SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CUROSURF® 120mg / vial Endotracheopulmonary Instillation Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 120mg (1.5ml) of phospholipid fraction from porcine lung (poractant alfa).

Composition per ml of suspension: phospholipid fraction from porcine lung 80mg/ml, equivalent to about 74mg/ml of total phospholipids and 0.9mg/ml of low molecular weight hydrophobic proteins.

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Endotracheopulmonary instillation suspension

A white to yellow sterile suspension for endotracheopulmonary instillation in single dose vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment, including early rescue of Respiratory Distress Syndrome (RDS) or hyaline membrane disease in newborn babies.

Prophylactic use in premature infants requiring intubation for stabilisation at risk from RDS or with evidence of surfactant deficiency where the mother had not received appropriate ante-natal corticosteroids.

4.2 Posology and method of administration

4.2.1 Posology

4.2.1.1 Rescue treatment

The recommended starting dose is 100-200mg/kg (1.25-2.5ml/kg), administered in a single dose as soon as possible after diagnosing RDS.
Additional doses of 100mg/kg (1.25ml/kg), each at about 12-hourly intervals, may also be administered if RDS is considered to be the cause of persisting or deteriorating respiratory status of the infants (maximum total dose of 300-400mg/kg).

4.2.1.2 Prophylaxis

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

4.2.2 Method of administration

CUROSURF should only be administered by those trained and experienced in the care, resuscitation and stabilisation of preterm infants. CUROSURF is administered via the endotracheopulmonary route in infants whose heart rate and arterial oxygen concentration or oxygen saturation are being continuously monitored as it is usually feasible in neonatal units.

CUROSURF is available in ready to use vials that should be stored in a refrigerator at +2°C to +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, in order to obtain a uniform suspension.

The suspension should be withdrawn from the vial using a sterile needle and syringe following the instruction described in section 6.6. A suitable catheter or tube should then be used to instil CUROSURF into the lungs.

CUROSURF can be administered either by:

a. Disconnecting the baby from the ventilator

Disconnect the baby momentarily from the ventilator and administer 1.25 to 2.5ml/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 baby to the ventilator at the same settings as before administration. Further doses (1.25ml/kg) that may be required can be administered in the same manner.

OR

b. Without disconnecting the baby from the ventilator

Administer 1.25 to 2.5ml/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 (1.25ml/kg) that may be required can be administered in the same manner.

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

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 haemo-gas analysis,

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

OR

c. 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 and extubation to CPAP is an option either in the delivery room or later after admission to the neonatal unit (INtubation SURfactant Extubation -INSURE)

OR

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

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 visualisation of the vocal cords by laryngoscopy. Curosurf is instilled by a single bolus over 0.5-3 minutes. After Curosurf® instillation, the tube is immediately removed. CPAP treatment should be continued during the whole procedure.

Thin catheters CE marked for this intended use should be used for surfactant administration.

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(s) or to any of the excipients listed in section 6.1.
No specific contraindications are yet known.

4.4 Special warnings and precautions for use

Prior to starting the treatment with CUROSURF the infants general condition should be stabilised. 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 inspiratory pressure on the ventilator should be obstructing the 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 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.

In the event of occurrence of episodes of bradycardia, hypotension, and reduced oxygen saturation (see section 4.8) administration of CUROSURF should be stopped and suitable 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 pulmonary compliance (chest expansion) and oxygenation can improve rapidly, thus requiring prompt adjustment of ventilator settings.

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.

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. 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 only one study 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.

There is no information available on effects of initial doses other than 100 or 200mg/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.

4.5 Interaction with other medicinal products and other forms of interaction
Not known

4.6 Fertility, pregnancy and lactation
Not relevant

4.7 Effects on ability to drive and use machines
Not relevant

4.8 Undesirable effects
Undesirable side 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 (showed with the MedDRA Preferred Term) and to the following frequency: very common (≥ 1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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

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

The occurrence of intracranial haemorrhages after CUROSURF instillation has been related to reduction in mean arterial blood pressure and early peaks in arterial oxygenation (PaO_2). Avoidance of high PaO_2 peaks by ventilator adjustment immediately after instillation is recommended (see section 4.2).

