NDA 20-044/s-004

Glaxo Wellcome Inc.
Five Moore Drive
P0 Box 13398
Research Triangle Park, NC 27709

Attention: Sara Nelson
Associate Director, Regulatory Affairs

Dear Ms. Nelson:

Please refer to your supplemental new drug application dated July 30, 1999, received August 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exosurf (colfosceril) Neonatal for Intratracheal Suspension.

This supplemental new drug application addresses the geriatric use experience with this product.

We have completed the review of this supplemental application. And have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text, with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

1. In the heading on the first page of the PI, increase the prominence of the drug name.
2. Under CLINICAL PHARMACOLOGY, subsection “Prophylactic Treatment,” correct the error in Table 1. In the column under “Single Dose 700 to 1100 g” and “Exosurf n=224” and in line “Death through 1 year,” there is a number which should be "20‡."
3. Under PRECAUTIONS, subsection “Carcinogenesis, Mutagenesis, Impairment of Fertility,” delete the phrase “...at concentrations up to 10000 mcg/plate.”

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted July 30, 1999). These revisions are terms of the approval of this application.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-044/s-004.” Approval of this submission by FDA is not required before the labeling is used.

EXOSURF NEONATAL®

PRODUCT INFORMATION

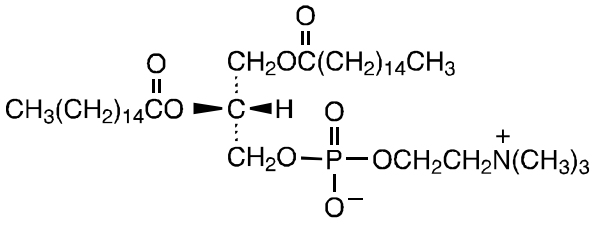
(colfosceril palmitate, cetyl alcohol, tyloxapol) for Intratracheal Suspension

DESCRIPTION: EXOSURF NEONATAL (colfosceril palmitate, cetyl alcohol, tyloxapol) for Intratracheal Suspension is a protein-free synthetic lung surfactant stored under vacuum as a sterile lyophilized powder. EXOSURF NEONATAL is reconstituted with preservative-free Sterile Water for Injection prior to administration by intratracheal instillation. Each 10-mL vial contains 108 mg colfosceril palmitate, commonly known as dipalmitoylphosphatidylcholine (DPPC), 12 mg cetyl alcohol, 8 mg tyloxapol, and 47 mg sodium chloride. Sodium hydroxide or hydrochloric acid may have been added to adjust pH. When reconstituted with 8 mL Sterile Water for Injection, the EXOSURF NEONATAL suspension contains 13.5 mg/mL colfosceril palmitate, 1.5 mg/mL cetyl alcohol, and 1 mg/mL tyloxapol in 0.1 N NaCl. The suspension appears milky white with a pH of 5 to 7 and an osmolality of 185 mOsm/kg.

The chemical names and structural formulas of the components of EXOSURF NEONATAL are as follows:

colfosceril palmitate

(*R*)-4-hydroxy-*N,N,N*-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacosan-1-aminium hydroxide inner salt, 4-oxide



cetyl alcohol

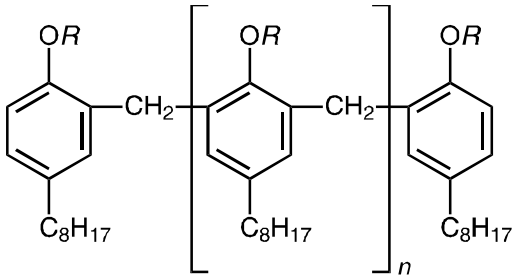
(1-hexadecanol)

$CH_3(CH_2)_{14}CH_2OH$

tyloxapol

4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane

EXOSURF NEONATAL®
(colfosceril palmitate, cetyl alcohol, tyloxapol)
for Intratracheal Suspension



