

## **SUMMARY OF PRODUCT CHARACTERISTICS**

1) **NAME OF THE MEDICINAL PRODUCT:**  
**CUROSURF 80 MG/ML ENDOTRACHEOPULMONARY INSTILLATION SUSPENSION**

2) **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

One 1.5 ml vial contains:

Active ingredient: phospholipid fraction from porcine lung 120 mg.

One 3 ml vial contains:

Active ingredient: phospholipid fraction from porcine lung 240 mg.

CUROSURF is a natural surfactant, prepared from porcine lungs, containing almost exclusively phospholipids, in particular phosphatidylcholine (about 70% of the total phospholipid content) and about 1% of surfactant-specific low molecular weight hydrophobic proteins SP-B and SP-C.

3) **PHARMACEUTICAL FORM**

Sterile suspension in single-dose vials for endotracheal or endobronchial administration.

4) **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of Respiratory Distress Syndrome (RDS) in preterm babies.

Prophylactic use in premature infants at risk for RDS.

4.2 **Posology and method of administration**

Posology

CUROSURF should only be administered in hospital by a medical staff trained and experienced in neonatal intensive care for preterm infants, having available suitable equipment for ventilation and monitoring of babies with RDS.

**Treatment:** the recommended dose is 100-200 mg/kg (1.25-2.5 ml/kg) of body weight administered as a single bolus dose. It is possible to administer additional doses of 100 mg/kg, each one at about 12-hourly intervals, in infants still requiring assisted ventilation and supplementary oxygen (maximum total dose: 300-400 mg/kg).

It is recommended to start treatment as soon as possible after diagnosing RDS.

**Prophylaxis:** 100-200 mg/kg (1.25-2.5 ml/kg) of body weight should be administered as soon as possible (within 15 minutes) after birth. Further doses of 100 mg/kg each can be given 6-12 hours after the first dose, and then at 12-hour intervals in case of occurrence of RDS requiring mechanical ventilation (maximum total dose: 300-400 mg/kg).

Method of administration

CUROSURF is available in ready-to-use vials to be stored at a temperature ranging between +2 and +8°C.

The vial should be warmed to room temperature before use, for example by holding it in the hand for a few minutes, and gently turned upside down a few times, without shaking, until the suspension appears homogeneous.

The suspension should be withdrawn from the vial by using a sterile needle and syringe, following the instruction described under section 6.6.

CUROSURF can be administered either by:

- a. Disconnecting the infant from the mechanical ventilator

Disconnect the infant momentarily from the ventilator and administer 1.25 to 2.5 ml/kg (100-200 mg/kg) of the suspension as a single bolus, directly into the lower trachea via the endotracheal tube. Perform approximately one minute of hand-bagging and then reconnect the infant to the ventilator at the same settings as before administration. Further doses (1.25 ml/kg equal to 100 mg/kg) that may be required can be administered on identical terms;

or

b. Without disconnecting the infant from the mechanical ventilator

Administer 1.25 to 2.5 ml/kg (100-200 mg/kg) of the suspension as a single bolus, directly into the lower trachea by passing a catheter through the suction port and into the endotracheal tube. Further doses (1.25 ml/kg equal to 100 mg/kg) that may be required can be administered following the same procedure.

c) Intubation Surfactant Extubation (INSURE)

There is a third option of administration, which is intubation of the newborn to administer the surfactant. Doses are the same indicated for modalities under points a) and b). In this case a bagging technique is used and after surfactant administration and extubation, nasal CPAP may be applied (Continuous Positive Airway Pressure).

d) Less Invasive Surfactant Administration with a thin (LISA) or similar catheter

Alternatively, in spontaneously breathing preterm infants Curosurf can also be administered through the Less Invasive Surfactant Administration (LISA) technique using a thin catheter. Doses are the same indicated for modalities under points a), b) and c). A small diameter catheter is placed into the trachea of infants on CPAP, ensuring continuous spontaneous breathing, with direct visualization of the vocal cords by laryngoscopy. Curosurf is instilled by a single bolus over 0.5 – 3 minutes. After Curosurf<sup>®</sup> instillation, the tube is immediately removed. CPAP treatment should be continued during the whole procedure.

