SUMMARY OF PRODUCT CHARACTERISTICS

CUROSURF®

1. NAME OF THE MEDICINAL PRODUCT

CUROSURF® 80 mg/ml SUSPENSION FOR ENDOTRACHEOPULMONARY INSTILLATION

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 approximately 1% of specific low molecular weight hydrophobic proteins SP-B and SP-C.

3. PHARMACEUTICAL FORM

Sterile suspension in single-dose vials for endotracheopulmonary instillation.

White to yellow suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Respiratory Distress Syndrome (RDS) in preterm babies.
Prophylactic use in premature infants at high risk for RDS.

4.2 Posology and method of administration

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

Rescue Treatment: the recommended dose is a single dose of 100-200 mg/kg (1.25-2.5 ml/kg) of body weight administered in a single dose. It is possible to administer additional doses of 100 mg/kg, each one at about 12 hour 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 (1.25-2.5 ml/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 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 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The suspension should be withdrawn from the vial by using a sterile needle and syringe following the instruction described in section 6.6.

CUROSURF can be administered either by:

a. Disconnecting the infant from the 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 equivalent to 100 mg/kg) that may be required can be administered in the same manner;

or

b. Without disconnecting the infant from the 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 equivalent to 100 mg/kg) that may be required can be administered in the same manner.

c. Intubation Surfactant Extubation (INSURE)
A third method consists of intubating the neonate for the sole purpose of administering the surfactant. The doses are the same as those indicated at points a) and b). In this case the neonate is ventilated manually and after administration of the surfactant and extubation, nasal CPAP (Continuous Positive Airway Pressure) may be applied.

d. Less Invasive Surfactant Administration with a thin catheter (LISA)
In spontaneously breathing preterm infants CUROSURF can also be administered through a less invasive technique (LISA) with a thin catheter. Doses are the same indicated for administration methods under points a), b) and c). Keeping the infant breathing spontaneously under CPAP and with a direct view of the vocal cords using a laryngoscope, a small-diameter catheter is placed in the infant's trachea. CUROSURF is instilled by a single bolus over 0.5 – 3 minutes. After CUROSURF instillation, the catheter is immediately removed. CPAP treatment should be continued during the whole procedure.

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

It is recommended to frequently control blood gases whatever administration is used, as, after administration, an immediate increase of PaO_2 or oxygen saturation is generally observed.

It is however advisable to continuously monitor transcutaneous PaO_2 or oxygen saturation to avoid hyperoxia.

Special populations

Renal or hepatic failure
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 are yet known.

4.4 Special warnings and precautions for use

TREATMENT
Prior to starting the treatment with CUROSURF neonates general conditions 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 should be increased until the obstruction in the endotracheal tube has been cleared.

Infants whose ventilation becomes markedly impaired during or shortly after instillation may have mucus plugging 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.

In the event of episodes of bradycardia, hypotension, and reduced oxygen saturation (see section 4.8) administration of CUROSURF should be stopped and suitable measures to normalize 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 can improve rapidly, thus requiring prompt reduction of the inspiratory pressure peak without waiting for confirmation from a check of blood gases.

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 (nasal-CPAP) can be used in maintenance therapy of neonates treated with surfactant, but only in units equipped to perform this technique.

New-borns 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 of 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.
Particular attention must be paid to infants born following a prolonged rupture of the membranes (greater than 3 weeks) since they 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 new-borns may present other complications associated with their immaturity. After administration of CUROSURF a transient depression of cerebral-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 by the LISA technique, an increased frequency of bradycardia, apnoea and reduced oxygen saturation can occur. These events are generally short-lasting, without consequences during administration and easily managed. In the event of their exacerbation, it is necessary to discontinue the therapy in place and treat the ongoing complications.

PROPHYLAXIS
Prophylaxis with surfactant should only be performed in facilities which can provide neonatal intensive care with continuous monitoring and treatment in accordance with the following recommendations:

a) prophylaxis (within 15 min after birth) should be given to almost all infants under 27 weeks' gestation;

b) prophylaxis should be considered for infants over 26 weeks and under 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;

c) considering other risk factors, prophylaxis should also be considered in preterm new-borns 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 neonates it is recommended that surfactant be early administered at the first signs of RDS.

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 new-borns with severe hypotension has not been studied.

This medicine contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium-free'.

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 according to MedDRA	Adverse reaction	Frequency
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
	Apnoea	Not known
Investigations	Oxygen saturation decreased	Rare
	Abnormal electroencephalogram	Not known
Injury, poisoning and procedural complications	Endotracheal intubation complication	Not known

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

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.