[*R* is $CH_2CH_2O(CH_2CH_2O)_mCH_2CH_2OH$;
m is 6 to 8; *n* is not more than 5]

CLINICAL PHARMACOLOGY: Surfactant deficiency is an important factor in the development of the neonatal respiratory distress syndrome (RDS). Thus, surfactant replacement therapy early in the course of RDS should ameliorate the disease and improve symptoms. Natural surfactant, a combination of lipids and apoproteins, exhibits not only surface tension reducing properties (conferred by the lipids), but also rapid spreading and adsorption (conferred by the apoproteins). The major fraction of the lipid component of natural surfactant is DPPC, which comprises up to 70% of natural surfactant by weight.

Although DPPC reduces surface tension, DPPC alone is ineffective in RDS because DPPC spreads and adsorbs poorly. In EXOSURF NEONATAL, which is protein free, cetyl alcohol acts as the spreading agent for the DPPC on the air-fluid interface. Tyloxapol, a polymeric long-chain repeating alcohol, is a nonionic surfactant which acts to disperse both DPPC and cetyl alcohol. Sodium chloride is added to adjust osmolality.

Pharmacokinetics: EXOSURF NEONATAL is administered directly into the trachea. Human pharmacokinetic studies of the absorption, biotransformation, and excretion of the components of EXOSURF NEONATAL have not been performed. Nonclinical studies, however, have shown that DPPC can be absorbed from the alveolus into lung tissue where it can be catabolized extensively and reutilized for further phospholipid synthesis and secretion. In the developing rabbit, 90% of alveolar phospholipids are recycled. In premature rabbits, the alveolar half-life of intratracheally administered H^3-labeled phosphatidylcholine is approximately 12 hours.

Animal Studies: In animal models of RDS, treatment with EXOSURF NEONATAL significantly improved lung volume, compliance, and gas exchange in premature rabbits and lambs. The amount and distribution of lung water were not affected by treatment with EXOSURF NEONATAL of premature rabbit pups. The extent of lung injury in premature rabbit pups undergoing mechanical ventilation was reduced significantly by treatment with EXOSURF NEONATAL. In premature lambs, neither systemic blood flow nor flow through the ductus arteriosus were affected by treatment with EXOSURF NEONATAL. Survival was significantly better in both premature rabbits and premature lambs treated with EXOSURF NEONATAL.

Clinical Studies: EXOSURF NEONATAL has been studied in the United States and Canada in controlled clinical trials involving more than 4400 infants. Over 10 000 infants have received EXOSURF NEONATAL through an open, uncontrolled, North American study designed to provide the drug to premature infants who might benefit and to obtain additional safety information (EXOSURF NEONATAL Treatment IND).

Prophylactic Treatment: The efficacy of a single dose of EXOSURF NEONATAL in prophylactic treatment of infants at risk of developing RDS was examined in three double-blind, placebo-controlled studies, one involving 215 infants weighing 500 to 700 g, one involving 385 infants weighing 700 to 1350 g, and one involving 446 infants weighing 700 to 1100 g. The infants were intubated and placed on mechanical ventilation, and received 5 mL/kg of EXOSURF NEONATAL or placebo (air) within 30 minutes of birth.

The efficacy of one versus three doses of EXOSURF NEONATAL in prophylactic treatment of infants at risk of developing RDS was examined in a double-blind, placebo-controlled study of 823 infants weighing 700 to 1100 g. The infants were intubated and placed on mechanical ventilation, and received a first 5-mL/kg dose of EXOSURF NEONATAL within 30 minutes. Repeat 5-mL/kg doses of EXOSURF NEONATAL or placebo (air) were given to all infants who remained on mechanical ventilation at approximately 12 and 24 hours of age. An initial analysis of 716 infants is available.

The major efficacy parameters from these studies are presented in Table 1.

