

PRODUCT MONOGRAPH

PrSURVANTA[®]

beractant, intratracheal suspension

100 mg phospholipids/4 mL and 200 mg phospholipids/8 mL

Lung Surfactant (Bovine)

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SURVANTA[®]

beractant, intratracheal suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intratracheal	100 mg phospholipids / 4 mL suspension 200 mg phospholipids / 8 mL suspension	Sodium Chloride 0.9% <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

SURVANTA (beractant, intratracheal suspension) is a sterile, non-pyrogenic pulmonary surfactant and natural bovine lung extract. It is supplemented with three synthetically derived lipids; colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid and tripalmitin. These latter lipids are added to standardize the composition and to mimic the surface-tension lowering properties of natural lung surfactant. The resulting composition provides an average concentration of 25 mg/mL phospholipids and less than 1.0 mg/mL protein. The formulation is an off-white to light brown opaque liquid.

INDICATIONS AND CLINICAL USE

SURVANTA (beractant, intratracheal suspension) is indicated for:

- Prevention (prophylaxis) and
- Treatment (rescue) of Respiratory Distress Syndrome (RDS/Hyaline Membrane Disease) in premature infants

Prevention

For prophylactic treatment of infants at risk of developing RDS or who have evidence of pulmonary immaturity.

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give

SURVANTA as soon as possible after an airway has been established, preferably within 15 minutes of birth.

Rescue Treatment

For rescue treatment of infants who have developed RDS.

To treat infants with RDS confirmed by X-ray and who require mechanical ventilation, give SURVANTA as soon as possible after an airway has been established, preferably by eight hours of age.

SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

The use of SURVANTA (beractant, intratracheal suspension) in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with the use of SURVANTA in conjunction with experimental therapies for RDS (*e.g.*, high frequency ventilation or extra-corporeal membrane oxygenation).

CONTRAINDICATIONS

There are no known contraindications to treatment with SURVANTA (beractant, intratracheal suspension).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Administer in a highly supervised clinical setting
- SURVANTA can rapidly affect oxygenation and lung compliance. Therefore, frequent and careful clinical observation and monitoring of systemic oxygenation are essential to avoid hyperoxia.
- Transient episodes of bradycardia and decreased oxygen saturation may occur during dosing.

General

SURVANTA (beractant, intratracheal suspension) is intended for intratracheal use only (see **DOSAGE AND ADMINISTRATION**).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Usage of SURVANTA 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. Vigilant clinical attention should be given to all infants prior to, during, and after administration of SURVANTA. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported (see **ADVERSE REACTIONS**). If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

The use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with the use of SURVANTA in conjunction with experimental therapies for RDS (*e.g.*, high frequency ventilation or extra-corporeal membrane oxygenation).

Intracranial Hemorrhage

In one of the single-dose rescue studies and one of the multi-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than in control patients (63.3% vs. 30.8%, $p=0.001$ and 48.8% vs. 34.2%, $p=0.047$, respectively). However, when all controlled studies were pooled, there was no difference between treatment groups in incidences of intracranial hemorrhage.

Carcinogenesis and Mutagenesis

Mutagenicity studies were negative. Carcinogenicity studies were not conducted with SURVANTA.

Immune

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in clinical trials (see **Table 2**). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants.

Respiratory

Endotracheal Tube Blockage Due to 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. In the multiple-dose studies performed with SURVANTA, there were 4 reports of endotracheal tube blockage out of 1,691 doses (0.2%).

Oxygenation

SURVANTA can rapidly affect oxygenation and lung compliance. In some infants, hyperoxia may occur within minutes of administration of SURVANTA. If hyperoxia develops, and transcutaneous oxygen saturation is in excess of 95%, FiO_2 should be reduced until saturation is 90 to 95%. If the improvement in chest expansion seems excessive, peak ventilator inspiratory pressures should be immediately reduced. Failure to reduce inspiratory ventilatory pressures rapidly can result in lung overdistention and fatal pulmonary air leaks.

Hyperoxia, cyanosis and reflux through the endotracheal tube, additionally to bradycardia and decreased oxygen saturation, have been the most frequently reported complications in clinical trials. If reflux occurs, drug administration should be stopped and if necessary, peak inspiratory pressure on the ventilator should be increased by 4 to 5 cm H_2O until clearing of the endotracheal tube occurs.

Rales

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is necessary if clear-cut signs of airway obstruction are present.

Sexual Function/Reproduction

Beractant up to 500 mg phospholipids/kg/day, approximately one-third the premature infant dose based on $\text{mg/m}^2/\text{day}$, was administered subcutaneously to newborn rats for five days. These rats reproduced normally and there were no observable adverse effects in their offspring.

Monitoring and Laboratory Tests

Vigilant clinical attention should be given to all infants prior to, during, and after administration of SURVANTA. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most commonly reported adverse experiences were associated with the dosing procedure.

In the multiple-dose controlled clinical trials, each dose of SURVANTA (beractant, intratracheal suspension) was divided into four quarter-doses. Each quarter dose was instilled through a catheter inserted into the endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator.

Transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses. Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse 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.

Table 1 summarizes all adverse experiences reported during controlled clinical trials.

There were no statistically significant differences between treatments in the type or number of events reported.

Table 1				
Number of Infants with Adverse Events (All Controlled Studies)				
(Events with an incidence $\geq 0.2\%$ are specified)				
Body System/Event	SURVANTA		Sham Air	
	N=840	%	N=851	%
Respiratory				
Decreased oxygenation	9	1.1	3	0.4
Problems with ET tube	4	0.5	1	0.1
Blood from ET tube	3	0.4	0	0.0
Pulmonary hemorrhage	2	0.9	1	0.1
N = 225 for SURVANTA				
N = 238 for Sham Air				
Other respiratory adverse events	4	0.5	3	0.4
Cardiovascular				
Aortic thrombosis	3	0.4	0	0.0
Hypotension	3	0.4	0	0.0