It is recommended to frequently control blood gases whatever administration modality is used as, after administration, an immediate increase in PaO<sub>2</sub> or oxygen saturation is generally observed. It is however advisable to continuously monitor transcutaneous PO<sub>2</sub> or oxygen saturation to avoid hyperoxia.

Special population

Renal or Hepatic impairment

The safety and efficacy of CUROSURF in patients with renal or hepatic impairment have not been evaluated.

#### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

No specific contraindications to CUROSURF use are known so far.

#### **4.4 Special warnings and precautions for use**

TREATMENT

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

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

Infants whose ventilation parameters become markedly impaired during or shortly after instillation may have mucus plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration.

Suctioning prior to dosing may lower 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, unless life-threatening conditions occur.

In the event of occurrence of episodes of bradycardia, hypotension and reduced oxygen saturation (see section 4.8), the administration of CUROSURF should be stopped and suitable measures to normalize heart rate should be considered and undertaken. After stabilization, the infant can still be treated with appropriate monitoring of vital signs.

After administration of CUROSURF lung expansion can improve rapidly, thus requiring a prompt reduction in peak inhalation pressure without waiting for confirmation from blood gas control.

The improvement in alveolar gas exchange may result in a rapid increase in arterial oxygen concentration: therefore, a rapid adjustment of the inhaled oxygen concentration should be made to avoid hyperoxia. In order to maintain proper blood oxygenation values, continuous monitoring of transcutaneous PaO<sub>2</sub> or oxygen saturation is also advisable in addition to periodic haemogasanalysis.

The continuous positive pressure nasal ventilation (nasal-CPAP) can be used in maintenance therapy of neonates treated with surfactant, but only in units properly equipped for 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 an appropriate antibiotic therapy.

In cases of unsatisfactory response to treatment with CUROSURF or rapid relapse, it is advisable to consider the possibility of other immaturity-related complications, such as persistent Botallo ductus open or other lung diseases such as pneumonia, before administering the next dose.

Particular caution is required for infants born following very prolonged rupture of the membranes (greater than 3 weeks), as they are subject to 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 mortality and morbidity associated with preterm birth, as preterm infants may exhibit other complications associated with their immaturity. After administration of CUROSURF a transient depression of the cerebro-electrical activity, lasting from 2 to 10 minutes, has been recorded. This finding has been observed in one study only and its impact is not clear.

When Curosurf is administered with the LISA technique, an increase in frequency of bradycardia, apnoea and reduced oxygen saturation has been reported. These events are generally of brief duration, without consequences during administration and easily managed. If these events become serious, stop the surfactant treatment and treat the complications.

#### PROPHYLAXIS

Prophylaxis with surfactant should only be performed in facilities in which interventions of neonatal intensive care are possible and continuous monitoring is available according to the following recommendations:

a) prophylaxis (within 15 minutes from birth) should be given to almost all babies under 27 weeks gestation;

b) prophylaxis should be considered for babies over 26 weeks but below 30 weeks gestation if intubation is required in the delivery suite or if the mother has not received prenatal corticosteroids; when prenatal corticosteroids have been given, surfactant should be administered only if RDS develops;

c) by taking into account other risk factors, prophylaxis should be considered in preterm infants when any of the following conditions are present: perinatal asphyxia, maternal diabetes, multiple pregnancies, male sex, family history of RDS and caesarean section.

In all other preterm newborns, it is recommended that surfactant be administered at the first signs of RDS.

There is no information available on effects of initial doses other than 100 or 200 mg/kg, more frequent dosing (intervals lower than 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.

