

DATASHEET

SURVANTA

Bovine lung lipids in dispersion 200 mg/8mL

PRESENTATION

Survanta, (beractant) is a sterile, non-pyrogenic pulmonary surfactant intended for intratracheal use only. It is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which dipalmitoylphosphatidylcholine, palmitic acid and tripalmitin are added to standardize the composition and to mimic the surface-tension lowering properties of natural lung surfactant. It is dispersed in 0.9% sodium chloride solution and heat-sterilized. Survanta contains no preservatives. It contains two hydrophobic, low molecular weight, surfactant-associated proteins commonly known as SP-B and SP-C. It does not contain the hydrophilic, large molecular weight surfactant-associated protein known as SP-A.

Each mL of Survanta contains 25 mg of phospholipids. It is an off-white to light brown liquid supplied in single use glass vials containing 8 mL (200 mg phospholipid).

USES

Actions

The mode of action of Survanta is biophysical rather than biochemical, i.e. it reduces surface tension and concomitantly increases lung compliance.

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

In vitro, Survanta reproducibly lowers minimum surface tension to less than 8 dynes/cm on 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 Survanta doses improve lung pressure-volume measurements, lung compliance, and oxygenation in premature rabbit and sheep.

In clinical studies of premature infants with respiratory distress syndrome (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/ApO_2). Significantly decreased need for respiratory support, as indicated by a lower mean airway pressure, was also observed. In most cases these effects were maintained for at least 72 hours after the administration of the single dose of Survanta.

In prophylactic studies of premature infants at high risk of the respiratory distress syndrome, 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/ApO_2 and FIO_2 (Fraction of inspired oxygen) at 72 hours of age, and reduced the mortality from any cause.

PHARMACOKINETICS

The metabolic disposition of Survanta in humans has not been studied. In animal experiments using premature rabbit and sheep models, the metabolic fates of isotope-labelled phosphatidylcholine, palmitic acid and tripalmitin were characterized. Clearance of these components occurs in two phases: clearance from alveolar airspaces and subsequent clearance from the lung tissue. In premature sheep, the labelled phosphatidylcholine in Survanta and natural sheep surfactant were cleared equivalently from the alveolar airspaces with only about 20% of the administered dose recovered in alveolar washes at 24 hours. There was little or no clearance from the lungs for either surfactant. These isotope experiments showed that the labelled phosphatidylcholine in Survanta entered endogenous surfactant phosphatidylcholine metabolic pathways and was recycled back to the airspaces for reutilization. In premature rabbits, airspace clearance was similar for Survanta, natural calf surfactant and natural rabbit surfactant, although there was less lung clearance of Survanta than the natural surfactants.

In contrast to the phosphatidylcholine in Survanta, labelled palmitic acid was rapidly cleared from both the airspaces and the lungs of premature rabbits and sheep. Some of the palmitate was incorporated into lung lipid, primarily phosphatidylcholine, while much of the palmitate left the lungs. The tripalmitin in Survanta distributed to the airspaces and lung tissue of premature sheep similarly to phosphatidylcholine.

Limited animal experiments have not found effects of Survanta on endogenous surfactant metabolism. Precursor incorporation and subsequent secretion of saturated phosphatidylcholine in premature sheep was not changed by either natural surfactant or Survanta treatments. However, when the intra-animal variability was minimized by comparing a treated to an untreated lung in the same animal, natural surfactant stimulated both precursor incorporation and secretion in adult rabbits. Survanta stimulated endogenous surfactant secretion alone, and the effect was not as large as for natural surfactant.

Clinical studies

Clinical effects of Survanta 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.

Prevention Studies

Infants of 600-1250g birth weight and 23-29 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 $FiO_2 \geq 0.30$. Results of the studies at 28 days of age are shown in Table 1.