Table 1				
Number of Infants with Adverse Events (All Controlled Studies)				
(Events with an incidence \geq 0.2% are specified)				
Body System/Event	SURVANTA		Sham Air	
	N=840	%	N=851	%
Bradycardia	2	0.2	1	0.1
Other cardiovascular adverse events	7	0.8	9	1.0
Gastrointestinal				
Intestinal perforations	2	0.2	5	0.6
Volvulus	2	0.2	0	0.0
Other gastrointestinal adverse events	4	0.5	5	0.6
Renal				
Renal failure	2	0.2	2	0.2
Other renal adverse events	2	0.2	1	0.1
Hematologic				
Coagulopathy	2	0.2	0	0.0
Other hematologic adverse events	0	0	3	0.4
Central Nervous System				
Seizure	6	0.7	6	0.7
Other CNS adverse events	0	0.0	1	0.1
Systemic				
Sepsis	2	0.2	1	0.1
Other systemic adverse events	2	0.2	3	0.4
Other Adverse Events	3	0.4	3	0.4
At Least 1 Event	49	5.8	40	4.7

A clinical study compared the above quarter-dose administration regimen to the same procedure using two half-doses and another two half-dose procedure with uninterrupted ventilation accomplished by passing the catheter through a neonatal suction valve in the endotracheal tube. With the first dose there was significantly less endotracheal tube reflux observed in the group with the quarter-dose regimen ($p=0.007$) than in the group with uninterrupted ventilation. With the first dose there was significantly less oxygen desaturation in the group with uninterrupted ventilation ($p=0.008$) than in the other group receiving two half doses. There were no differences in these events after later doses and no differences in heart rate after any doses (see **DOSAGE AND ADMINISTRATION, Administration, Dosing Procedures**).

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in **Table 2**.

Table 2		
Percentage of Infants with Concurrent Events		
	SURVANTA (%)	Control (%)
Patent ductus arteriosus	46.9	47.1
Intracranial hemorrhage	48.1	45.2
Severe intracranial hemorrhage	24.1	23.3
Pulmonary air leaks	10.9	24.7 *
Pulmonary interstitial emphysema	20.2	38.4 *

	SURVANTA (%)	Control (%)
Necrotizing enterocolitis	6.1	5.3
Apnea	65.4	59.6
Severe apnea	46.1	42.5
Post-treatment sepsis	20.7	16.1 **
Post-treatment infection	10.2	9.1
Pulmonary hemorrhage	7.2	5.3
* p < 0.001 ** p < 0.05		

In one of the single-dose rescue studies and one of the multi-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than in control patients (63.3% vs. 30.8%, p=0.001 and 48.8% vs. 34.2%, p=0.047, respectively). However, when all controlled studies were pooled, there was no difference between treatment groups in incidences of intracranial hemorrhage.

Follow-up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted-age follow-up evaluations have been completed in 631 (345 treated) of 916 surviving infants. There was significantly less cerebral palsy and need for supplemental oxygen in SURVANTA infants than controls. Wheezing at the time of examination was more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Final twelve-month follow-up data from the multiple-dose studies are available from 521 (272 treated) of 909 surviving infants. There was significantly less wheezing in SURVANTA infants than controls in contrast to the six-month results. There was no difference in the incidence of cerebral palsy at twelve months.

Twenty-four month adjusted-age evaluations were completed in 429 (226 treated) of 906 surviving infants. There were significantly fewer SURVANTA infants with rhonchi, wheezing, tachypnea or neurological findings, compared to infants treated with Sham Air, at the time of examination. No other differences were found.

Abnormal Hematologic and Clinical Chemistry Findings

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count, serum sodium, potassium, bilirubin, and creatinine. IgG or IgM antibodies to surfactant-associated proteins SP-B and SP-C were not detected.

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 completed to date.

DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For Intratracheal Administration Only

SURVANTA (beractant, intratracheal suspension) should be administered by or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants.

During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported (see ADVERSE REACTIONS). If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA. Therefore, frequent and careful clinical observation and monitoring of systemic oxygenation are essential to avoid hyperoxia.

Review of audiovisual instructional materials describing dosage and administration procedures is recommended before using SURVANTA. Materials are available upon request.

Recommended Dose and Dosage Adjustment

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every six hours, or administration after 48 hours of age.

Each dose of SURVANTA is 100 mg of phospholipids/kg birth weight (4 mL/kg). The SURVANTA Dosing Chart (**Table 3**) shows the total dosage for a range of birth weights.

Weight (grams)	Total Dose (mL)	Weight (grams)	Total Dose (mL)
600-650	2.6	1301-1350	5.4
651-700	2.8	1351-1400	5.6
701-750	3.0	1401-1450	5.8
751-800	3.2	1451-1500	6.0
801-850	3.4	1501-1550	6.2
851-900	3.6	1551-1600	6.4
901-950	3.8	1601-1650	6.6
951-1000	4.0	1651-1700	6.8
1001-1050	4.2	1701-1750	7.0
1051-1100	4.4	1751-1800	7.2 *
1101-1150	4.6	1801-1850	7.4 *
1151-1200	4.8	1851-1900	7.6 *
1201-1250	5.0	1901-1950	7.8 *
1251-1300	5.2	1951-2000	8.0 *
* suggested dosages based on limited clinical experience in uncontrolled trials			

Four doses of SURVANTA can be administered in the first 48 hours of life. Doses should be given no more frequently than every six hours.

Administration

Directions for Use

SURVANTA should be inspected visually for discolouration prior to administration. The colour of SURVANTA is off-white to light brown.

If settling occurs during storage, swirl the vial gently (do not shake) to redisperse. Some foaming at the surface may occur during handling and is inherent to the nature of the product. SURVANTA does not require sonication before use.

SURVANTA is stored refrigerated (2 to 8°C). Before administration, SURVANTA should be warmed by standing at room temperature for at least 20 minutes or warmed in the hand for at least eight minutes.

Artificial warming methods should not be used. If a prevention dose is to be given, preparation of SURVANTA should begin before the infant's birth.

Unopened, unused vials of SURVANTA that have been warmed to room temperature may be returned to the refrigerator within 24 hours of warming, and stored for future use. SURVANTA

should not be warmed and returned to the refrigerator more than once. Each single-use vial of SURVANTA should be entered only once. Used vials with residual drug should be discarded.

Dosing Procedures

General

SURVANTA is administered intratracheally. It can be instilled through a 5 French end-hole catheter inserted into the infant's endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator OR by inserting the catheter through a neonatal suction valve without disconnecting the endotracheal tube from the ventilator or by instillation through the secondary lumen of a double lumen endotracheal tube.

If the drug is instilled through an end-hole catheter, the length of the catheter should be shortened so that the tip of the catheter protrudes just beyond the endotracheal tube above the infant's carina. SURVANTA should not be instilled into a mainstem bronchus.

To ensure homogenous distribution of SURVANTA throughout the lungs, each dose is divided into fractional doses. Each dose can be administered in two half-doses or in four quarter-doses. Each fractional dose is administered with the infant in a different position.