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 neonates 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 neonates 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 moderate adverse events, without consequences during administration, were more frequent in the group treated with the LISA technique than in the standard treatment control group, in particular: oxygen desaturation (57.4% for the LISA group vs 26.6% for the standard group), apnea (21.8% vs 12.8%), bradycardia (11.9% vs 2.8%), frothing 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 with respect to the 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 treated with LISA method and 3.8% in the group treated 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 the two groups. These events could be either complications of prematurity or consequences of other treatments used in preterm infants.

Reporting of suspected adverse reactions

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

There have been no reports of overdose following the administration of CUROSURF. However, if such should occur, 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 hydration 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 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 end of expiration, so that adequate gas exchange is maintained throughout the ventilation cycle.
Deficiency of lung surfactant, whatever its cause, leads to severe respiratory failure which in preterm infants is known as Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease.

RDS is the principal cause of mortality and acute morbidity in preterm infants and may also be responsible for long-term respiratory and neurological sequelae. The possibility of combating this

deficiency of endogenous pulmonary surfactant by the administration of supplementary surfactant directly into the lower respiratory tract is what led to the development of CUROSURF.
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 extensively documented in various animal models.
In immature rabbit foetuses obtained by hysterectomy and immediately sacrificed before starting to breathe, the administration of CUROSURF caused a marked improvement in lung expansion.
In premature rabbits ventilated with 100% oxygen there was a dramatic improvement of tidal volume and lung-thorax compliance, compared to the control animals, after instillation of CUROSURF via a tracheal cannula.
Also in premature rabbits, maintaining a standardised tidal volume of about 10 ml/kg, treatment with CUROSURF increased lung-thorax compliance to a level similar to that of full term new-born animals.
Clinical efficacy and safety
Large international both open and controlled clinical trials have documented the therapeutic effects of CUROSURF in neonates with RDS and preterm infants at risk for RDS.
Preterm new-born 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 showed 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 technique (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 at the primary endpoint (survival without bronchopulmonary dysplasia at 36 gestational weeks). On the secondary endpoints LISA was superior in increasing survival without major complications and in reducing the frequency of other morbidities associated with prematurity. The need for mechanical ventilation was significantly reduced in the group treated with LISA technique.

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

Acute toxicity studies in different animal species by intraperitoneal and intra-tracheal routes did not elicit either signs of lung or systemic toxicity, or mortality.
Subacute endotracheal toxicity studies (14 days) in rats, dogs and rabbits showed neither clinical effects or haematological changes, 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 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 endotracheal 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 during tests.

6) PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

Not known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (+2°C to +8°C). Protect from light. Do not use any residual quantity in the vial after the first aspiration.
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.

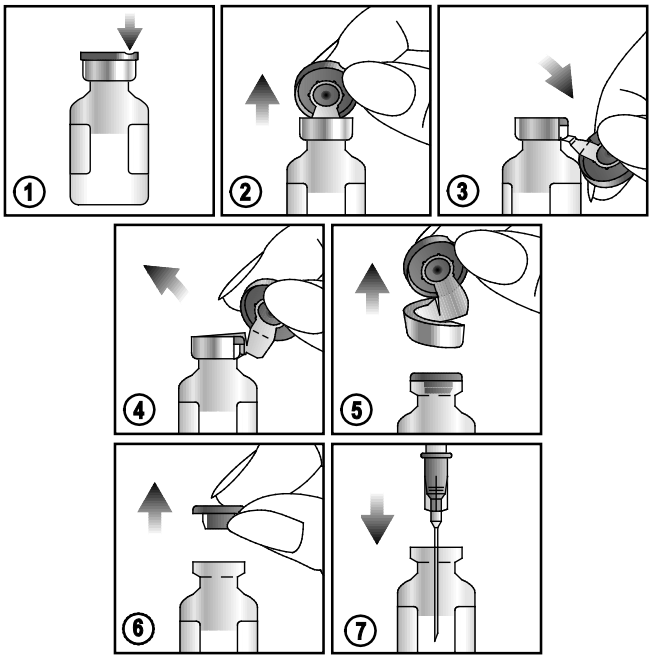
6.5 Nature and contents of container

Single-dose vial in clear colourless glass, volume of 5 ml, provided with a chlorobutyl rubber stopper and a plastic and aluminium cap.
One vial of 3 ml 80 mg/ml (240 mg/vial)
One vial of 1.5 ml 80 mg/ml (120 mg/vial)
Two vials of 1.5 ml 80 mg/ml (120 mg/vial)
Not all pack sizes may be marketed.

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 withdraw 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 stopper 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. LICENCE HOLDER AND MANUFACTURER

Licence Holder:
Teva Israel Ltd

124 Dvora HaNevi'a St, Tel Aviv 6944020 Israel
Manufacturer:
Chiesi Farmaceutici S.P.A.,
Parma, Italy.

8. REGISTRATION NUMBER

068.79.28250

The leaflet was revised in September 2025 according to MOHs guidelines.