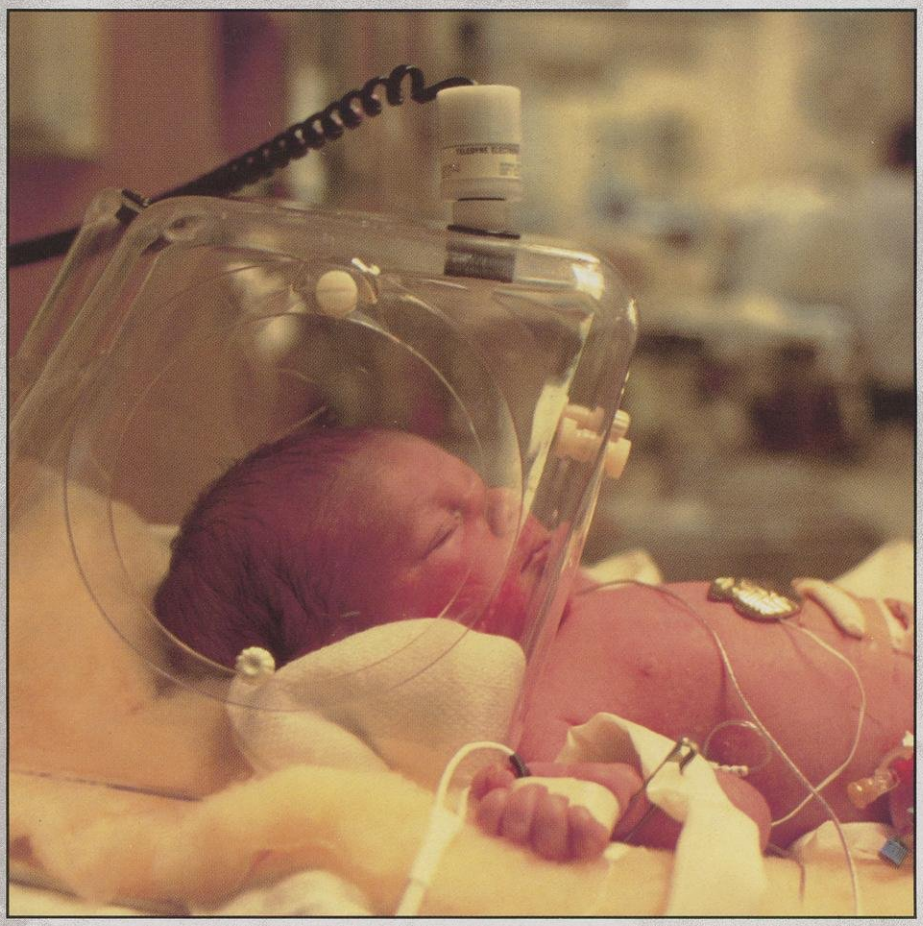
Exosurf Neonatal advertisement.