To administer SURVANTA in two half-doses, the recommended positions are:

- Head and body turned approximately 45° to the right
- Head and body turned approximately 45° to the left

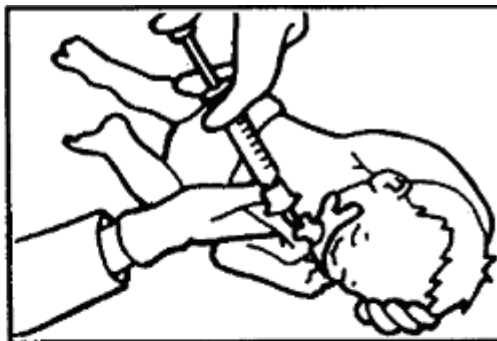
To administer SURVANTA in four quarter-doses, the recommended positions are:

- Head and body inclined 5 to 10° down, head and body turned to the right
- Head and body inclined 5 to 10° down, head and body turned to the left
- Head and body inclined 5 to 10° up, head and body turned to the right
- Head and body inclined 5 to 10° up, head and body turned to the left

The positions for four quarter-doses are illustrated below:



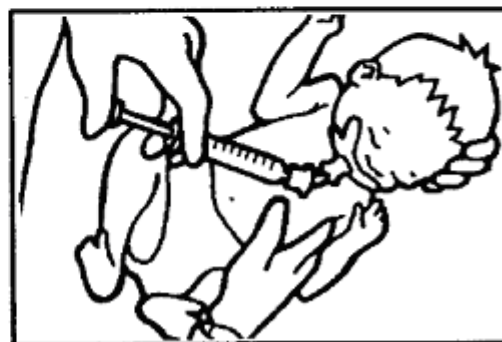
1. Infant's head and body inclined down, head and body turned to the right.



2. Head and body inclined down, head and body turned to the left.



3. Head and body inclined up, head and body turned to the right.



4. Head and body inclined up, head and body turned to the left.

The dosing procedure is facilitated if one person administers the dose while another person positions and monitors the baby.

The different methods of administering SURVANTA were evaluated in clinical trials. In the six single-dose and four multiple-dose controlled clinical trials that established safety and efficacy, SURVANTA was instilled through a catheter that was inserted into the infant's endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator. Each dose was administered in four quarter-doses as described above.

This method of administering SURVANTA was compared to two other methods in a multi-centre, randomized clinical study involving 299 infants weighing 600 g or more with RDS requiring mechanical ventilation. The other methods evaluated were:

- Two half-doses administered by inserting the catheter through the endotracheal tube while the endotracheal tube was briefly disconnected from the ventilator. The half-doses were administered in the two positions described above.

- Two half-doses administered without disconnecting the endotracheal tube from the ventilator by inserting the catheter through a neonatal suction valve into the endotracheal tube. The half-doses were administered in the two positions described above.

There were no significant differences among the three groups in average FiO_2 , a/APO_2 , or MAP at 72 hours of age, or in the incidence of pulmonary air leaks, pulmonary interstitial emphysema, patent ductus arteriosus, or mortality at 72 hours of age.

Administration of SURVANTA using a double-lumen endotracheal tube is functionally equivalent to the use of the neonatal suction valve; *i.e.*, delivery of SURVANTA at the distal end of the endotracheal tube without interrupting mechanical ventilation. If an infant is already intubated with a single-lumen endotracheal tube, the infant should not be reintubated with a double-lumen endotracheal tube solely for the purpose of administering SURVANTA.

First Dose

Instillation Through End-Hole Catheter

Determine the total dose of SURVANTA from the SURVANTA Dosing Chart (**Table 3**) based on the infant's birth weight. Slowly withdraw the entire contents of the vial into a plastic syringe through a large-gauge needle (*e.g.*, at least 20 gauge). Do not filter SURVANTA and avoid shaking.

Attach the pre-measured 5 French end-hole catheter to the syringe. Fill the catheter with SURVANTA. Discard excess SURVANTA through the catheter so that only the total dose to be given remains in the syringe.

Before administering SURVANTA, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering SURVANTA. The infant should be allowed to stabilize before proceeding with dosing.

First Fractional Dose – Prevention Strategy

In the prevention strategy, weigh, intubate and stabilize the infant. Administer the dose as soon as possible after birth, preferably within 15 minutes. Position the infant appropriately and gently inject the first fractional dose through the catheter over two to three seconds.

After administration of the first fractional dose, remove the catheter from the endotracheal tube.

Manually ventilate with a hand-bag with sufficient oxygen to prevent cyanosis, at a rate of 60 breaths/minute and sufficient positive pressure to provide adequate air exchange and chest wall excursion.

First Fractional Dose – Rescue Strategy

In the rescue strategy, the first dose should be given as soon as possible after the infant is placed on a ventilator for management of RDS. In the clinical trials, immediately before instilling the first fractional dose, the infant's ventilator settings were changed to rate 60/minute, inspiratory time 0.5 second, and FiO₂ 1.0.

Position the infant appropriately and gently inject the first fractional dose through the catheter over two to three seconds. After administration of the first fractional dose, remove the catheter from the endotracheal tube. Return the infant to the mechanical ventilator.

Remaining Fractional Doses – Prevention and Rescue Strategies

In both strategies, ventilate the infant for at least 30 seconds or until stable. Reposition the infant for instillation of the next fractional dose.

Instill the remaining fractional doses using the same procedures. After instillation of each fractional dose, remove the catheter and ventilate for at least 30 seconds or until the infant is stabilized. After instillation of the final fractional dose, remove the catheter without flushing it.

Do not suction the infant for one hour after dosing unless signs of significant airway obstruction occur.

After completion of the dosing procedure, resume usual ventilator management and clinical care.

Instillation Through Secondary Lumen of a Double-Lumen Endotracheal Tube

Ensure that the infant is intubated with the appropriate size double-lumen endotracheal tube. Determine the total dose of SURVANTA from the SURVANTA Dosing Chart (**Table 3**) based on the infant's birth weight. Slowly withdraw the total dose from the vial into a plastic syringe through a large-gauge needle (*e.g.*, at least 20 gauge). Do not filter SURVANTA and avoid shaking.

Before administering SURVANTA, assure proper placement and patency of the endotracheal tube. At the discretion of the clinician, the endotracheal tube may be suctioned before administering SURVANTA. The infant should be allowed to stabilize before proceeding with dosing.