Table 1: Efficacy Assessments— Prophylactic Treatment

Number of Doses:	Single Dose		Single Dose		Single Dose		1 vs 3 Doses	
Birth Weight Range:	500 to 700 g		700 to 1350 g		700 to 1100 g		700 to 1100 g	
Treatment Group:	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF	EXOSURF 1 Dose	EXOSURF 3 Doses
Number of Infants:	n = 106	n = 109	n = 185	n = 176	n = 222	n = 224	n = 356	n = 360
	% of Infants		% of Infants		% of Infants		% of Infants	
Death ≤ day 28*	53	50	11	6	21	15	16	9[†]
Death through 1 year*	59	60	14	11	30	20[#]	17	12[†]
Death from RDS[§]	25	13[†]	4	3	10	5[‖]	3	2
Intact cardiopulmonary survival*,[¶]	29	25	69	78[†]	65	68	74	78
Bronchopulmonary dysplasia *,[#]	43	44	23	18	19	21	8	12
RDS Incidence[§]	73	81	46	42	55	55	63	68

* "Intent-to-treat" analyses (as randomized) except for the 700 to 1350 -g, single-dose study in which infants with congenital infections and anomalies were excluded.

† $P<0.05$.

‡ $P<0.01$.

§ "As-treated" analyses.

‖ $P = 0.051$.

¶ Defined by survival through 28 days of life without bronchopulmonary dysplasia.

Defined by a combination of clinical and radiographic criteria.

Rescue Treatment: The efficacy of EXOSURF NEONATAL in the rescue treatment of infants with RDS was examined in two double-blind, placebo-controlled studies. One study enrolled 419 infants weighing 700

to 1350 g; the second enrolled 1237 infants weighing 1250 g and above. In the rescue treatment studies, infants received an initial dose (5 mL/kg) of EXOSURF NEONATAL or placebo (air) between 2 and 24 hours of life followed by a second dose (5 mL/kg) approximately 12 hours later to infants who remained on mechanical ventilation. The major efficacy parameters from these studies are presented in Table 2.

Table 2: Efficacy Assessments— Rescue Treatment

Number of Doses:	2 Doses		2 Doses	
Birth Weight Range:	700 to 1350 g		1250 g and above	
Treatment Group:	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF
Number of Infants:	n = 213	n = 206	n = 623	n = 614
	% of Infants		% of Infants	
Death ≤ day 28*	23	11†	7	4‡
Death through 1 year*	27	15†	9	6§
Death from RDS‖	10	3¶	3	1‡
Intact cardiopulmonary survival*,#	62	75¶	88	93¶
Bronchopulmonary Dysplasia*,**	18	15	6	3‡

* "Intent-to-treat" analyses (as randomized).

† $P<0.001$.

‡ $P<0.05$.

§ $P = 0.067$.

‖ "As-treated" analyses.

¶ $P<0.01$.

Defined by survival through 28 days of life without bronchopulmonary dysplasia.

** Defined by a combination of clinical and radiographic criteria.

Clinical Results: In these six controlled clinical studies, infants in the group receiving EXOSURF NEONATAL showed significant improvements in FiO_2 and ventilator settings that persisted for at least 7 days. Pulmonary air leaks were significantly reduced in each study. Five of these studies also showed a significant reduction in death from RDS. Further, overall mortality was reduced for all infants weighing >700 g. The one- versus three-dose prophylactic treatment study in 700 to 1100-g infants showed a further reduction in overall mortality with two additional doses.

Safety information is presented in Tables 3 and 4 (see ADVERSE REACTIONS). Beneficial effects in the group receiving EXOSURF NEONATAL were observed for some safety assessments. Various forms of pulmonary air leak and use of pancuronium were reduced in infants receiving EXOSURF NEONATAL in all six studies.

Follow-up data at 1 year adjusted age are available on 1094 of 2470 surviving infants. Growth and development of infants who received EXOSURF NEONATAL in this sample were comparable to infants who received placebo.

