg equal to 100-200 mg/kg of phospholipids) showed a rapid and dramatic improvement of oxygenation with reduction of the inhaled oxygen concentration ($FiO_2$) and increase of $PaO_2$ and of $PaO_2/FiO_2$ and $a/APO_2$ ratios; mortality rate and incidence of major pulmonary complications were shown to be reduced. The administration of a second or third dose of 100 mg/kg further reduced the incidence of pneumothorax and mortality.

### *Rescue treatment*

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

In Study 1, infants' 700-2000 g birth weight with RDS requiring mechanical ventilation and a $FiO_2 > 0.60$ were enrolled. CUROSURF 2.5 mL/kg single dose (200 mg/kg) or control (disconnection from the ventilator and manual ventilation for 2 minutes) was administered after RDS developed and before 15 hours of age. The results from Study 1 are shown below in Table 3.

**Table 3**

| **OUTCOME AT 28 DAYS** | **SINGLE DOSE CUROSURF n = 77 %** | **CONTROL n = 69 %** | **P-VALUE** |
|---|---|---|---|
| Mortality | 31 | 51 | ≤ 0.05 |
| Bronchopulmonary dysplasia | 16 | 26 | N.S |
| Pneumothorax | 18 | 35 | ≤ 0.05 |
| Pulmonary interstitial emphysema | 23 | 39 | ≤ 0.05 |

N.S: Not significant

In Study 2, infants 700-2000 g birth weight with RDS requiring mechanical ventilation and a $FiO_2 > 0.60$ were enrolled. In this two-arm trial, CUROSURF was administered after RDS developed and before 15 hours of age as a single-dose or as multiple doses. In the single-dose arm, infants received CUROSURF 2.5 mL/kg (200 mg/kg). In the

multiple-dose arm, the initial dose of CUROSURF was 2.5 mL/kg (200 mg/kg) and subsequent doses of CUROSURF were 1.25 mL/kg (100 mg/kg). The results from Study 2 are shown below in Table 4.

**Table 4**

| OUTCOME AT 28 DAYS | SINGLE-DOSE CUROSURF n = 176 % | MULTIPLE-DOSE CUROSURF n = 167 % | P-VALUE |
|---|---|---|---|
| Mortality | 21 | 13 | < 0.05 |
| Bronchopulmonary dysplasia | 12 | 13 | N.S. |
| Pneumothorax | 18 | 9 | < 0.05 |
| Pulmonary interstitial emphysema | 27 | 23 | N.S. |

N.S.: Not significant

***Less Invasive Surfactant Administration with a thin catheter (LISA) technique:***

In clinical trials in spontaneously breathing preterm infants CUROSURF was administered through the Less Invasive Surfactant Administration (LISA) technique using a thin catheter. Doses were the same as indicated for the other modalities. A small diameter catheter with a mark at 1.5 cm above the tip was placed into the trachea of infants on CPAP. The catheter was placed with this mark at the level of the vocal cord. Continuous spontaneous breathing was ensured with direct visualization of the vocal cords by laryngoscopy. CUROSURF was instilled by a single bolus over 0.5-3minutes. After CUROSURF instillation, the tube was immediately removed. CPAP treatment was continued during the whole procedure. The surfactant was administered using a suitable semi-rigid thin catheter.

A spontaneous clinical trial (Study 6) has compared the administration of CUROSURF with the LISA technique and the standard one (intubation, administration and mechanical ventilation) in two groups of preterm newborns with RDS and gestational age between 23 and 27 weeks (LISA group: n = 108, control group: n = 105). LISA technique was not inferior to the standard one on the primary end-point (survival without bronchopulmonary dysplasia at 36 gestational weeks). The need of mechanical ventilation was significantly reduced with LISA. Preterm infants in the LISA group achieved statistically significant treatment difference for composite secondary endpoints (survival without major complications such as IVH>II, cystic PVL, ROP requiring surgery), compared to infants in mechanical ventilation group. No statistically significant difference in treatment outcomes were found between LISA and control group for other secondary endpoints such as NEC requiring surgery, duration of mechanical ventilation or CPAP or oxygen supplementation.

**Table 5 - Survival without BPD (ITT population)**

| | **LISA group N = 107** | **Control Group N= 104** |
|---|---|---|
| **Survival without BPD, n (%)** | 72 (67.3%) | 61 (58.7%) |
| Death, n (%) | 10 (9.3%) | 12 (11.5%) |
| BPD, n (%) | 25 (23.4%) | 31 (29.8%) |
| **Cochran-Mantel-Haenszel test** | | |
| Odds ratio (95% CI) | 1.476 (0.829, 2.626) | |
| Difference between proportion: LISA – Control (95% CI) | 8.604 (-4.045, 21.253) | |
| p-value | 0.186 | |
| **Survival without BPD by GA, n (%)** | | |
| GA: 23-24$^{+6}$ weeks | 21 (51.2%) | 19 (47.5%) |
| GA: 25-26$^{+6}$ weeks | 51 (77.3%) | 42 (65.6%) |

***Prophylaxis***

Three randomised controlled trials (Studies 3, 4 and 5) were conducted in which prophylactic use of CUROSURF was compared with rescue treatment in premature infants considered to be at risk of RDS (for details, see Table 5). A meta-analysis of the three trials indicated that prophylactic treatment was associated with a reduction in the risk of severe RDS, a reduction in overall mortality and a reduction in chronic lung disease of the newborn (CLDN). Results are summarised in Table 6.