First Fractional Dose – Prevention Strategy

In the prevention strategy, weigh, intubate and stabilize the infant. Administer the dose as soon as possible after birth, preferably within 15 minutes. Attach the syringe containing SURVANTA to the secondary lumen. Position the infant appropriately and gently inject the first fractional dose through the secondary lumen over two to three seconds without interrupting ventilation. If manually ventilated, ventilate with a hand-bag with sufficient oxygen to prevent cyanosis, at a

rate of 60 breaths/minute, and sufficient positive pressure to provide adequate air exchange and chest wall excursion.

First Fractional Dose – Rescue Strategy

In the rescue strategy, the first dose should be given as soon as possible after the infant is placed on a ventilator for management of RDS. Immediately before instilling the first fractional dose, change the infant's ventilator settings to rate 60/minute, inspiratory time 0.5 second, and FiO₂ 1.0.

Position the infant appropriately and gently inject the first fractional dose through the secondary lumen over two to three seconds without interrupting mechanical ventilation.

Remaining Fractional Doses – Prevention and Rescue Strategies

In both strategies, ventilate the infant for at least 30 seconds or until stable. Reposition the infant for instillation of the next fractional dose.

Instill the remaining fractional doses using the same procedures. After instillation of each fractional dose, ventilate for at least 30 seconds or until the infant is stabilized. After instillation of the final fractional dose, remove the syringe from the secondary lumen, inject 0.5 mL of air to flush the secondary lumen and cap it.

After completion of the dosing procedure, resume usual ventilator management and clinical care.

Repeat Doses

The need for additional doses of SURVANTA is determined by evidence of continuing respiratory distress.

- Dose no sooner than six hours after the preceding dose if the infant remains intubated and requires at least 30% inspired oxygen to maintain a PaO₂ less than or equal to 80 torr. In controlled clinical trials, 60% of patients (prevention) and 79% of patients (rescue) required more than one dose of SURVANTA. 34.8% of patients (prevention) and 52.2% of patients (rescue) required four doses.
- Radiographic confirmation of RDS should be obtained before administering additional doses to those who received a prevention dose.

The dosage of SURVANTA for each repeat doses is also 100 mg phospholipids/kg and is based on the infant's birth weight. The infant should not be reweighed for determination of the SURVANTA dosage. Use the SURVANTA Dosing Chart to determine the total dosage.

Prepare SURVANTA and position the infant for administration of each fractional dose as previously described. After instillation of each fractional dose, remove the dosing catheter from the endotracheal tube and ventilate the infant for at least 30 seconds or until stable.

In the clinical studies, ventilator settings used to administer repeat doses were different than those used for the first dose. For repeat doses, the FiO₂ was increased by 0.20 or an amount sufficient to prevent cyanosis. The ventilator delivered a rate of 30/minute with an inspiratory time less than 1.0 second. If the infant's pretreatment rate was 30 or greater, it was left unchanged during SURVANTA instillation.

Manual hand-bag ventilation should not be used to administer repeat doses. During the dosing procedure, ventilator settings may be adjusted at the discretion of the clinician to maintain appropriate oxygenation and ventilation.

After completion of the dosing procedure, resume usual ventilator management and clinical care.

Dosing Precautions

If an infant experiences bradycardia or oxygen desaturation during the dosing procedure, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After the infant has stabilized, resume the dosing procedure.

Rales and moist breath sounds can occur transiently after administration of SURVANTA. Endotracheal suctioning or other remedial action is necessary if clear-cut signs of airway obstruction are present.

OVERDOSAGE

Overdosage with SURVANTA (beractant, intratracheal suspension) has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Deficiency of pulmonary surfactant is an important factor in the development of Respiratory Distress Syndrome (RDS) in premature infants. SURVANTA (beractant, intratracheal suspension) replenishes surfactant and restores surface activity to the lungs of these infants. It reduces surface tension and concomitantly increases lung compliance.

Pharmacodynamics

Intratracheally administered SURVANTA distributes rapidly to the alveolar surfaces and stabilizes the alveoli against collapse during respiration thereby increasing alveolar ventilation.

In clinical studies of premature infants with RDS, a significant improvement in oxygenation was demonstrated after treatment with a single dose of SURVANTA. These infants showed a decreased need for supplemental oxygen and an increase in the arterial/alveolar oxygen ratio (a/ApO₂). Significantly decreased need for respiratory support, as indicated by a lower mean airway pressure, was also observed.

In prophylactic studies of premature infants at high risk of RDS, multiple doses (up to four doses within 48 hours) of SURVANTA reduced the incidence and mortality of RDS, reduced the incidence of pulmonary air leaks and pulmonary interstitial emphysema, improved a/ApO₂ and FiO₂ (Fraction of inspired oxygen) at 72 hours of age, and reduced mortality from any cause.

No information is available about the metabolic fate of the surfactant-associated proteins in SURVANTA. The metabolic disposition in humans has not been studied.

STORAGE AND STABILITY

Store unopened vials at refrigeration temperature (2 to 8°C). Protect from light. Store vials in carton until ready for use.

Unopened, unused vials of SURVANTA that have been warmed to room temperature may be returned to the refrigerator within twenty-four hours of warming, and stored for future use. Drug should not be warmed and returned to the refrigerator more than once. Each single use vial of SURVANTA should be entered with a needle only once. Used vials with residual drug should be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

SURVANTA (beractant, intratracheal suspension) is supplied in single-use glass vials containing 4 mL or 8 mL of SURVANTA.

4 mL: Each milliliter contains 25 mg of phospholipids (100 mg phospholipids/4 mL) suspended in 0.9% sodium chloride solution.

8 mL: Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution.

The colour is off-white to light brown.

Composition

Components	Quantities (mg/mL)
Total Phospholipids	25
Disaturated Phosphatidylcholine	11.0-15.5
Triglycerides	0.5-1.75
Free Fatty Acids	1.4-3.5
Protein	0.1-0.4
Sodium Chloride	9.0

Fortification lipids are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant.

SURVANTA is heat-sterilized and does not contain preservatives. Its protein content includes two hydrophobic surfactant-associated proteins of low molecular weight, commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Trade name: SURVANTA

Generic name: Not applicable

USAN name: Beractant

Chemical name: None

Other names: Surfactant TA

Molecular formula and molecular mass: Not applicable

Structural formula: Not applicable

Physicochemical properties: Not applicable

Description: A natural product isolated from bovine lung extracts (Bovine Lung Lipids) containing phospholipids, neutral lipids, fatty acids and protein. It is fortified by the addition of the synthetic lipids, namely dipalmitoyl-phosphatidylcholine (colfosceril palmitate), palmitic acid and tripalmitin (fortification lipids). It is formulated as a sterile, aqueous liquid for intratracheal instillation.