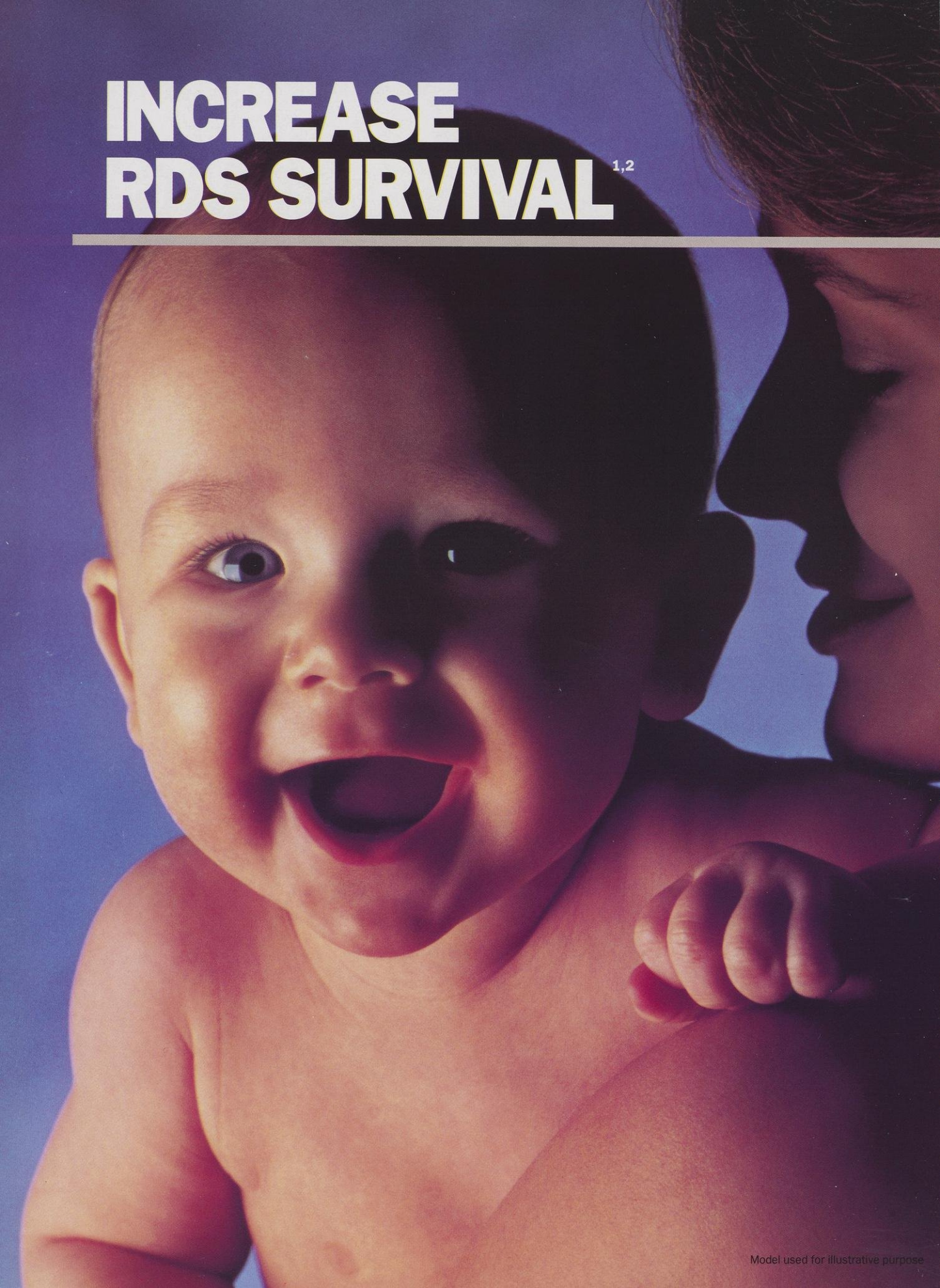
[s.l.]: [s.n.], 1989

SURVIVING RDS IS HARD ENOUGH...



THE LAST THING HE NEEDS IS IVH

INCREASE RDS SURVIVAL[1,2]

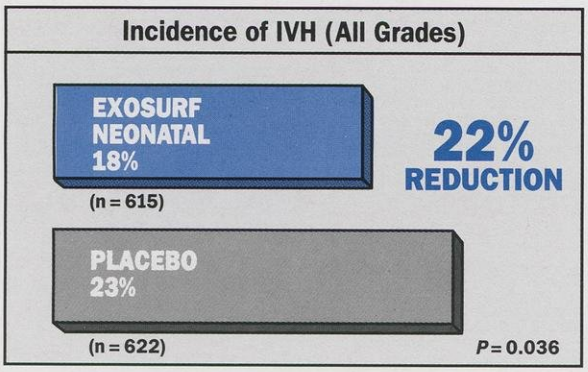


Model used for illustrative purpose

REDUCE THE RISK OF CEREBRAL HEMORRHAGE

Significant IVH Reduction in Infants ≥1250 g

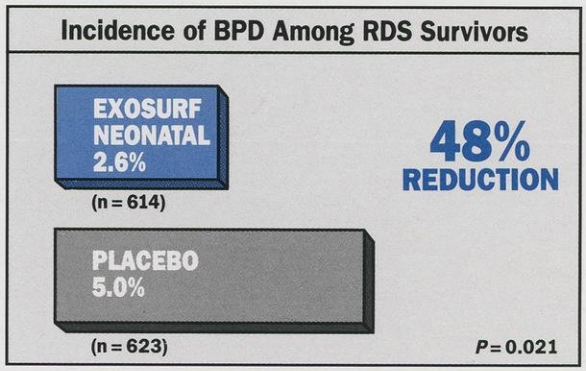
Despite successes in improving the survival of infants with RDS, intraventricular hemorrhage (IVH) remains a serious problem.[3-5] However, in a recently reported placebo-controlled rescue trial in infants ≥1250 g, EXOSURF Neonatal actually *reduced* the incidence of IVH.[2] In trials of smaller infants (<1250 g), EXOSURF Neonatal has never been observed to significantly increase IVH.