## Table 6

| | |
|---|---|
| **Study 3** | *Perinatal Parameters and Treatments*: gestational age 28 weeks (mean for both Prophylaxis and Rescue), Prenatal corticosteroids 25% (Prophylaxis) and 32% (Rescue).<br><br>*Administration method*: neonates randomised to the prophylaxis group (n=75) were intubated, connected to the ventilator, and received surfactant (dose of 200 mg/Kg = 2.5 mL/kg) within 10 minutes after delivery via 5/F feeding tube inserted into the tracheal tube. After surfactant instillation, the neonate was ventilated manually or artificially with the level of $FiO_2$ needed to maintain a pink skin colour and a pressure providing adequate chest movements. Rescue-eligible neonates (n=72) who required assisted ventilation with $FiO_2 \geq 0.6$ at 6 to 24 hours after birth were given a dose of 200 mg/kg surfactant via the tracheal tube, as described above. Again, the ventilatory settings were modified depending on the response to surfactant instillation. Duration of mechanical ventilation and time in > 21% oxygen were the same in both groups, and there was no difference in neonatal or overall mortality. |
| **Study 4** | *Perinatal Parameters and Treatments*: gestational age 28.9 weeks (Prophylaxis) and 28.3 weeks (Rescue), Prenatal corticosteroids 17% (Prophylaxis) and 11% (Rescue).<br><br>*Administration method*: newborns assigned to the prophylaxis group were systematically intubated in the delivery room and after stabilisation (but within 15 minutes after birth) received one dose of 100 mg/kg birth weight of Curosurf. As soon as the surfactant was delivered, the patients were placed on intermittent positive pressure ventilation (IPPV) for at least 3 hours. These infants were eligible to receive up to three additional doses of 100 mg/ kg birth weight of Curosurf within 48 h after birth if, at 6 and/or 18,30 and 42 hours of life, their $PaO_2/FiO_2$ ratio was < 150 (mmHg) (or 20 kPa) at a ventilatory mean airway pressure (MAP) of 8 $cmH_2O$. Infants assigned to the rescue group were treated in the delivery room. They were intubated and subjected to IPPV only after significant respiratory distress (irregular breathing pattern, Silverman score > 3, cyanosis with post-ductal $PaO_2$ < 50 mmHg (or 6.6 kPa) with $FiO_2 \geq 0.3$ given in a hood and/or $PaCO_2$ > 55 mmHg (or 7.3 kPa)). Those who were intubated received surfactant rescue therapy with 100 mg/kg birth weight of Curosurf if, between 3 and 18 hours after birth, they developed RDS meeting the following criteria: (1) typical radiogram (decreased lung volume, generalised reticulogranular pattern, air bronchogram extending beyond the cardiac silhouette); (2) a $PaO_2/FiO_2$ ratio < 150 (mmHg) (or 20 kPa) at an MAP of 8 $cmH_2O$. They were eligible to receive up to three additional doses of 100 mg/kg birth weight of Curosurf within 48 h after birth if, at 6 hours after the first dose and then at 12 hours after the second and the third doses, they had a $PaO_2/FiO_2$ ratio < 150 (mmHg) (or 20 kPa) at an MAP of 8 $cmH_2O$.<br><br>Compared with rescue therapy (n=122), prophylaxis (n=134) decreased the need for oxygenation and ventilatory support within 3-72 hours. |
| **Study 5** | *Perinatal Parameters and Treatments*: gestational age 28 weeks (median, both for Prophylaxis and for Rescue), Prenatal corticosteroids 28% (both for Prophylaxis and for Rescue).<br><br>*Administration method*: neonates randomised to prophylaxis were intubated immediately after birth and given a single bolus of Curosurf, injected via the tracheal tube as previously described. The dose was calculated on the basis of 200 mg of phospholipids/kg body weight and standardised for expected birth weight as follows: 160 mg for group 24-25 weeks; 240 mg for group 26-28 weeks; 280 mg for group 29-30 weeks. The surfactant was administered within the first 10 minutes of birth, if possible before the first breath. During the subsequent 1-minute period of manual bag ventilation, fraction of inspired oxygen ($FiO_2$) was adjusted to the needs of the neonate. Following this period the neonate was extubated if they presented sustained and effective spontaneous breathing. Otherwise, the neonate was shifted from manual to mechanical ventilation. Control infants were assisted according to the "routine" of each unit. For ethical reasons no placebo was administered and intubation was not performed unless indicated on clinical grounds. Neonates randomised to the prophylaxis or control group who subsequently developed radiological and clinical RDS requiring intermittent positive pressure ventilation (IPPV) were, irrespective of the FiO2-level, eligible for treatment with a single endotracheal bolus dose of Curosurf (200 mg/kg) administered as previously described. Rescue treatment was recommended as soon as these criteria were fulfilled.<br><br>Mean maximum $FiO_2$ during the first 28 days was lower in neonates given prophylaxis than in controls: 0.57 (SD 0.25) versus 0.66 (SD 0.25) ($p < 0.01$). There was also a significant reduction of maximum inspiration: expiration ratio in the neonates given prophylaxis compared with controls ($p < 0.05$), while other parameters of ventilation were not different between the groups. |