Physical description: Off-white to light brown opaque.

CLINICAL TRIALS

Study Demographics and Trial Design

Clinical effects of SURVANTA (beractant, intratracheal suspension) were demonstrated in six single-dose and four multiple-dose randomized, multi-center, controlled clinical trials involving approximately 1700 infants. Three open trials, including a Treatment IND, involved more than 8500 infants. Each dose of SURVANTA in all studies was 100 mg phospholipids/kg birth weight and was based on published experience with Surfactant TA, a lyophilized powder dosage form of SURVANTA having the same composition.

The studies were of two basic designs: **treatment** or **rescue** studies in which surfactant was given to low birthweight infants with established RDS, and **prevention** studies in which surfactant was given shortly after birth to infants at highest risk for RDS.

Table 5 Summary of Patient Demographics for Clinical Trials in Prevention (Prophylaxis) and Treatment (Rescue) of Respiratory Distress Syndrome (RDS/Hyaline Membrane Disease) in Premature Infants						
	Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Gestational Age (weeks)	Gender (% Male / Female)
Prevention Studies	Study 1	Randomised, multicenter, double blind, placebo-controlled study	Beractant, intratracheal suspension 100 mg phospholipids/kg birth weight within 15 minutes of birth. Infants could receive three additional doses in the first 48 hours. SURVANTA Placebo (Sham Air)	119	26.6	52/48
				124	26.6	48/52
	Study 2*	Randomised, multicenter, double blind, placebo-controlled study	Beractant, intratracheal suspension 100 mg phospholipids/kg birth weight within 15 minutes of birth. Infants could receive three additional doses in the first 48 hours. SURVANTA Placebo (Sham Air)	91	26.5	60/40
				96	26.8	59/41
Rescue Studies	Study 3*	Randomised, multicenter, double blind, placebo-controlled study	Beractant, intratracheal suspension 100 mg phospholipids/kg birth weight within 8 hours of birth. Infants could receive three additional doses in the first 48 hours. SURVANTA Placebo (Sham Air)	198	27.8	61/39
				193	27.6	51/49
	Study 4	Randomised, multicenter, double blind, placebo-controlled study	Beractant, intratracheal suspension 100 mg phospholipids/kg birth weight within 8 hours of birth. Infants could receive three additional doses in the first 48 hours. SURVANTA Placebo (Sham Air)	204 203	27.5 27.4	57/43 58/42
* Study discontinued when Treatment IND initiated						

Study Results

Prevention Studies

Infants of 600-1250 g birth weight and 23 to 29 weeks estimated gestational age were enrolled in two multiple-dose studies. A dose of SURVANTA was given within 15 minutes of birth to prevent the development of RDS. Up to three additional doses in the first 48 hours, as often as every 6 hours, were given if RDS subsequently developed and infants required mechanical ventilation with an $\text{FiO}_2 \geq 0.30$. Results of **Studies 1 and 2** at 28 days of age are shown in **Table 6**.

	Study 1			Study 2 ^a		
	SURVANTA (n=119)	Control (n=124)	P-Value	SURVANTA (n=91)	Control (n=96)	P-Value
Incidence of RDS (%)	27.6	63.5	<0.001	28.6	48.3	0.007
Death due to RDS (%)	2.5	19.5	<0.001	1.1	10.5	0.006
Death or BPD due to RDS (%)	48.7	52.8	0.536	27.5	44.2	0.018
Death due to any cause (%)	7.6	22.8	0.001	16.5 ^b	13.7	0.633
Air Leaks ^c (%)	5.9	21.7	0.001	14.5	19.6	0.374
Pulmonary interstitial emphysema (%)	20.8	40.0	0.001	26.5	33.2	0.298

a Study discontinued when Treatment IND initiated
b No cause of death in the SURVANTA group was significantly increased; the higher number of deaths in this group was due to the sum of all causes.
c Pneumothorax or pneumopericardium

Rescue Studies

Infants of 600-1750 g birth weight with RDS requiring mechanical ventilation and an $\text{FiO}_2 \geq 0.40$ were enrolled in two multiple-dose rescue studies. The initial dose of SURVANTA was given after RDS developed and before 8 hours of age. Infants could receive up to three additional doses in the first 48 hours, as often as every 6 hours, if they required mechanical ventilation and an $\text{FiO}_2 \geq 0.30$. Results of **Studies 3 and 4** at 28 days of age are shown in **Table 7**.

	Study 3 ^a			Study 4		
	SURVANTA (n=198)	Control (n=193)	P-Value	SURVANTA (n=204)	Control (n=203)	P-Value
Death due to RDS (%)	11.6	18.1	0.071	6.4	22.3	<0.001
Death or BPD due to RDS (%)	59.1	66.8	0.102	43.6	63.4	<0.001
Death due to any cause (%)	21.7	26.4	0.285	15.2	28.2	0.001
Air Leaks ^b (%)	11.8	29.5	<0.001	11.2	22.2	0.005
Pulmonary interstitial emphysema (%)	16.3	34.0	<0.001	20.8	44.4	<0.001

a Study discontinued when Treatment IND initiated
b Pneumothorax or pneumopericardium

Acute Clinical Effects

Marked improvements in oxygenation may occur within minutes of administration of SURVANTA. All controlled clinical studies with SURVANTA provided information regarding the acute effects of SURVANTA on the arterial-alveolar oxygen ratio (a/APO₂), FiO₂, and mean airway pressure (MAP) during the first 48 to 72 hours of life. Significant improvements in these variables were sustained for 48 to 72 hours in SURVANTA-treated infants in four single-dose and two multiple-dose rescue studies and in two multiple-dose prevention studies. In the single-dose prevention studies, the FiO₂ improved significantly.

DETAILED PHARMACOLOGY

In vitro, SURVANTA (beractant, intratracheal suspension) reproducibly lowers minimum surface tension to less than 8 dynes/cm as measured by the pulsating bubble surfactometer and Wilhelmy Surface Balance. *In situ*, SURVANTA restores pulmonary compliance to excised rat lungs artificially made surfactant-deficient. *In vivo*, single doses of SURVANTA improve lung pressure-volume measurements, lung compliance, and oxygenation in premature rabbits and sheep.

