CUROSURF®

Poractant alfa (Phospholipid fraction of porcine lung) 80 mg/ml

Presentation

Sterile suspension in single-dose vials for intratracheal or intrabronchial administration.

One 1.5ml clear, colourless vial closed with a chlorobutyl rubber stopper contains phospholipid fraction from porcine lung, 120 mg (80 mg/ml). The stopper is held in place by an aluminium ring and covered with a plastic cap.

One 3 ml clear, colourless vial closed with a chlorobutyl rubber stopper contains phospholipid fraction from porcine lung, 240 mg (80 mg/ml). The stopper is held in place by an aluminium ring and covered with a plastic cap.

Uses

Actions

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 specific low molecular weight hydrophobic proteins SP-B and SP-C.

Lung surfactant is a mixture of substances, mainly phospholipids and specific proteins, lining the internal surface of alveoli. Their main function is to lower pulmonary surface tension. This surface tension lowering activity is essential to stabilise alveoli, and to avoid collapse at the end of 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 surfactant properties of CUROSURF® favour its uniform distribution in the lungs and spreading at the air-liquid interfaces in the alveoli.
The therapeutic effects of CUROSURF® have been documented in 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 of oxygenation with reduction of the inhaled oxygen concentration (FiO₂) and increase of PaO₂, and of PaO₂/ FiO₂ and a/APO₂ 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 seems to further reduce the incidence of pneumothorax and mortality.

**Pharmacokinetics**

CUROSURF® remains mainly in the lungs following intratracheal administration. A half-life of 67 hours of 14C-labelled dipalmitoyl-phosphatidylcholine has been measured in newborn rabbits.

48 hours after administration, only traces of surfactant lipids could be found in serum and organs other than lungs.

**Indications**

Treatment of Respiratory Distress Syndrome (RDS) in pre-term babies.

Prophylactic use in premature infants at risk for RDS.

**Dosage and Administration**

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

**Method of Administration:** CUROSURF® is available in ready-to-use vials that should be stored in a refrigerator at +2 to +8°C. 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 by using a sterile needle and syringe following the instructions described in section “Pharmaceutical Precautions”.
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 PaO₂ 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)

It is recommended to frequently control blood gases, as, after administration, an immediate increase of PaO₂ or oxygen saturation is generally observed (See Warnings and Precautions).
It is however advisable to continuously monitor transcutaneous PO2 or oxygen saturation to avoid hyperoxia.

**Contraindications**

No specific contraindications are known yet.

**Warnings and Precautions**

CUROSURF® should only be administered in hospital, by those trained and experienced in the care and resuscitation of preterm infants, where suitable equipment for ventilation and monitoring of babies with RDS is available.

Efficacy has not been shown following prolonged rupture of the membranes (longer than 3 weeks) or clearly shown in infants with meconium aspiration or group B streptococcal infection.

The baby's general conditions should be stabilised. Correction of acidosis, hypotension, anaemia, hypoglycaemia and hypothermia is also recommended.

CUROSURF® has a very rapid onset of action. It is, therefore, necessary to frequently monitor infants receiving CUROSURF® by arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

Transient episodes of bradycardia, hypotension and decreased oxygen saturation have been reported after administration of surfactants. If these occur, stop administration of CUROSURF® and initiate appropriate measures to alleviate the condition. After the condition is stabilised, resume administration.

Surfactant administration can be expected to reduce the severity of RDS or the risk of its reoccurrence, but cannot be expected to completely eliminate mortality and morbidity associated with preterm birth, as preterm babies may be exposed to other complications due to their immaturity.

Acute toxicity studies in different animal species administered CUROSURF® by intraperitoneal and intratracheal routes did not elicit either signs of lung or systemic toxicity, or mortality. Subacute intratracheal toxicity studies (14 days) in dogs, rabbits and rats showed neither clinical effects nor haematological changes, nor macroscopic variations related to the treatment. Moreover, CUROSURF® did not reveal any evidence of direct toxicity in the rat by intraperitoneal route (4 weeks).

CUROSURF® given by parenteral route in guinea pigs 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.

### Adverse 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).

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

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 (PaO₂). Avoidance of high PaO₂ peaks by ventilator adjustment immediately after instillation is recommended (see Dosage and Administration).

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 bacteremia (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.

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**Interactions**

Not known.

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**Overdosage**

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, paying particular attention to fluid and electrolyte balance.

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**Pharmaceutical Precautions**

Shelf life is 18 months. This shelf-life refers to the unopened and correctly stored product.

The product must be stored at +2 to +8°C, protected from light.
Unopened, unused vials of CUROSURF that have warmed to room can be returned to refrigerator within 24 hours for future use.

Do not warm to room temperature and return unopened vials to refrigerator more than once.

After opening, discard the unused portion of the medicine.

**INSTRUCTIONS FOR USE 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 colored 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

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**Medicine Classification**

Prescription Medicine
Package Quantities

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.

Further Information

The physiological and therapeutic effects of CUROSURF® in surfactant deficiency have been extensively documented 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.

Excipients:
Sterile sodium chloride for injection containing sodium chloride and water.

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