Two-dose treatment. Incidence of IVH in infants weighing 1250 g or more.
Adapted from Long et al[2] (p1700)

Significant BPD Reduction in Infants ≥1250 g

In the rescue trial involving over 1200 infants, administration of EXOSURF Neonatal significantly reduced the incidence of bronchopulmonary dysplasia (BPD) by nearly 50% ($P = 0.021$).



Two-dose treatment. Incidence of BPD in 28-day survivors following RDS in infants weighing 1250 g or more.
Adapted from Long et al[2] (p1699)

No Increase in Sepsis

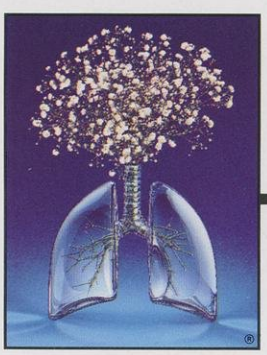
No difference in the incidence of sepsis has been seen with EXOSURF Neonatal during placebo-controlled trials (n = 1517). The rate of sepsis was similar in an open trial of 11,455 infants.[6]

No Animal Proteins

EXOSURF is purely synthetic and carries no known infectious or immunologic risks.

Other Safety Considerations

Various forms of pulmonary air leak were reduced in all controlled trials. A single controlled study in infants 500-699 g reported a significant increase in pulmonary hemorrhage.[7] Significant increases in apnea were reported in three controlled trials.[1,2,8] Apnea appears to be a marker for improved survival.[2]

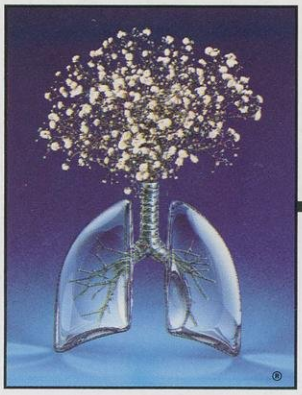


Exosurf® NEONATAL™
(Colfosceril Palmitate, Cetyl Alcohol, Tyloxapol) For Intratracheal Suspension/10-mL vial

INCREASES RDS SURVIVAL... REDUCES RISKS*

Please see brief summary of full prescribing information on following page.

*Increased pulmonary hemorrhage was noted in one trial of infants 500-699 g[7]; increased apnea has been noted in some trials.[1,2,8]



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PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING

INDICATIONS AND USAGE: Exosurf Neonatal is indicated for: 1. **Prophylactic** treatment of infants with birth weights of less than 1350 grams who are at risk of developing RDS (see PRECAUTIONS), 2. **Prophylactic** treatment of infants with birth weights greater than 1350 grams who have evidence of pulmonary immaturity, and 3. **Rescue** treatment of infants who have developed RDS.

CONTRAINDICATIONS: There are no known contraindications to treatment with Exosurf Neonatal.