Surface-tension lowering cannot be directly measured *in vivo*. To assess the nonclinical activity at several doses of SURVANTA, indicators of pulmonary function were measured in animals: arterial blood gases, pulmonary compliance, and lung pressure-volume curves.

Human Pharmacology

Clinical dose-response studies were not done with SURVANTA. The clinical dose of 100 mg phospholipids/kg/dose was selected because previous experience with the same dose of the lyophilized powder formulation of Surfactant TA demonstrated its acute efficacy and safety.

Animal Pharmacology

Activity Studies

Table 8 summarizes relevant aspects of experimental design and results of the animal experiments with SURVANTA and Surfactant TA, a biochemically equivalent powder formulation of SURVANTA. The studies are presented in order of increasing maturity of the animals.

All studies reported in **Table 8** were single-dose studies, because early deaths of premature animals hamper the ability to study responses to multiple-doses of surfactant in surfactant-deficient animals.

Table 8
Animal Activity Studies

Study Identifier	Drug	Animal (N)	Dose	Measure of Response	Results
A-1	SURVANTA	27-day rabbits 59 treated	15 mg/kg, 30 mg/kg, 50 mg/kg, 100 mg/kg at birth & after 15 & 30 minutes of ventilation	1) compliance 2) pressure-volume curves	1) 100 mg/kg: increased compliance at all times (P<0.05) 50 mg/kg: increased compliance only with dose at birth (P<0.05) 2) Treatment at birth: 30, 50, 100 mg/kg: increased volume (P=0.05); 15 mg/kg: no effect Treatment at 30 minutes: no effect
A-2	Surfactant TA	27-day rabbits 30 treated 26 control	75 mg/kg	1) PIP 2) tidal volume 3) compliance	1) decreased PIP (P<0.005) 2) no difference 3) increased compliance (P<0.005)
A-3	Surfactant TA	27-day rabbits 7 treated	75 mg/kg	compliance	Increased compliance (P<0.01)
A-4	SURVANTA (SUR) Calf lung surfactant (CSA) Rabbit surfactant (RSA) No control	28-day rabbits SUR = 38 CSA = 32 RSA = 34	75 mg/kg	PIP, compliance, terminal pH, pCO ₂	No difference between the three surfactants
A-5	Surfactant TA (STA) Sheep surfactant (SSA) Rabbit surfactant (RSA) Human surfactant (HSA)	120-122-day lambs STA = 5 SSA = 5 RSA = 5 HSA = 7 Control = 5	50 mg/kg	1) PIP 2) ventilation efficiency index (VEI) 3) tidal volume 4) compliance	1) STA not different than control 2) SSA > HSA, STA (P<0.05) STA, SSA, RSA, HSA > control (P<0.01)
A-6	SURVANTA (SUR) Sheep surfactant (SSA)	132-day lambs SUR = 5 SSA = 5 Control = 7	100 mg/kg	PIP, pO ₂ , pCO ₂ , FiO ₂ , compliance	Control animals sacrificed at 5 hours due to terminal respiratory failure Treated animals survived to 24 hours: no difference between SUR and SSA
A-7	Surfactant TA	130-147-day premature baboons 10 treated 5 control	100 mg/kg	1) a/APO ₂ , FiO ₂ , MAP 2) compliance 3) pressure-volume curve	1) At 16 hours, decreased a/APO ₂ , increased FiO ₂ , MAP (P<0.005) 2) Increased compliance (P<0.005) 3) Increased volume at all pressures (P<0.001)

Metabolic Studies

Lung clearance behaviour of SURVANTA was also investigated in some of the experiments above using radiolabeled lipid components. SURVANTA clearance occurs in two phases: initial clearance from the airspaces and subsequent clearance from the lungs.

1. Premature Animals

In preterm rabbits, airspace clearance of SURVANTA with labeled phosphatidylcholine showed that, by six hours, 45 to 60% of the labeled lipid was cleared from the alveoli to become lung-associated. At six hours, there was essentially no loss of the SURVANTA lipid from the total lung.

In preterm sheep, SURVANTA was cleared equivalently from the airspaces with only about 20% of the treatment dose recovered in alveolar washes at 24 hours. However, as in preterm rabbits, there was little or no clearance of SURVANTA from the lungs.

2. Three-Day-Old Rabbits

Older animals offer the opportunity to study surfactant clearance over longer periods of time than is possible in premature animals. The clearance of labeled SURVANTA components in full-term, three-day-old rabbits and in adult animals was examined in a study.

SURVANTA with ¹⁴C-choline-labeled phosphatidylcholine was given intratracheally to 3-day old rabbits.

After a dose of 100 mg/kg, there was about 22% clearance of the label from the total lung over 24 hours. About 45% of the tracheally-injected label was recovered in alveolar wash at 24 hours.

3. Adult Rabbits

SURVANTA with labeled phosphatidylcholine was given to adult rabbits. After tracheal injection of approximately 90 mg/kg SURVANTA, the labeled phosphatidylcholine was rapidly lost from the alveolar wash, with 10% recovered at 24 hours. About 55% of the label was recovered in the total lung at 24 hours. These data confirm earlier work with natural surfactants that showed different clearance behaviour in adult animals.

Distribution

A clearance study performed on 27-day premature rabbits, also examined the distribution of SURVANTA in the animals' lungs. In order to measure the distribution of the SURVANTA, rabbits were treated at birth or 30 minutes after the onset of ventilation with 50 mg/kg of SURVANTA radiolabeled with ¹⁴C-dipalmitoylphosphatidylcholine.

Following sacrifice the lungs were removed, frozen over dry ice, and sectioned into 80 pieces. ¹⁴C radioactivity was then counted in the lipid extracts of the lung pieces and normalized by the protein contents of the lung pieces and by the number of counts that would have been received had the distribution been totally uniform.

Rabbits given surfactant after 30 minutes of ventilation had increased percentages of lung pieces that received <20%, 20 to 40%, and >200% the expected dose, indicating a non-uniform surfactant distribution after a period of ventilation.

TOXICOLOGY

Acute Toxicity Studies

SURVANTA (beractant, intratracheal suspension) was evaluated for acute intratracheal toxicity in mice and rats, for subchronic intratracheal toxicity in rats and ferrets, and for sensitization potential in guinea pigs. Two acute toxicity studies are summarized in **Table 9**.