EXOSURF NEONATAL®
(colfosceril palmitate, cetyl alcohol, tyloxapol)
for Intratracheal Suspension

INDICATIONS AND USAGE: EXOSURF NEONATAL is indicated for:

1. **Prophylactic** treatment of infants with birth weights of less than 1350 g who are at risk of developing RDS (see PRECAUTIONS),
2. **Prophylactic** treatment of infants with birth weights greater than 1350 g who have evidence of pulmonary immaturity, and
3. **Rescue** treatment of infants who have developed RDS.

For **prophylactic** treatment, the first dose of EXOSURF NEONATAL should be administered as soon as possible after birth (see DOSAGE AND ADMINISTRATION: General Guidelines for Administration).

Infants considered as candidates for **rescue** treatment with EXOSURF NEONATAL should be on mechanical ventilation and have a diagnosis of RDS by both of the following criteria:

1. Respiratory distress not attributable to causes other than RDS, based on clinical and laboratory assessments.
2. Chest radiographic findings consistent with the diagnosis of RDS.

During the clinical development of EXOSURF NEONATAL, all infants who received the drug were intubated and on mechanical ventilation. For three-dose prophylactic treatment with EXOSURF NEONATAL, the first dose of drug was administered as soon as possible after birth and repeat doses were given at approximately 12 and 24 hours after birth if infants remained on mechanical ventilation at those times. For rescue treatment, two doses were given; one between 2 and 24 hours of life, and a second approximately 12 hours later if infants remained on mechanical ventilation. Infants who received rescue treatment with EXOSURF NEONATAL had a documented arterial to alveolar oxygen tension ratio (a/A) <0.22.

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.

Instillation of EXOSURF NEONATAL should be performed **only** by trained medical personnel experienced in airway and clinical management of unstable 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 g at birth, the incidence of pulmonary hemorrhage (10% vs 2% in the placebo group) was significantly increased in the group receiving EXOSURF NEONATAL. None of the five studies involving infants with birth weights >700 g showed a significant increase in pulmonary hemorrhage in the group receiving EXOSURF NEONATAL. In a cross-study analysis of these five studies, pulmonary hemorrhage was reported for 1% (14/1420) of infants in the placebo group and 2% (27/1411) of infants in the group receiving EXOSURF NEONATAL. Fatal pulmonary hemorrhage occurred in three infants; two in the group receiving EXOSURF NEONATAL 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 group receiving EXOSURF NEONATAL.

Pulmonary hemorrhage in infants treated with either EXOSURF NEONATAL or placebo 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.

In more than 7700 infants in the open, uncontrolled study, pulmonary hemorrhage was reported in 4%, but fatal pulmonary hemorrhage was reported rarely (0.4%).

In the controlled clinical studies, infants treated with EXOSURF NEONATAL who received steroids more than 24 hours prior to delivery or indomethacin postnatally had a lower rate of pulmonary hemorrhage than other infants treated with EXOSURF NEONATAL. Attention should be paid to early and aggressive diagnosis and treatment (unless contraindicated) of patent ductus arteriosus during the first 2 days of life (while the ductus arteriosus is often clinically silent). Other potentially protective measures include attempting to decrease FiO_2 preferentially over ventilator pressures during the first 24 to 48 hours after dosing, and attempting to decrease PEEP minimally for at least 48 hours after dosing.

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 g, 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 group receiving placebo and the group receiving EXOSURF NEONATAL (see Table 1). Data on multiple doses in infants in this weight class are not yet available. Accordingly, clinicians should carefully evaluate the potential risks and benefits of administration of EXOSURF NEONATAL in these infants.

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 mcg/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 group receiving EXOSURF NEONATAL, particularly various forms of pulmonary air leak and use of pancuronium (see CLINICAL PHARMACOLOGY: Clinical Results). Tables 3 and 4 summarize the results of the major safety evaluations from the controlled clinical studies.