WARNINGS: Intratracheal Administration Only: Exosurf Neonatal should be administered only by instillation into the trachea (see DOSAGE AND ADMINISTRATION). **General:** The use of Exosurf Neonatal requires expert clinical care by experienced neonatologists and other clinicians who are accomplished at neonatal intubation and ventilatory management. Adequate personnel, facilities, equipment, and medications are required to optimize perinatal outcome in premature infants. Vigilant clinical attention should be given to all infants prior to, during, and after administration of Exosurf Neonatal. **Acute Effects:** Exosurf Neonatal can rapidly affect oxygenation and lung compliance. **Lung Compliance:** If chest expansion improves substantially after dosing, peak ventilator inspiratory pressures should be reduced immediately, without waiting for confirmation of respiratory improvement by blood gas assessment. Failure to reduce inspiratory ventilator pressures rapidly in such instances can result in lung overdistention and fatal pulmonary air leak. **Hyperoxia:** If the infant becomes pink and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced in small but repeated steps (until saturation is 90 to 95%) without waiting for confirmation of elevated arterial pO_2 by blood gas assessment. Failure to reduce FiO_2 in such instances can result in hyperoxia. **Hypocarbia:** If arterial or transcutaneous CO_2 measurements are <30 torr, the ventilator rate should be reduced at once. Failure to reduce ventilator rates in such instances can result in marked hypocarbia, which is known to reduce brain blood flow. **Pulmonary Hemorrhage:** In the single study conducted in infants weighing <700 grams at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the Exosurf Neonatal group. None of the five studies involving infants with birth weights >700 grams showed a significant increase in pulmonary hemorrhage in the Exosurf Neonatal group. In a cross-study analysis of these five studies, fatal pulmonary hemorrhage occurred in three infants; two in the Exosurf Neonatal group and one in the placebo group. Mortality from all causes among infants who developed pulmonary hemorrhage was 43% in the placebo group and 37% in the Exosurf Neonatal group. Pulmonary hemorrhage in both Exosurf Neonatal and placebo infants was more frequent in infants who were younger, smaller, male, or who had a patent ductus arteriosus. Pulmonary hemorrhage typically occurred in the first 2 days of life in both treatment groups. **Mucous Plugs:** Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the endotracheal tube, particularly if pulmonary secretions were prominent prior to drug administration. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the endotracheal tube. If endotracheal tube obstruction from such plugs is suspected, and suctioning is unsuccessful in removing the obstruction, the blocked endotracheal tube should be replaced immediately.

PRECAUTIONS: General: In the controlled clinical studies, infants known prenatally or postnatally to have major congenital anomalies, or who were suspected of having congenital infection, were excluded from entry. However, these disorders cannot be recognized early in life in all cases, and a few infants with these conditions were entered. The benefits of Exosurf Neonatal in the affected infants who received drug appeared to be similar to the benefits observed in infants without anomalies or occult infection. **Prophylactic Treatment—Infants <700 Grams:** In infants weighing 500 to 700 grams, a single prophylactic dose of Exosurf Neonatal significantly: improved FiO_2 and ventilator settings, reduced pneumothorax, and reduced death from RDS, but increased pulmonary hemorrhage (see WARNINGS). Overall mortality did not differ significantly between the placebo and Exosurf Neonatal groups. Data on multiple doses in infants in this weight class are not yet available. **Rescue Treatment—Number of Doses:** A small number of infants with RDS have received more than two doses of Exosurf Neonatal as rescue treatment. Definitive data on the safety and efficacy of these additional doses are not available. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Exosurf Neonatal at concentrations up to 10,000 μg/plate was not mutagenic in the Ames Salmonella assay. Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Exosurf Neonatal. The effects of Exosurf Neonatal on fertility have not been studied.

ADVERSE REACTIONS:
General: Premature birth is associated with a high incidence of morbidity and mortality. Despite significant reductions in overall mortality associated with Exosurf Neonatal, some infants who received Exosurf Neonatal developed severe complications and either survived with permanent handicaps or died. In controlled clinical studies evaluating the safety and efficacy of Exosurf Neonatal, numerous safety assessments were made. In infants receiving Exosurf Neonatal, pulmonary hemorrhage, apnea and use of methylxanthines were increased. A number of other adverse events were significantly reduced in the Exosurf Neonatal group, particularly various forms of pulmonary air leak and use of pancuronium. ***Reflux:*** Reflux of Exosurf Neonatal into the endotracheal tube during dosing has been observed and may be associated with rapid drug administration. If reflux occurs, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until the endotracheal tube clears. ***>20% Drop in Transcutaneous Oxygen Saturation:*** If transcutaneous oxygen saturation declines during dosing, drug administration should be halted and, if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O for 1 to 2 minutes. In addition, increases of FiO_2 may be required for 1 to 2 minutes.