The only acute toxicity observed in preclinical studies was dyspnea, and, in extreme cases, death from asphyxiation. These findings occurred in saline-treated control animals as well as in SURVANTA-treated animals.

Subacute Toxicity Studies

One rat and three ferrets multidose, subacute toxicity studies were conducted with SURVANTA. Ferrets were chosen as a non-rodent model because their pulmonary structure resembles that of man. The four subacute toxicity studies are summarized in **Table 10 to 13**.

Carcinogenicity Studies

Carcinogenicity studies have not been performed with SURVANTA.

Mutagenicity Studies

Mutagenicity studies were negative.

Reproduction and Teratology Studies

Beractant up to 500 mg phospholipids/kg/day, approximately one-third the premature infant dose based on mg/m²/day, was administered subcutaneously to newborn rats for five days. These rats reproduced normally and there were no observable adverse effects in their offspring.

Special Studies

A special toxicity study was undertaken to determine the antigenicity of SURVANTA. A group of 10 adult male guinea pigs was administered three doses of SURVANTA intraperitoneally on alternate days followed three weeks later by a single intratracheal challenge dose. Two positive control groups were administered sensitization and challenge doses of egg albumin according to the same schedule and routes of administration for the group administered SURVANTA. Cyanosis, dyspnea, unsteady gait, ataxia, convulsions and deaths were observed in both egg-albumin-treated groups, but no such manifestations of anaphylaxis were seen in the group administered SURVANTA.

Table 9
Acute Toxicity Studies of SURVANTA®

Species/ Study No.	Sex	Age (weeks)	Route of Administration	Dose Range		Vehicle	Signs	Lethality	Time of Death
				mg/kg ^a	mL/kg				
Mouse T84-296	Male ^b	5	Intratracheal	160	4	0.9% saline	Rales	No deaths ^c	--
Rat T84-296	Male ^b	5	Intratracheal	160	4	0.9% saline	Rales	No deaths	--
T85-287	Male	5	Intratracheal	100	4	0.9% saline	Minimal inflammatory response in both groups. Minimal pulmonary inflammatory reactions plus minimal to mild intra-alveolar microgranulomata; still present 7 days after treatment	No deaths	--
a	mg phospholipid/kg body weight								
b	This study was conducted as exploratory research; not all GLP requirements were met. Lyophilized Surfactant TA.								
c	One of ten mice died 12 days after treatment but the death was not considered treatment-related.								

Group	T₀	T₁	T₂	T₃	T₄
Dosage (mg phospholipid/kg/day)	0 (sham-treated)	0 (0.9% saline)	100	100 (every other day)	200 (100 b.i.d.)
Dose Volume (mL/kg)	---	4	4	4	8 (4 b.i.d.)
No. Deaths / No. Treated	0/10	1/10*	1/11*	2/10*	6/13*
Body Weight Gain	75%	63%	66%	70%	57%
Toxic Signs	Dyspnea (attributed to intratracheal catheter)	Acute respiratory distress immediately after treatment (attributed to transient airway obstruction by saline or test surfactant)			
Hematology	---	Bone marrow M:E ratios of saline- and surfactant-treated rats slightly higher than values for sham-treated rats			
Clinical Chemistry	---	No biologically-meaningful differences from values for sham-treated rats			
Organ Heights	---	No abnormalities	Increased absolute or relative lung weights		
Anatomic Pathology	Interstitial pneumonia without granulomatous changes in 2/10 sham-treated and 10/10 saline-treated rats		Pulmonary changes characterized by granulomatous pneumonia with fat-positive material in 30/30 surfactant-treated rats (consistent with treatment route and lipid nature of surfactant)		

* Deaths were attributed to mechanical suffocation, not surfactant toxicity.

Group	T₀	T₁	T₂
Dosage (mg phospholipid/kg/day)	0 (0.9% saline)	100	300
Dose Volume (mL/kg, q.i.d.)	12	4	12
No. Deaths / No. Treated	0/12	0/12	0/12
Body Weight Gain	M 5.2% F 6.5%	5.7% 2.9%	5.0% 2.1%
Toxic Signs	Occasional gasping or licking during treatment	Occasional gasping or licking in both groups. Infrequent episodes of ataxia or prostration in high-dosage group attributed to transient airway obstruction	
Hematology	--	No toxicologically-meaningful differences from controls	
Clinical Chemistry	--	No toxicologically-meaningful differences from controls	
Organ Weights	--	Dose-related increased lung weights	
Anatomic Pathology	None	Mild inflammatory changes in the lungs at the end of the 3-day treatment period and after a 1-month recovery period	

Group	T₀	T₁	T₂	T₃
Dosage (mg phospholipid/kg/day)	0 (sham-treated)	0 (0.9% saline)	100	100
Dose Volume (mL/kg)	---	8	4	8
No. Deaths/ No. Treated	0/8	0/8	0/8	0/8
Body Weight Gain	24%	24%	22%	21%
Toxic Signs	None	Dyspnea immediately after treatment (attributed to transient airway obstruction by saline or test surfactant)		
Hematology	--	No statistically significant differences from values for sham-treated ferrets		
Clinical Chemistry	--	No statistically significant differences from values for sham-treated ferrets		
Organ Weights	--	No statistically significant differences from values for sham-treated ferrets		
Anatomic Pathology	None	None	Sparsely-distributed, minimal to mild, pulmonary microgranulomata in 16/16 surfactant-treated ferrets (consistent with treatment route and lipid nature of test surfactant)	

Group	T₀	T₁	T₂
Dosage (mg phospholipid/kg/day)	0 (0.9% saline)	300	300, b.i.d.
Dose Volume (mL/kg, q.i.d.)	12, b.i.d.	12	12, b.i.d.
No. Deaths / No. Treated	0/10	1/10*	1/10*
Body Weight Gain	M 64.6% F 44.0%	62.7% 44.7%	46.4% 27.5%
Toxic Signs	Occasional gasping during treatment	Occasional gasping during treatment and infrequent episodes of prostration attributed to transient airway obstruction	
Hematology	--	No toxicologically-meaningful differences from controls	
Clinical Chemistry	--	No toxicologically-meaningful differences from controls	
Organ Weights	--	Increased lung weights	
Anatomic Pathology	None	Scattered pneumonic infiltrates in lung parenchyma of nearly all SURVANTA [®] -treated ferrets; most severe in high-dosage group	

* Deaths were attributed to mechanical suffocation.

