For the use of a Registered medical practitioner or a Hospital or a Laboratory only

Bovine Lipid Extract Surfactant Suspension

Neosurf

Each ml of suspension contains
Phospholipid ..... 27 mg
Surfactant-associated proteins SP- B and SP-C ..... 176-500 mcg
With Sodium chloride and Calcium chloride.
Contains no preservatives.

DOSAGE FORM
Available as a suspension in 5 ml and 3 ml sterile, single use, clear glass vials. It is for **INTRATRACHEAL USE ONLY.**

PHARMACOLOGY
NEOSURF suspension restores surfactant activity in neonates with neonatal respiratory distress syndrome (NRDS), thereby improving gaseous exchange by decreasing alveolar surface tension and promoting lung compliance.

NEOSURF suspension is an extract of natural bovine surfactant which contains numerous phospholipids, with dipalmitoylphosphatidylcholine (DPPC) being the most abundant. It also includes hydrophobic surfactant-associated proteins SP-B and SP-C, which facilitate phospholipid dispersion.
When administered intratracheally, **NEOSURF** suspension is rapidly adsorbed, forming an active phospholipid monolayer at the air-fluid interface.

The metabolic fate of **NEOSURF** suspension has not been investigated.

NEOSURF suspension can have an immediate effect on lung compliance, usually within 5 to 30 minutes. Clinical experience with **NEOSURF** suspension reveals that it significantly improves gas exchange and lung compliance by the 4-hour time-point. The fraction of inspired oxygen (FiO_2) requirements in these infants is reduced and significant decreases in ventilatory support requirements are observed. Clinical trials using **NEOSURF** suspension reveal a reduction in the severity of NRDS and its associated complications.

Clinical experience with **NEOSURF** suspension has shown it to be safe and effective when used with nitric oxide therapy, high frequency oscillation and extracorporeal membranous oxygenation.

INDICATIONS
NEOSURF suspension is indicated as rescue treatment for NRDS/ Hyaline Membrane Disease. For infants with NRDS confirmed by X-ray and who require mechanical ventilation, with arterial to alveolar oxygen ratio (P_aO_2/PAO_2) < 0.22, **NEOSURF** suspension is to be given as soon as possible after the oxygenation criteria are met.
The use of **NEOSURF** suspension in infants less than 380 g or greater than 4460 g birth weight has not been evaluated in controlled trials.

DOSAGE AND ADMINISTRATION
NEOSURF suspension is intended for **INTRATRACHEAL** instillation only after an endotracheal airway has been established.

Recommended Dosage
The recommended dosage of **NEOSURF** suspension is 5 mL/kg at 27 mg of phospholipids/mL, which equals 135 mg phospholipid/kg. As many as 3 subsequent doses of **NEOSURF** suspension can be given within the first 5 days of life. See **Repeat Doses** for details. Table 1 suggests the total dosage for a range of birth weights.

Table 1. NEOSURF Suspension Dosing Chart

Weight (grams)	Total Dose (mL)	Weight (grams)	Total Dose (mL)
600 – 650	3.2	1301–1350	6.8
651- 700	3.5	1351-1400	7.0
701-750	3.8	1401-1450	7.2
751-800	4.0	1451-1500	7.5
801-850	4.2	1501-1550	7.8
851-900	4.5	1551-1600	8.0
901-950	4.8	1601-1650	8.2
951-1000	5.0	1651-1700	8.5
1001-1050	5.2	1701-1750	8.8
1051-1100	5.5	1751-1800	9.0
1101-1150	5.8	1801-1850	9.2
1151-1200	6.0	1851-1900	9.5
1201-1250	6.2	1901-1950	9.8
1251-1300	6.5	1951-2000	10.0

Directions for Use
NEOSURF suspension does not require reconstitution or filtering before use. Vials are for single use only, to ensure sterility. When **NEOSURF** is stored below-10°C, it may or may not solidify depending on the lipid matrix within the suspension. Studies with **NEOSURF** have confirmed that the quality and stability of the products are not affected by its physical state when stored below-10°C.