Table 3: Safety Assessments*— Prophylactic Treatment

Number of Doses:	Single Dose		Single Dose		Single Dose		1 vs 3 Doses	
Birth Weight Range:	500 to 700 g		700 to 1350 g		700 to 1100 g		700 to 1100 g	
Treatment Group:	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF	EXOSURF 1 Dose	EXOSURF 3 Doses
Number of Infants:	n = 108	n = 107	n=193	n = 192	n = 222	n = 224	n = 356	n = 360
	% of Infants		% of Infants		% of Infants		% of Infants	
Intraventricular hemorrhage (IVH)								
Overall	51	57	31	27	36	36	38	35
Severe IVH	26	25	10	8	13	14	9	9
Pulmonary air leak (PAL)								
Overall	52	48	16	11	32	25	29	27
Pneumothorax	23	10†	5	6	19	11†	14	12
Pneumopericardium	1	4	2	0	<1	1	1	1
Pneumomediastinum	2	1	2	3	7	1‡	3	2
Pulmonary interstitial emphysema	43	44	13	7†	26	20	23	22
Death from PAL	4	6	<1	<1	2	1	2	1
Patent ductus arteriosus	49	53	66	70	50	55	59	57
Necrotizing enterocolitis	2	4	11	13	3	4	6	2†
Pulmonary hemorrhage	2	10‡	2	4	1	4	4	6
Congenital pneumonia	4	4	2	4	2	2	1	1
Nosocomial pneumonia	10	10	2	4	4	7	14	15
Nonpulmonary infections	33	35	34	39	28	29	35	34
Sepsis	30	34	30	34	23	24	30	27
Death from sepsis	4	4	3	3	1	2	3	2
Meningitis	4	6	3	1	2	3	1	2
Other infections	7	4	5	3	6	10	10	11
Major anomalies	3	1	2	4	7	4	4	4
Hypotension	70	77	52	47	59	62	54	50
Hyperbilirubinemia	22	21	63	61	27	31	20	21
Exchange transfusion	4	3	1	2	2	2	3	1
Thrombocytopenia§	21	25	not available		9	8	12	10
Persistent fetal circulation	0	1	1	1	0	2†	1	<1
Seizures	11	8	2	2	11	9	6	5
Apnea	34	33	76	73	55	65†	62	68
Drug therapy								
Antibiotics	96	99	98	96	98	99	>99	99

Diuretics	55	60	39	37	59	63	64	65
Anticonvulsants	14	18	23	24	20	16	9	8
Inotropes	46	40	20	20	26	20	28	27
Sedatives	62	71	65	64	63	57	52	52
Pancuronium	19	11	22	14†	19	13†	15	11
Methylxanthines	38	43	77	77	61	72†	75	82†

*All parameters were examined with "as-treated" analyses.

†$P<0.05$.

‡$P<0.01$.

§Thrombocytopenia requiring platelet transfusion.

Table 4: Safety Assessments*— Rescue Treatment

Number of Doses:	2 Doses		2 Doses	
Birth Weight Range:	700 to 1350 g		1250 g and above	
Treatment Group:	Placebo (Air)	EXOSURF	Placebo (Air)	EXOSURF
Number of Infants:	n = 213	n = 206	n = 622	n = 615
	% of Infants		% of Infants	
Intraventricular hemorrhage (IVH)				
Overall	48	52	23	18†
Severe IVH	13	9	5	4
Pulmonary air leak (PAL)				
Overall	54	34‡	30	18‡
Pneumothorax	29	20†	20	10‡
Pneumopericardium	4	1	1	2
Pneumomediastinum	8	4	5	2§
Pulmonary interstitial emphysema	48	25‡	24	13‡
Death from PAL	7	3	<1	1
Patent ductus arteriosus	66	57	54	45†
Necrotizing enterocolitis	3	3	1	2
Pulmonary hemorrhage	3	1	<1	1
Congenital pneumonia	2	3	2	2
Nosocomial pneumonia	5	7	2	2
Nonpulmonary infections	19	22	13	13
Sepsis	15	17	8	8
Death from sepsis	<1	<1	1	<1
Meningitis	1	<1	1	<1†
Other infections	5	8	5	6
Major anomalies	3	3	4	4
Hypotension	62	57	50	39§
Hyperbilirubinemia	17	19	12	10
Exchange transfusion	3	4	1	2
Thrombocytopenia‖	10	11	4	<1§
Persistent fetal circulation	1	1	6	2§
Seizures	10	10	6	3†
Apnea	48	65§	37	44†
Drug therapy				
Antibiotics	100	99	98	98
Diuretics	60	65	45	34‡
Anticonvulsants	17	17	10	5§
Inotropes	36	31	27	16‡