DOSAGE AND ADMINISTRATION: Preparation of Suspension: Exosurf Neonatal is best reconstituted immediately before use because it does not contain antibacterial preservatives. However, the reconstituted suspension is chemically and physically stable when stored at 2° to 30°C (36° to 86°F) for up to 12 hours following reconstitution. Solutions containing buffers or preservatives should not be used for reconstitution. **Do Not Use Bacteriostatic Water for Injection, USP.** Each vial of Exosurf Neonatal should be reconstituted only with **8 mL** of the accompanying diluent (preservative-free Sterile Water for Injection). **Dosage: Accurate determination of weight at birth is the key to accurate dosing.** ***Prophylactic Treatment:*** The first dose of Exosurf Neonatal should be administered as a single 5 mL/kg dose as soon as possible after birth. Second and third doses should be administered approximately 12 and 24 hours later to all infants who remain on mechanical ventilation at those times. ***Rescue Treatment:*** Exosurf Neonatal should be administered in two 5 mL/kg doses. The initial dose should be administered as soon as possible after the diagnosis of RDS is confirmed. The second dose should be administered approximately 12 hours following the first dose, provided the infant remains on mechanical ventilation. **Use of Special Endotracheal Tube Adapter:** With each vial of Exosurf Neonatal for Intratracheal Suspension, five different sized endotracheal tube adapters each with a special right angle Luer®-lock sideport are supplied. The adapters are clean but not sterile. **Administration:** The infant should be suctioned prior to administration of Exosurf Neonatal. Exosurf Neonatal suspension is administered via the sideport on the special endotracheal tube adapter **WITHOUT INTERRUPTING MECHANICAL VENTILATION.** Each Exosurf Neonatal dose is administered in two 2.5 mL/kg half-doses. Each half-dose is instilled slowly over 1 to 2 minutes (30 to 50 mechanical breaths) in small bursts timed with inspiration. After the first 2.5 mL/kg half-dose is administered in the midline position, the infant's head and torso are turned 45° to the **right** for 30 seconds while mechanical ventilation is continued. After the infant is returned to the midline position, the second 2.5 mL/kg half-dose is given in an identical fashion over another 1 to 2 minutes. The infant's head and torso are then turned 45° to the **left** for 30 seconds while mechanical ventilation is continued, and the infant is then turned back to the midline position. These maneuvers allow gravity to assist in the distribution of Exosurf Neonatal in the lungs. During dosing, heart rate, color, chest expansion, facial expressions, the oximeter, and the endotracheal tube patency and position should be monitored. **Suctioning should not be performed for two hours after Exosurf Neonatal is administered, except when dictated by clinical necessity.**

HOW SUPPLIED: Exosurf Neonatal for Intratracheal Suspension is supplied in a carton containing one 10 mL vial of Exosurf Neonatal for Intratracheal Suspension, one 10 mL vial of Sterile Water for Injection, and five endotracheal tube adapters (2.5, 3.0, 3.5, 4.0, and 4.5 mm I.D.). (NDC 0081-0207-01). Store Exosurf Neonatal for Intratracheal Suspension at 15° to 30°C (59° to 86°F) in a dry place.

EDUCATIONAL MATERIAL: A videotape on dosing is available from your Burroughs Wellcome Co. representative. This videotape demonstrates techniques for safe administration of Exosurf Neonatal and should be viewed by health care professionals who will administer the drug.

Licensed under U.S. Patent Nos. 4312860 and 4826821 500009

References: 1. Long W, Thompson T, Sundell H, et al. Effects of two rescue doses of a synthetic surfactant on mortality rate and survival without bronchopulmonary dysplasia in 700- to 1350-gram infants with respiratory distress syndrome. *J Pediatr.* 1991;118:595-605. **2.** Long W, Corbet A, Cotton R, et al. A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. *N Engl J Med.* 1991;325:1696-1703. **3.** Speer CP, Robertson B, Curstedt T, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. *Pediatrics.* 1992;89:13-20. **4.** Horbar JD, Soll RF, Schachinger H, et al. A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome. *Eur J Pediatr.* 1990;149:416-423. **5.** Cowan F, Whitelaw A, Wertheim D, Silverman M. Cerebral blood flow velocity changes after rapid administration of surfactant. *Arch Dis Child.* 1991;66:1105-1109. **6.** Russell L, White A, Andrews E, et al. Observational study of synthetic surfactant in 11,455 infants. Presented at the 1992 Meeting of the American Pediatric Society/Society for Pediatric Research; May 4-7, 1992; Baltimore, MD. **7.** Stevenson D, Walther F, Long W, et al. Controlled trial of a single dose of synthetic surfactant at birth in premature infants weighing 500 to 699 grams. *J Pediatr.* 1992;120:S3-S12. **8.** Corbet A, Bucciarelli R, Goldman S, et al. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multicenter controlled trial. *J Pediatr.* 1991;118:277-284.

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