NEOSURF suspension should be warmed to at a least room temperature, but no higher than body temperature before being administered. Warming can be accomplished in the following ways (times are approximate):

Method of Warming	Refrigerated Vials	Frozen Vials
In the hand	5 minutes	10 to 15 minutes
On the counter	20 minutes	60 minutes
In a 37°C water bath	2 minutes	5 minutes

Once at room temperature, gently swirl or invert the vial to suspend any precipitate and disperse larger lipid agglomerates. Inspect the vial for homogeneity. It is normal for warmed vials to have an even dispersion of fine but visible flecks of lipid. Contents should appear as an off-white to light yellow suspension. If contents are of a darker colour or do not disperse evenly, discard the vial.

Dosing Procedures
The infant should be suctioned before commencing the procedure and allowed to recover. Ensure proper placement of the endotracheal tube (ETT) via chest auscultation and radiograph if available, (1-2 cm below the vocal cords, 1-2 cm above the carina). **DO NOT INSTILL NEOSURF suspension DOWN THE RIGHT MAINSTEM BRONCHUS.**

NEOSURF suspension should be instilled as a single bolus dose or up to three aliquots, as tolerated, via a sterile #5 Fr feeding tube cut to the appropriate length so that it reaches the tip of the ETT. The infant is first disconnected from the ventilator and then an appropriate length #5Fr feeding tube is threaded into the ETT with the infant supine for the first aliquot, and then rotated to the left and right for subsequent aliquots. Alternately, to allow simultaneous mechanical ventilation or hand bagging, pass the feeding tube through the suction valve of a closed suctioning adaptor attached to the ETT. Instil each aliquot or dose over 2 to 3 seconds. After each aliquot is instilled, the infant should be ventilated manually for 30 seconds, using pressures sufficient to achieve good chest expansion before returning the infant to the ventilator. If the infant remains on mechanical ventilation during dosing, raise the pressure by 1 to 2 cm H_2O, if necessary, to assist with emptying of the ETT. Allow approximately 1-2 minutes recovery time after each aliquot. Ensure that oxygen saturation readings are about 95% before commencing the next aliquot.

The volume of surfactant will rise in the ETT during administration. If the surfactant is slow to subside, interrupt administration and hand-ventilate until the ETT is clear before continuing. If the surfactant fails to subside, investigate the possibility of a mucus plug. Small aliquots or a slow drip are not recommended, as this may lead to poor surfactant distribution and uneven lung compliance.

Monitoring After Administration
Once instillation is complete, new mechanical ventilatory parameters need to be established according to the $TcpO_2/TcpCO_2$ readings, the oxygen saturation monitor and chest expansion. $TcpO_2/TcpCO_2$ readings are preferred in infants of lower gestation (less than 32 weeks) and oxygen saturation readings preferred with older infants. Monitor tidal volume closely, as sudden lung compliance may occur without much chest movement. Start at pre-instillation settings and wean the pressures (PIP/PEEP), FiO_2 and the ventilator rate, as indicated by the infant's status. Follow-up blood gases one hour after dosing is a standard procedure for any infant who has received **NEOSURF** suspension(P_aO_2 should be between 60-70 torr, P_aCO_2 should be kept between 35-45 torr and pH between 7.35-7.45). Avoid suctioning for 2 hours post-**NEOSURF** suspension, unless absolutely necessary. Due to the immediate effect of **NEOSURF** suspension on lung compliance and oxygenation, FiO_2 should be decreased accordingly, to prevent hyperoxia. Chest expansion should be observed closely and ventilatory pressures (PIP/PEEP) decreased accordingly. High oxygen saturation levels (>95%) or high $TcpO_2/TcpCO_2$ readings (as confirmed by comparison to blood gas measurements) indicate that the infant should be weaned off FiO_2, ventilator rates and pressures. Failure to wean appropriately may result in a pneumothorax.

Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucus plugging of the ETT, particularly if pulmonary secretions were prominent prior to drug administration. In addition, surfactant may promote the movement of resident mucus. If suctioning is unsuccessful in removing the obstruction, the blocked ETT should be replaced immediately.

Repeat Doses
Neonates can receive up to 3 additional doses of **NEOSURF** suspension within the first 5 days of life. The criteria for an additional dose are a positive response to the previous dose and an increase in respiratory support as signalled by a gradual increase in FiO_2. This increase must be at least 10% greater than the FiO_2 required after the initial response to the previous dose of **NEOSURF** suspension.