Table 1

STUDY 1			
Number of Infants Studied	Survanta 204	Control 203	P-Value
Number of Infants Studied	119	124	-
Incidence of RDS (%)	27.6	63.5	<0.001
Death due to RDS (%)	2.5	19.5	<0.001
Death or BPD due to RDS (%)	48.7	52.8	0.54
Death due to any cause (%)	7.6	22.8	0
Air Leaks* (%)	5.9	21.7	0
Pulmonary interstitial emphysema (%)	20.8	40	0
* Pneumothorax or pneumopericardium			
Study 2**			
Number of Infants Studied	Survanta 91	Control 96	P-Value
Number of Infants Studied			-
Incidence of RDS (%)	28.6	48.3	0
Death due to RDS (%)	1.1	10.5	0
Death or BPD due to RDS (%)	27.5	44.2	0.01
Death due to any cause***(%)	16.5	13.7	0.63
Air Leaks* (%)	14.5	19.6	0.37
Pulmonary interstitial emphysema (%)	26.5	33.2	0.3
* pneumothorax or pneumopericardium			
** Study discontinued when Treatment IND initiated			
*** 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.			

Rescue Studies

Infants of 600-1750g birth weight with RDS requiring mechanical ventilation and an $FiO_2 \geq 0.40$ 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 $FiO_2 \geq 0.30$. Results of the studies at 28 days of age are shown in Table 2.

Table 2

Study 3*			
Number of Infants Studied	Survanta 198	Control 193	P-Value -
Death due to RDS (%)	11.6	18.1	0.07
Death or BPD due to RDS (%)	59.1	66.8	0.1
Death due to any cause (%)	21.7	26.4	0.28
Air Leaks* (%)	11.8	29.5	<0.001
Pulmonary interstitial emphysema (%)	16.3	34	<0.001
Study 4			
Number of Infants Studied	Survanta 204	Control 203	P-Value -
Incidence of RDS (%)	6.4	22.3	<0.001
Death or BPD due to RDS (%)	43.6	63.4	<0.001
Death due to any cause(%)	15.2	28.2	0
Air Leaks** (%)	11.2	22.2	0
Pulmonary interstitial emphysema (%)	20.8	44.4	<0.001
* Study discontinued when Treatment IND initiated			
** 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 2 multiple-dose prevention studies. In the single-dose prevention studies, the FiO₂ improved significantly.

INDICATIONS

Survanta is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. Survanta significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention

In premature infants less than 1250 g birthweight, or with evidence of surfactant deficiency, give Survanta as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by X-ray and requiring mechanical ventilation, give Survanta as soon as possible, preferably by 8 hours of age.

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN - NOT RECOMMENDED.

NEONATES

For Intratracheal Administration only.

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

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.

Dosage

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

SURVANTA DOSING CHART

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	1401 - 1450	5.8
751 - 800	3.2	1451 - 1500	6
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	1651 - 1700	6.8
1001 - 1050	4.2	1701 - 1750	7
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	1901 - 1950	7.8
1251 - 1300	5.2	1951 - 2000	8

Four doses of Survanta can be administered in the first 48 hours of life. Doses should be given no more frequently than every 6 hours.

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 in the nature of the product.

Survanta is stored refrigerated (2-8°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 8 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 8 hours of warming and stored for future use. Medicine 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 medicine should be discarded.

SURVANTA DOES NOT REQUIRE RECONSTITUTION OR SONICATION BEFORE USE.

Dosing Procedures

General

Survanta is administered intratracheally via instillation through a 5 French end-hole catheter in one of the following ways: by inserting catheter into the infant's endotracheal tube by briefly disconnecting the endotracheal tube from the ventilator; 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 medicine 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 mainstream 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:

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

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

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

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

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-center, randomized clinical study involving 299 infants weighing 600 g or more with RDS requiring mechanical ventilation. The other methods evaluated were:

- o 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.
- o 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/PAO_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. This method of delivery should produce less hypoxia and less bradycardia immediately post-dosing. However, there is no difference in short-term or long-term outcome when compared to other methods of administration. 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 based on the infant's birth weight. Slowly withdraw the entire contents of the vial into a plastic syringe through a large-gauge needle (eg at least 20 gauge). **DO NOT FILTER SURVANTA AND AVOID SHAKING.**

Attach the premeasured 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.