#### 4.5 **Interaction with other medicinal products and other forms of interaction**

Not known.

#### 4.6 **Fertility, pregnancy and lactation**

Not applicable.

#### 4.7 **Effects on ability to drive and use machines**

Not applicable.

#### 4.8 **Undesirable effects**

Undesirable effects observed during treatment in clinical trials and integrated with those collected during post-marketing experience are listed in the table below according to System Organ Class (using the MedDRA Preferred Term) and the following frequency: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ); very rare ( $<1/10,000$ ); not known (cannot be estimated from the available data).

<b>System organ class according to MedRA</b>	<b>Adverse reactions</b>	<b>Frequency</b>
Infections and infestations	Sepsis	Uncommon
Nervous system disorders	Intracranial haemorrhage	Uncommon
Cardiac disorders	Bradycardia	Rare
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchopulmonary dysplasia	Rare
	Pneumothorax	Uncommon
	Pulmonary haemorrhage	Rare
	Hyperoxia	Not known
	Neonatal cyanosis	Not known
Investigations	Apnoea	Not known
	Decreased oxygen saturation	Rare
Injury, poisoning and procedural	Abnormal electroencephalogram	Not known
	Endotracheal intubation complication	Not known

complications		
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Apnoea and sepsis may occur as a consequence of infant immaturity.

The occurrence of intracranial haemorrhages after CUROSURF instillation has been associated with a reduction in mean arterial blood pressure and early peaks in arterial oxygenation (PaO<sub>2</sub>). Avoidance of high PaO<sub>2</sub> peaks by ventilator adjustment immediately after instillation is recommended.

In clinical studies conducted to date a slight tendency towards an increased incidence of persistent Botallo ductus open has been reported in newborns treated with CUROSURF (as with other surfactants).

Formation of antibodies against the protein components of CUROSURF has been observed, but so far without any evidence of clinical relevance.

Preterm newborns have a relatively high incidence of cerebral haemorrhage and cerebral ischemia, reported as periventricular leukomalacia and haemodynamic anomalies such as persistent Botallo ductus open 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 (or septicaemia). Seizures may also occur in the perinatal period. In addition, preterm babies 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.

#### 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 (NINSAPP) some 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 ) were reported, with no statistically significant difference between groups. These events could be either complications of prematurity or consequences of other treatments used in these preterm babies.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via the national reporting system listed in Appendix V.

### **4.9 Overdose**

There have been no reports of overdose following the administration of CUROSURF. However, in the event of accidental overdose, and only in the presence of clear clinical effects on the infant's respiration, ventilation or oxygenation, it is suggested to aspirate, as much of the suspension as possible and the baby should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

## 5) **PHARMACOLOGICAL PROPERTIES**

### 5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: lung surfactant, ATC code: R07AA02.

Lung surfactant is a mixture of substances, mainly phospholipids and specific proteins, lining the internal surface of pulmonary alveoli. Their main function is to lower pulmonary surface tension. This surface tension lowering activity is essential to stabilize alveoli, and to avoid collapse at the end of expiration, so that adequate gas exchange is maintained throughout the whole ventilation cycle.

Deficiency of lung surfactant, from whatever cause, leads to severe respiratory failure that in preterm babies is known as Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD).

RDS represents the major cause of acute mortality and morbidity in preterm babies and may be responsible for long-term respiratory and neurologic complications.

CUROSURF was developed to replace this deficiency of endogenous pulmonary surfactant by instillation of supplementary surfactant directly into the lower respiratory tract. The surfactant properties of CUROSURF promotes its uniform distribution in the lungs and spreading at the air-liquid interface in the alveoli. The physiological and therapeutic effects of this product have been extensively documented in various animal models.