All infants exhibiting respiratory deterioration should be evaluated for a patent ductus arteriosus (PDA), pneumothorax and pulmonary haemorrhage before retreatment with **NEOSURF** suspension. The regimen for repeat doses is the same as for the initial dose. See **Dosing Procedures** for details.

CONTRAINDICATIONS
Use of **NEOSURF** suspension is contraindicated in infants with active pulmonary haemorrhage.

WARNINGS AND PRECAUTIONS
Drug interactions
There are no known drug interactions between **NEOSURF** suspension and other substances. **NEOSURF** suspension is not known to interfere with laboratory results.
Clinical experience with **NEOSURF** suspension has shown it to be safe and effective when used with nitric oxide therapy, high frequency oscillation and extracorporeal membranous oxygenation.

General
NEOSURF suspension is intended for **intratracheal** use only (**See DOSAGE and ADMINISTRATION**).
Use of NEOSURF suspension should be restricted to a highly supervised clinical setting with immediate availability of experienced neonatologists and other clinicians experienced with intubation, ventilator management and general care of premature infants.
The use of **NEOSURF suspension** in infants with birth weights less than 380 g or greater than 4460 g has not been evaluated in controlled trials.
A higher rate of sepsis has been described in those infants treated with **NEOSURF** suspension than those in the control arm. Physicians caring for these infants should be aware of this increased risk, take appropriate precautionary measures and be vigilant for any signs and symptoms of sepsis.

Carcinogenesis and Mutagenesis
No studies have been performed to investigate the carcinogenesis or mutagenesis of **NEOSURF** suspension.

Immunogenicity
Long-term studies comparing **NEOSURF** suspension to placebo (sham air) treatment demonstrated no significant differences in development of allergic manifestations.

Ophthalmologic
Hyperoxia may occur within minutes of administration of **NEOSURF** suspension. If hyperoxia develops and oxygen saturation is in excess of 95%, FiO_2 should be reduced until saturation is 90-95%, to decrease the risk of retinopathy of prematurity.

Respiratory
Vigilant clinical attention should be given to all infants prior to, during and after administration of **NEOSURF** suspension. Infants receiving **NEOSURF** suspension should be monitored for oxygenation with a transcutaneous oxygen probe or oxygen saturation monitor as well as occasional blood gas measurements. In addition, CO_2 (carbon dioxide) levels should be monitored with transcutaneous CO_2 probe correlated with blood gas readings.
NEOSURF suspension can rapidly affect oxygenation and lung compliance. If the improvement in chest expansion seems excessive, peak ventilator inspiratory pressures should be reduced immediately to avoid over distension and pulmonary air leaks. Monitor tidal volume after dosing, as sudden lung compliance may occur without much chest movement.
During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported (see **UNDESIRABLE EFFECTS**). If these occur, the dosing procedure should be stopped and appropriate measures to alleviate the condition initiated. After stabilization, the dosing procedure can be resumed.

Administration techniques used with other surfactant products, such as slow administration or the use of small test aliquots are not recommended with **NEOSURF** suspension. Unlike other products that require a slow drip to prevent reflux, **NEOSURF** suspension has a much lower viscosity and a higher protein content, both of which promote more rapid distribution. Slow administration may lead to uneven distribution, resulting in uneven lung compliance.

If the surfactant dose fails to subside in the ETT with additional pressures as recommended in the **DOSAGE AND ADMINISTRATION** section, consider the possibility of a mucus plug.

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Mucus Plugs: Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucus plugging of the ETT, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucus plugs obstructing the ETT. After dosing, exogenous surfactant may encourage the transport of resident mucus. If ETT obstruction from such plugs is suspected and suctioning is unsuccessful in removing the obstruction, the blocked ETT should be replaced immediately.

Monitoring and Laboratory Tests
Correction of acidosis, hypotension, hypoglycaemia and hypothermia is recommended prior to administration.

UNDESIRABLE EFFECTS
Adverse drug reaction overview
Very common adverse events occurring in ≥ 10% of infants who received **NEOSURF** (bovine lipid extract surfactant), in descending order of frequency, were patent ductus arteriosus, decreased post-dose pulmonary function values, intraventricular haemorrhage of all grades, sepsis, retinopathy of prematurity, bradycardia and severe intraventricular haemorrhage.