Sedatives	72	68	76	64‡
Pancuronium	34	17§	33	15‡
Methylxanthines	62	74§	49	53

*All parameters were examined with "as-treated" analyses.

†$P<0.05$.

‡$P<0.001$.

§$P<0.01$.

||Thrombocytopenia requiring platelet transfusion.

Pulmonary Hemorrhage: See WARNINGS.

Abnormal Laboratory Values: Abnormal laboratory values are common in critically ill, mechanically ventilated, premature infants. A higher incidence of abnormal laboratory values in the group receiving EXOSURF NEONATAL was not reported.

Events During Dosing: Data on events during dosing are available from more than 8800 infants in the open, uncontrolled clinical study (Table 5).

Table 5: Events During Dosing in the Open, Uncontrolled Study*

Treatment Type: Number of Infants:	Prophylactic Treatment n = 1127	Rescue Treatment n = 7711
	% of Infants	% of Infants
Reflux of EXOSURF NEONATAL	20	31
Drop in O_2 saturation (≥20%)	6	22
Rise in O_2 saturation (≥10%)	5	6
Drop in transcutaneous pO_2 (≥20 mm Hg)	1	8
Rise in transcutaneous pO_2 (≥20 mm Hg)	2	5
Drop in transcutaneous pCO_2 (≥20 mm Hg)	<1	1
Rise in transcutaneous pCO_2 (≥20 mm Hg)	1	3
Bradycardia (<60 beats/min)	1	3
Tachycardia (>200 beats/min)	<1	<1
Gagging	1	5
Mucous plugs	<1	<1

*Infants may have experienced more than one event. Investigators were prohibited from adjusting FiO_2 and/or ventilator settings during dosing unless significant clinical deterioration occurred.

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.

Greater Than Twenty Percent 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.

Mucous Plugs: See WARNINGS.

OVERDOSAGE: There have been no reports of massive overdosage with EXOSURF NEONATAL.

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 and remains sterile (when reconstituted using aseptic techniques) 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) as follows:

1. Fill a 10- or 12-mL syringe with 8 mL of preservative-free Sterile Water for Injection using an 18- or 19-gauge needle;
2. Allow the vacuum in the vial to draw the Sterile Water into the vial ;
3. Aspirate as much as possible of the 8 mL out of the vial into the syringe (while maintaining the vacuum), then SUDDENLY release the syringe plunger.

Step 3 should be repeated three or four times to assure adequate mixing of the vial contents. If vacuum is not present, the vial of EXOSURF NEONATAL should not be used.

The appropriate dosage volume for the entire dose (5 mL/kg) should then be drawn into the syringe from **below** the froth in the vial (again maintaining the vacuum). If the infant weighs less than 1600 g, unused EXOSURF NEONATAL suspension will remain in the vial after the entire dose is drawn into the syringe. If the infant weighs more than 1600 g, at least two vials will be required for each dose.

Reconstituted EXOSURF NEONATAL is a milky white suspension with a total volume of 8 mL per vial. Each milliliter of reconstituted EXOSURF NEONATAL contains 13.5 mg colfosceril palmitate, 1.5 mg cetyl alcohol, 1 mg tyloxapol, and sodium chloride to provide a 0.1 N concentration. If the suspension appears to separate, gently shake or swirl the vial to resuspend the preparation. The reconstituted product should be inspected visually for homogeneity immediately before administration; if persistent large flakes or particulates are present, the vial should not be used.

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 administeredapproximately 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. 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 (see PRECAUTIONS).