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 2-3 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.

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 2-3 seconds. After administration of the first fractional-dose, remove the catheter from the endotracheal tube. Return the infant to the mechanical ventilator.

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 1 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 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.

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 2-3 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.

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 2-3 seconds without interrupting mechanical ventilation.

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 0.5mL 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 dosage of Survanta for 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.

The need for additional doses of Survanta is determined by evidence of continuing respiratory distress. Using the following criteria for redosing, significant reductions in mortality due to RDS were observed in the multiple-dose clinical trials with Survanta.

Dose no sooner than 6 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.

Radiographic confirmation of RDS should be obtained before administering additional doses to those who received a prevention dose.

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 unnecessary unless clear-cut signs of airway obstruction are present.

CONTRAINDICATIONS

None known.

WARNINGS AND PRECAUTIONS

Survanta is intended for intratracheal use only.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management and general care of premature infants. 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. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in Survanta-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among Survanta-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

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 use of Survanta in conjunction with experimental therapies for RDS (eg. high-frequency ventilation or extracorporeal membrane oxygenation).

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.

Carcinogenesis, Impairment of Fertility and Mutagenesis.

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with Survanta.

ADVERSE EFFECTS

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

In the multiple-dose controlled clinical trials, each dose of Survanta 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.

A clinical study compared the above noted quarter-dose administration regimen to the administration of two half-doses with interrupted ventilation as described above and the administration of two half-doses accomplished by passing the catheter through a neonatal suction valve in the endotracheal tube, with uninterrupted ventilation. With the first dose, there was significantly less endotracheal tube reflux observed in the group with the quarter-dose regimen ($p=.007$) than in the group with uninterrupted ventilation. With the first dose there was significantly less oxygen desaturation in the group with uninterrupted ventilation ($p=.008$) 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 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 3.

Table 3

All Controlled Studies			
Concurrent Event	Survanta (%)	Control (%)	P-Value*
Patent ductus arteriosus	46.9	47.1	0.81
Intracranial hemorrhage	48.1	45.2	0.24
Severe intracranial hemorrhage	24.1	23.3	0.69
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.43
Apnea	65.4	59.6	0.28
Severe apnea	46.1	42.5	0.11
Post-treatment sepsis	20.7	16.1	0.01
Post-treatment infection	10.2	9.1	0.34
Pulmonary hemorrhage	7.2	5.3	0.17

* P-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in Survanta patients than control patients (63.3% v 30.8%, $P=0.001$; and 48.8% v 34.2%, $P=0.047$, respectively). The rate in a Treatment IND involving approximately 8100 infants was lower than in the controlled trials.

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.

More than 4300 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to Survanta.

Respiratory

Lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular

Hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardio-respiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal

Abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal

Renal failure, hematuria.

Hematologic

Coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System

Seizures.

Endocrine/Metabolic

Adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal

Inguinal hernia.

Systemic

Fever, deterioration.

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. 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 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, and tachypnea at the time of examination. No other differences were found.

INTERACTIONS

No interactions have been observed between Survanta and the concomitant use of medicines commonly used in neonatal intensive care such as catecholamines, indomethacin, tolazoline, pancuronium, phenobarbitone, opiates, antibiotics and parenteral nutrients. Also, medicines given prenatally to mothers such as tocolytics and corticosteroids have not interfered with the use of Survanta in the neonate.

OVERDOSAGE

Overdosage with Survanta has not been reported.

Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after Survanta is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

Pharmaceutical precautions

Store refrigerated (2°C to 8°C) and protect from light.

Medicine classification

Prescription Medicine

Package quantities

Single use vials containing 8 mL.

Further information

Unopened, unused vials of Survanta that have been warmed to room temperature may be returned to the refrigerator within eight (8) hours of warming, and stored for future use. Survanta should not be warmed and re-refrigerated more than once. Unused vials with residual medicine should be discarded.

NAME AND ADDRESS

Abbott Laboratories (NZ) Ltd
4 Pacific Rise
Mt Wellington
Auckland

DATE OF PREPARATION

May 2006
Version 01