Common adverse events occurring in ≥ 1% and < 10% of infants who received **NEOSURF** in descending order of frequency, were pulmonary interstitial emphysema, periventricular leukomalacia, pneumothorax, pulmonary haemorrhage, endotracheal tube complications, necrotizing enterocolitis, respiratory acidosis, convulsions, hypotension, apnoea, hydrocephalus and pneumonia.

Due to the rapid effect of **NEOSURF** on lung compliance and oxygenation, infants should be monitored for respiratory parameters and any of the common adverse events.

Clinical trial adverse drug reactions
Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a double-blinded, comparative, multicentre clinical trial comparing the safety and efficacy of **NEOSURF** suspension and Exosurf Neonatal (colfosceril palmitate; Glaxo Wellcome), 568 infants received **NEOSURF** suspension and 565 received Exosurf as rescue treatment for NRDS.

Adverse events occurring in ≥1% of infants treated with **NEOSURF** suspension are summarized by body system and in order of descending frequency in Table 2, below. The incidence of these events in Exosurf-treated infants is provided for comparison.

Table 2
Adverse events in ≥1% of infants treated with NEOSURF suspension compared with infants treated with Exosurf Neonatal

Body System / Event	NEOSURF N = 568	Exosurf Neonatal N = 565	Statistically Significant p-value
Infections			
Sepsis	28%	23%	<0.05
Nervous System Disorders			
Intraventricular haemorrhage, total	29%	29%	
Intraventricular haemorrhage, Grades III and IV	12%	11%	
Periventricular leukomalacia	8%	7%	
Convulsion	2%	1%	
Hydrocephalus	1%	<1%	
Eye Disorders			
Retinopathy of prematurity	19%	20%	
Cardiac Disorders			
Patent ductus arteriosus	44%	44%	
Bradycardia	13%	15%	
Vascular Disorders			
Hypotension	2%	2%	
Respiratory Disorders			
Pulmonary interstitial emphysema	9%	17%	<0.0005
Pneumothorax	8%	12%	<0.05
Pulmonary haemorrhage	8%	7%	
Endotracheal tube complication	6%	6%	
Respiratory acidosis *	4%	2%	<0.05
Apnoea	2%	4%	
Pneumonia	1%	<1%	<0.05
Gastrointestinal Disorders			
Necrotizing enterocolitis	6%	7%	
Investigations			
Decreased pulmonary function **	39%	41%	

* Almost all incidences of respiratory acidosis occurred at one study site.
** The term "decreased pulmonary function" covered incidences of a fall in saturation or oxygenation, or an increase in CO_2 values after dosing.

The most frequent events reported to occur in either treatment group were patent ductus arteriosus in almost half of the infants and decreased pulmonary function (defined as incidences of a fall in saturation or oxygenation or an increase in CO_2 values after dosing) in approximately one-third of the infants. These events occurred with similar frequency in either treatment group and are anticipated complications when infants in distress are handled.
Sepsis and pneumonia occurred significantly more frequently in **NEOSURF** suspension-treated infants than in those who received Exosurf. Notwithstanding this higher incidence of sepsis, death due to infections was comparable between the two arms of the study.
Although the incidence of pulmonary haemorrhage was low (<1%) within the first two hours after dosing, it was observed to increase to 8% before discharge from intensive care. This was not significantly different from the incidence of pulmonary haemorrhage with Exosurf. For the 750 - 1250 gram birth weight group receiving **NEOSURF**, 7 of 32 deaths (22%) were attributed to pulmonary haemorrhage.
There was a significantly greater incidence of respiratory acidosis following treatment with **NEOSURF** suspension. All incidences of respiratory acidosis occurred within 2 hours of dosing and almost all incidences following either surfactant occurred at one study centre, perhaps due to too rapid weaning of the ventilatory pressure and rate with decreased minute ventilation.

Significantly fewer infants who received **NEOSURF** suspension developed pulmonary interstitial emphysema or pneumothorax than did those who were treated with Exosurf. This may reflect the increased ventilatory requirements of infants who received Exosurf. Thus, a reduction in ventilatory pressure following treatment with **NEOSURF** suspension may protect infants from pulmonary air leaks. Table 3, below, summarizes the adverse events that were reported to occur within 2 hours post-dose, in ≥1% of infants treated with **NEOSURF** suspension. The incidence of these events in Exosurf-treated infants is provided for comparison.