In immature rabbit fetuses obtained by hysterectomy and sacrificed prior to their first breath, the administration of CUROSURF induced a marked improvement in lung expansion. In premature newborn rabbits ventilated with 100% O<sub>2</sub>, CUROSURF instillation via a tracheal cannula induces a very significant improvement in the tidal volume and lung-thorax compliance as compared to control animals. Moreover, in premature rabbits, by maintaining a standardized tidal volume of about 10 ml/kg, the treatment with CUROSURF increases the lung-thorax compliance to a level comparable to that of mature newborn animals.

#### ***Clinical efficacy and safety***

Large international controlled and open clinical trials have documented the therapeutic effects of CUROSURF in newborn babies with RDS and preterm babies 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 in oxygenation with reduction in the inhaled oxygen concentration (FiO<sub>2</sub>) and increase in PaO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> and a/APO<sub>2</sub> ratios; mortality rate and incidence of major pulmonary complications were shown to be reduced.

The administration of a second or a third dose of 100 mg/kg seems to further reduce the incidence of pneumothorax and mortality.

A spontaneous clinical trial ( NINSAPP) 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).On the secondary end-points LISA was superior in increasing survival without major complications and in reducing the frequency of other morbidities associated with prematurity. The need of mechanical ventilation was significantly reduced with LISA.

## **5.2 Pharmacokinetic properties**

In newborn rabbits after administration by the intratracheal route CUROSURF tends to remain mainly in the lungs, with <sup>14</sup>C-labelled dipalmitoyl-phosphatidylcholine half-life equal to 67 hours. 48 hours after administration only traces of surfactant lipids could be found in serum and organs other than lungs.

## **5.3 Preclinical safety data**

Acute toxicity studies in different animal species by intraperitoneal and intratracheal routes did not evidence either signs of lung and systemic toxicity or mortality.

Subacute toxicity studies (14 days) by intratracheal route in rats, dogs and rabbits showed no clinical effects or changes in haematological parameters, nor macroscopic variations related to the treatment. Moreover, CUROSURF did not reveal any evidence of direct toxicity in rats by intraperitoneal route (4 weeks).

CUROSURF given by parenteral route to guinea pigs does not cause active anaphylactic reactions or stimulate the production of antibodies detectable by passive cutaneous anaphylactic reaction. Similarly, no anaphylactic reactions were observed by intratracheal route. Furthermore, there is no evidence of dermal sensitizing potential (Magnusson and Kligman test).

Curosulf did not show any evidence of mutagenic or clastogenic activity in the tests used.

## **6) PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride, water for injections

### **6.2 Incompatibilities**

Not known.

### **6.3 Shelf life**

18 months. The proposed shelf-life refers to the product in its unopened package and properly stored.

### **6.4 Special precautions for storage**

Store in a refrigerator (2°C-8°C).

Store in the original package in order to protect from light.

Do not use any residual quantity in the vial after the first aspiration.

Unused and unopened 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.

### **6.5 Nature and contents of container**

5 ml single-dose neutral glass vials, provided with a chlorobutyl rubber stopper and a plastic and aluminium cap.

One 3 ml 80 mg/ml vial (240 mg/vial)

One 1.5 ml 80 mg/ml vial (120 mg/vial)

### **6.6 Special precautions for disposal and other handling**

The vial should be warmed to room temperature prior to its use and gently turned upside down without shaking, in order to obtain a homogeneous suspension.

The suspension should be withdrawn from the vial by using a sterile needle and syringe.

In order to draw the suspension, carefully follow the instructions below:

- 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

For single use only. Discard any unused portion left in the vial. Do not keep unused portions for later administrations.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

- 7) **MEDICINE SCHEDULE**  
Prescription Medicine
- 8) **SPONSOR**  
Douglas Pharmaceuticals Ltd, P.O. Box 45027, Auckland 0610
- 9) **DATE OF FIRST APPROVAL**  
09 September 2004
- 10) **DATE OF REVISION OF THE TEXT**  
03 August 2017

Summary table of changes

<b>Section Changed</b>	<b>Summary of new information</b>