In clinical studies performed to date a slight tendency towards an increased incidence of patent ductus arteriosus has been reported in infants treated with CUROSURF. This phenomenon has also been reported with other exogenous surfactants and is attributed to haemodynamic changes induced by the rapid expansion of the lungs with surfactant administration.

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

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

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.

<u>Reporting of suspected adverse reactions</u>
Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

There have been no reports of overdosage following the administration of CUROSURF. However, in the unlikely event of accidental overdose, 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 baby should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory, Lung surfactants, ATC code: R07AA02

Lung surfactant is a mixture of substances, mainly phospholipids and specific proteins, lining the internal surface of alveoli and capable of lowering pulmonary surface tension.

This surface tension lowering activity is essential to stabilise alveoli, and to avoid collapse at end-expiration so that adequate gas exchange is maintained throughout the ventilatory cycle.

Deficiency of lung surfactant, from whatever cause, leads to severe respiratory failure which in preterm babies is known as respiratory distress syndrome (RDS) or hyaline membrane disease (HMD). RDS is a major cause of acute mortality and acute morbidity in the preterm baby and may also be responsible for long term respiratory and neurologic sequelae.

CUROSURF was developed to replace this deficiency of endogenous pulmonary surfactant by intratracheal administration of exogenous surfactant.

The surface properties of CUROSURF favour its uniform distribution in the lungs and spreading at the air-liquid interfaces in the alveoli. The physiological and therapeutic effects of CUROSURF in surfactant deficiency have been documented extensively in various animal models.

In immature rabbit foetuses obtained by hysterectomy and immediately sacrificed the administration of CUROSURF caused a marked improvement in lung expansion.

In premature newborn rabbits ventilated with 100% oxygen there was a dramatic improvement of tidal volume and lung-thorax compliance compared to the control animals, after administration of CUROSURF via a tracheal cannula.

Also in premature newborn rabbits, treatment with CUROSURF (maintaining a standardised tidal volume of about 10 ml/Kg), increased the compliance of the lung-thorax system to a level similar to that of mature newborn animals.

Clinical efficacy and safety
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 preterms 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

CUROSURF remains mainly in the lungs following intratracheal administration with a half-life of ^{14}C-labelled dipalmitoyl-phosphatidylcholine of 67 hours in newborn rabbits. Only traces of surfactant lipids can be found in serum and organs other than the lungs 48 hours after administration.

5.3 Preclinical safety data

Acute toxicity studies performed in different animal species by intraperitoneal and intratracheal routes did not elicit signs of lung or systemic toxicity, nor mortality.

The subacute intratracheal toxicity study in the dog, rabbit and rat (14 days) showed no clinical effects or haematological changes, nor macroscopic variations. Moreover, CUROSURF did not reveal any evidence of direct toxicity in the rat by intraperitoneal route (4 weeks).

CUROSURF 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 sensitising potential (Magnusson and Kligman test).

CUROSURF did not show any evidence of mutagenic or clastogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydrogen carbonate (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 18 months
For single use only. Discard any unused suspension.

6.4 Special precautions for storage

Store in a refrigerator at (2°C - 8°C). Store in the original package in order to protect from light.
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.

6.5 Nature and contents of container

Single dose clear colourless Type I glass vials (5ml), provided with a cap in plastic and aluminium and a chlorobutyl rubber stopper, containing 1.5 ml of suspension

6.6 Special precautions for disposal and other handling

The vial should be warmed to room temperature**,** before use, and gently turned upside down, without shaking, in order to obtain a homogeneous suspension.
The suspension should be withdrawn from the vial 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 administration.

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

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PA 0584/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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