Table 3
Adverse events within 2 hours of dosing in ≥1% of infants treated with NEOSURF suspension or Exosurf Neonatal

Body System / Event	NEOSURF N = 568	Exosurf Neonatal N = 565	Statistically Significant p-value
Cardiac Disorders			
Bradycardia	11%	14%	
Respiratory System Disorders			
Endotracheal tube complications	6%	6%	
Respiratory acidosis*	4%	2%	< 0.05
Pulmonary haemorrhage	<1%	1%	
Investigations			
Decreased pulmonary function**	39%	41%	

* Almost all incidences of respiratory acidosis occurred at one study site.
** The term "decreased pulmonary function" covered incidences of a fall in saturation or oxygenation or an increase in CO_2 values.

Decreased pulmonary function (reported incidences of a fall in saturation or oxygenation or an increase in CO_2 values), bradycardia and endotracheal tube complications occurred with the same frequency in each treatment group and are commonly associated with the handling and treatment of premature infants. As discussed above, respiratory acidosis occurred, for the most part, at one site and may have been due to inadequate monitoring of lung compliance at that site.

Other adverse events that were reported to occur within 2 hours after administration of **NEOSURF** suspension, but at a frequency of <1% were: acidosis; hypertension; hypotension; hypoxia; patent ductus arteriosus; pneumonia; pneumothorax and pulmonary haemorrhage.

Less common clinical trial adverse drug reactions
Uncommon adverse events that were reported to occur in < 1% of infants treated with **NEOSURF** suspension were:

Infections and infestations: miscellaneous infections other than pneumonia.

Blood and lymphatic system: neonatal coagulation disorder, neonatal jaundice; thrombocytopenia.

Endocrine disorders: hypercalcaemia; hypoglycaemia.

Metabolism and nutritional: acidosis; hyperkalemia.

Nervous system disorders: abnormal electroencephalogram; cerebral infarction; encephalopathy; ependymitis; meningitis.

Cardiac disorders: cardiac arrest; cardiomegaly; cor pulmonale; hypertrophic cardiomyopathy; pneumopericardium; pulmonary oedema; pulmonary valve stenosis; supraventricular tachycardia.

Vascular disorders: haemorrhage; hypertension.

Respiratory disorders: asphyxia; bronchopulmonary dysplasia; hypoxia; pulmonary hypertension.

Gastrointestinal disorders: enteritis; gastrointestinal haemorrhage; gastrointestinal reflux; ileus; intestinal perforation; pneumoperitoneum.

Hepato-biliary disorders: hepatomegaly.

Skin disorders: cellulitis.

Renal and urinary disorders: anuria; hydronephrosis; hydroureter; nephrocalcinosis.

General disorders: growth retardation; neonatal hypothermia.

Abnormal hematologic and clinical chemistry findings
Laboratory values were not collected in clinical trials. However, respiratory acidosis was reported as an adverse event in 4% of infants receiving **NEOSURF** suspension and 2% of those receiving Exosurf (p<0.05). Respiratory acidosis occurred primarily at one study centre. Lung compliance and oxygenation should be monitored closely, as ventilation parameters may change rapidly after dosing

Post-market adverse drug reactions
No new adverse reactions have been reported, nor has there been an increase in the incidence of known adverse reactions identified in the clinical trials.

Three infants at one site, who were administered very small aliquots of 1 mL at a time without rotation of the infant, developed pulmonary haemorrhage, intraventricular haemorrhage and/or periventricular leukomalacia, and died. The very small doses given without rotation may have led to uneven surfactant distribution and uneven lung compliance.

OVERDOSAGE
No evidence of human overdose with **NEOSURF** suspension has been documented. Based on animal data, overdosage may result in acute airway obstruction.

SHELF-LIFE: See on pack

STORAGE AND HANDLING INSTRUCTIONS
On receipt of the vials, **NEOSURF** should be stored immediately as below:
Frozen (below –10°C); at this temperature, it has a shelf-life of 36 months.
or
In the refrigerator (2–8°C) for a maximum period of 10 months.
Store vials in their cartons until ready for use.
Unopened vials warmed to room temperature for less than 6 hours may be returned to their previous storage condition for a maximum of two times.

PACKAGING INFORMATION
NEOSURF suspension …… 5 ml vial
NEOSURF suspension …… 3 ml vial

Last updated January 2012

Cipla