**Table 7**

| Outcomes | Combined prophylaxis | Results MH[1] Rescue | RRR[3] | Odds ratio between groups | 95% Confidence intervals (CI) and p-value | Adjusted ORs[4] |
|---|---|---|---|---|---|---|
| Severe RDS | 18.9 % | 29.7 % | 36.4 % | 0.55 | 0.38 – 0.79<br>p = 0.001 | 0.5<br>0.33 – 0.74 |
| Pulmonary complications[2] | 12.2 % | 20.6 % | 40.8 % | 0.54 | 0.35 – 0.82 | |
| Mortality | 15.1 % | 25.5 % | 40.7 % | 0.52 | 0.35 – 0.76<br>p < 0.001 | 0.47<br>0.30 – 0.73 |
| CLDN in survivors at 28 days after birth | 24.4 % | 31.7 % | 23 % | 0.67 | 0.45 – 1.00<br>p = 0.05 | 0.54<br>0.34 – 0.86 |

[1] Mantel-Haenszel odds ratios were corrected for the random effects term within country.

[2] Pneumothorax plus pulmonary interstitial complications.

[3] Relative reduction or risk ratio.

[4] The adjusted odds ratios take into account the random effects term and the effect of the significant covariates gender, birth weight and prenatally given corticosteroids.

Studies regarding antenatal corticosteroids for accelerating foetal lung maturation for women at risk of preterm birth support the continued use of a single course of antenatal corticosteroids. Treatment with antenatal corticosteroids reduces the risk of neonatal death, respiratory distress syndrome, cerebroventricular haemorrhage, necrotising enterocolitis, infectious morbidity, need for respiratory support and neonatal intensive care unit admission. There is evidence in studies and current clinical practice to suggest benefit across a wide range of gestational ages from 26 to 34 + 6 weeks. Furthermore, there is evidence to suggest benefit in the subgroups of women with premature rupture of membranes and those with hypertension syndromes. A single course of antenatal corticosteroids should be considered routine for preterm delivery.

## 5.2 PHARMACOKINETIC PROPERTIES

CUROSURF is administered directly to the target organ, the lung, where biophysical effects occur at the alveolar surface. No human pharmacokinetic studies to characterise the absorption, biotransformation or excretion of CUROSURF have been performed.

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

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

No data available for genotoxicity and reproductive toxicity effects.

### Carcinogenicity

Studies to assess potential carcinogenic of CUROSURF, or other surfactants have not been conducted. Mutagenicity studies with CUROSURF, which included gene mutation assays in bacteria (the Ames test) and Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovarian cells, an assay of unscheduled DNA synthesis in HeLa S3 cells and an *in vivo* mouse micronucleus test, were negative.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

The excipients include: sodium chloride, sodium bicarbonate and water for injections.

The pH may be adjusted as required with sodium bicarbonate to a pH of 6.2 (5.5 - 6.5). CUROSURF contains no preservatives.

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store CUROSURF in a refrigerator at +2 to +8ºC.

Unopened vials of CUROSURF may be warmed to room temperature for up to 24 hours prior to use. CUROSURF should not be warmed to room temperature and returned to the refrigerator more than once.

Store in the original package to protect from light and moisture. Do not shake. Vials are for single use only. After opening the vial, discard the unused portion of the drug.

## 6.5 NATURE AND CONTENTS OF CONTAINER

CUROSURF is available in sterile, ready-to-use rubber-stoppered glass Type 1 clear vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension. One vial per carton.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**CAS number**

129069-19-8

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

Chiesi Australia Pty Ltd
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Australia
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## 9 DATE OF FIRST APPROVAL

13 January 2005

## 10 DATE OF REVISION

24 November 2022

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| 3 & 4.2 | Spelling correction. |