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. The adapters should be used as follows:

1. Select an adapter size that corresponds to the inside diameter of the endotracheal tube.
2. Insert the adapter into the endotracheal tube with a firm push-twist motion.
3. Connect the breathing circuit wye to the adapter.
4. Remove the cap from the sideport on the adapter. Attach the syringe containing drug to the sideport.
5. After completion of dosing, remove the syringe and RECAP THE SIDEPORT.

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 dose of EXOSURF NEONATAL 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. If heart rate slows, the infant becomes dusky or agitated, transcutaneous oxygen saturation falls more than 15%, or EXOSURF NEONATAL backs up in the endotracheal tube, dosing should be slowed or halted and, if necessary, the peak inspiratory pressure, ventilator rate, and/or FiO_2 turned up. On the other hand, rapid improvements in lung function may require immediate reductions in peak inspiratory pressure, ventilator rate, and/or FiO_2. (See WARNINGS and see below for additional information concerning administration.)

Suctioning should not be performed for two hours after EXOSURF NEONATAL is administered, except when dictated by clinical necessity.

General Guidelines for Administration: Administration of EXOSURF NEONATAL should not take precedence over clinical assessment and stabilization of critically ill infants.

Intubation: Prior to dosing with EXOSURF NEONATAL, it is important to ensure that the endotracheal tube tip is in the trachea and not in the esophagus or right or left mainstem bronchus. Brisk and symmetrical chest movement with each mechanical inspiration should be confirmed prior to dosing, as should equal breath sounds in the two axillae. In prophylactic treatment, dosing with EXOSURF NEONATAL need not be delayed for radiographic confirmation of the endotracheal tube tip position. In rescue treatment, bedside

confirmation of endotracheal tube tip position is usually sufficient, if at least one chest radiograph subsequent to the last intubation confirmed proper position of the endotracheal tube tip. Some lung areas will remain undosed if the endotracheal tube tip is too low.

Monitoring: Continuous electrocardiogram and transcutaneous oxygen saturation monitoring during dosing are essential. In most infants treated prophylactically, it should be possible to initiate such monitoring prior to administration of the first dose of EXOSURF NEONATAL. For subsequent prophylactic and all rescue doses, arterial blood pressure monitoring during dosing is also highly desirable. After both prophylactic and rescue dosing, frequent arterial blood gas sampling is required to prevent post-dosing hyperoxia and hypocarbia (see WARNINGS).

Ventilatory Support During Dosing: The 5-mL/kg dosage volume may cause transient impairment of gas exchange by physical blockage of the airway, particularly in infants on low ventilator settings. As a result, infants may exhibit a drop in oxygen saturation during dosing, especially if they are on low ventilator settings prior to dosing. These transient effects are easily overcome by increasing peak inspiratory pressure on the ventilator by 4 to 5 cm H_2O for 1 to 2 minutes during dosing. FiO_2 can also be increased if necessary. In infants who are particularly fragile or reactive to external stimuli, increasing peak inspiratory pressure by 4 to 5 cm H_2O and/or FiO_2 20% just prior to dosing may minimize any transient deterioration in oxygenation. However, in virtually all cases it should be possible to return the infant to predose settings within a very short time of dose completion.

Postdosing: At the end of dosing, position of the endotracheal tube should be confirmed by listening for equal breath sounds in the two axillae. Attention should be paid to chest expansion, color, transcutaneous saturation, and arterial blood gases. Some infants who receive EXOSURF NEONATAL and other surfactants respond with rapid improvements in pulmonary compliance, minute ventilation, and gas exchange (see WARNINGS). Constant bedside attention of an experienced clinician for at least 30 minutes after dosing is essential. Frequent blood gas sampling also is absolutely essential. Rapid changes in lung function require immediate changes in peak inspiratory pressure, ventilator rate, and/or FiO_2.

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 0173 -0207-01).

Store EXOSURF NEONATAL for Intratracheal Suspension at 15° to 30°C (59° to 86°F) in a dry place.

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