REFERENCES

1. Bhat R, Dziedzic K, Bhutani VK, et al. Effect of single dose surfactant on pulmonary function. *Crit Care Med* 1990;18(6):590-594.
2. Fujiwara T, Konishi M, Chida S. Exogenous surfactant therapy in infants with RDS: Comparison of early vs late treatment. *Pediatr Res* 1984;18:353A.
3. Fujiwara T, Onishi M, Nanby H. Surfactant supplementation of neonatal respiratory distress syndrome (RDS): Results of a multifacility cooperative comparative control trial. *Shonika Rinsho* 1987;40(3):549-568.
4. Gitlin JD, Soll RF, Parad RB. Randomized controlled trial of exogenous surfactant for the treatment of hyaline membrane disease. *Pediatrics* 1987;79(1):31-37.
5. Horbar JD, Philip AGS, Little G, et al. Multicenter trial of single dose surfactant for treatment of respiratory distress syndrome (abstract # 1254). *Pediatr Res* 1988;23:410A.
6. Horbar JD, Soll RF, Sutherland JM. A multicenter randomized controlled trial of single dose surfactant therapy for respiratory distress syndrome. *N Eng J Med* 1989;320(15):959-965.
7. Konishi M, Fujiwara T, Naito T. Surfactant replacement therapy in neonatal respiratory distress syndrome. *Eur J Pediatr* 1988;87: 20-25.
8. Konishi T, Fujiwara T, Shimada S. Method of surfactant replacement therapy in RDS: Multicenter randomized study for determination of the replacement dose. *Shonika Rinsho* 1986;39(1): 161-174.
9. Raju TNK, Bhat R, McCulloch KM. Double-blind controlled trial of single-dose treatment with bovine surfactant in severe hyaline membrane disease. *Lancet* 1987;651-656.
10. Soll RF, Hoekstra R, Fangman J. Multicenter trial of single-dose Surfactant TA (STA) for prevention of respiratory distress syndrome (abstract 1344). *Pediatr Res* 1988;23(4):425A.
11. Soll RF, Duc C, Minoli I, et al. European study of single dose surfactant TA (STA) for treatment of respiratory distress syndrome (RDS) (abstract # 1943). *Pediatr Res* 1988;23:525A.
12. Soll RF, Hoekstra RE, Fangman JJ, et al. Multicenter trial of single-dose modified bovine surfactant extract (Survanta*) for prevention of respiratory distress syndrome. *Pediatrics* 1990;85(6):1092-1102.

13. Vohr BR, Coll CG, Roberts JD. Decreased morbidities during the first year in very low birth weight (<1250 g) infants treated with single dose Surfactant TA (STA) for prevention of RDS. *Pediatr Res* 1989;25(4):abstract # 1393.
14. Ware J, Taeusch HW, Soll RF, et al. Health and development outcomes of a surfactant controlled trial: follow-up at 2 years. *Pediatrics* 1990;85(6):1103-1107.
15. Zola EM, Gunkel JH, Chan RK, et al. Comparison of three dosing procedures for administration of bovine surfactant to neonates with respiratory distress syndrome. *J Ped* 1993;122(3):453-459.

PART III: CONSUMER INFORMATION
SURVANTA[®]
beractant, intratracheal suspension

This leaflet is Part III of a three-part "Product Monograph" published when SURVANTA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SURVANTA[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SURVANTA is used to prevent and to treat Respiratory Distress Syndrome (also called Hyaline Membrane Disease) in premature infants. Respiratory Distress Syndrome is a breathing problem that affects premature babies whose lungs are not developed enough to make surfactant (a liquid that coats the inside of the lungs). Without surfactant, the lungs would not expand adequately and the baby might not be able to breathe in enough oxygen.

What it does:

When infants are born at full-term, their lungs contain an adequate amount of a substance called pulmonary surfactant that lowers the surface tension in the lung alveoli (the air sacs in the lungs where oxygen is exchanged) and prevents alveolar collapse during breathing. Premature infants may lack adequate amounts of pulmonary surfactant, which can result in Respiratory Distress Syndrome (RDS), a condition that makes breathing difficult.

SURVANTA[®] is a natural bovine lung extract containing a mixture of substances which mimic the surface-tension lowering properties of natural lung surfactant. When administered into the trachea soon after birth or early in the premature infant's life, SURVANTA[®] spreads throughout the lungs, allowing the alveoli to expand and remain open for proper oxygen exchange at the alveolar level.

When it should not be used:

There are no known contraindications to treatment with SURVANTA.

What the ingredients are:

SURVANTA is composed of different types of lipids (including phosphatidylcholine and other phospholipids, triglycerides, and free fatty acids), proteins, and sodium chloride.

What dosage forms it comes in:

SURVANTA is available in a 4 mL vial (100 mg strength) and an 8 mL vial (200 mg strength).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- SURVANTA[®] should only be given by Health Professionals experienced in treating premature babies with Respiratory Distress Syndrome.
- During and after receiving a dose, the baby will need to be monitored closely for any clinical changes.

INTERACTIONS WITH THIS MEDICATION

There are no known drug interactions with SURVANTA.

PROPER USE OF THIS MEDICATION

SURVANTA is administered by or under the supervision of clinicians experienced in intubation, ventilator management, and general care of premature infants.

Usual dose:

The dose of SURVANTA is based on the infant's birth weight (100 mg/kg birth weight). Four doses of SURVANTA can be administered in the first 48 hours of life. Doses should be given no more frequently than every six hours.

Overdose:

Overdosage with SURVANTA has not been reported.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most side effects occur during the dosing procedure. Common side effects include slow heartbeat and decreased oxygen in the blood. Less common side effects include paleness, low blood pressure, high blood pressure, decreased carbon dioxide in the blood, increased carbon dioxide in the blood, and temporary suspension of breathing. All of these side effects can be treated.

HOW TO STORE IT

Vials are stored at 2 to 8°C, protected from light.

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following three ways:

- **Report on line at:**
www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting
 - **Call toll-free at 1-866-234-2345**
 - **Complete a Canada Vigilance Reporting Form and:**
 - **Fax toll-free to 1-866-678-6789**
 - **Mail to: Canada Vigilance Program**
Health Canada
Postal Locator 1908C
Ottawa, ON K1A 0K9
- Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at:**
www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting

Note: Should you require information related to the management of side effects, contact your healthcare professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

The most recent version of this document plus the full product monograph, prepared for healthcare professionals can be found at www.abbvie.com or by contacting the sponsor, AbbVie Corporation, St-Laurent QC, H4S 1Z1 at 1-888-704-8271.

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