SURVANTA- beractant suspension
AbbVie Inc.

SURVANTA
(beractant)
intratracheal suspension
Sterile Suspension
For Intratracheal Administration Only

DESCRIPTION

SURVANTA® contains beractant, a pulmonary surfactant, which is a natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins (SP) to which colfosceril palmitate (dipalmitoylphosphatidylcholine), palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant. The resulting composition provides 25 mg/mL of phospholipids (including 11.0-15.5 mg/mL of disaturated phosphatidylcholine), 0.5-1.75 mg/mL of triglycerides, 1.4-3.5 mg/mL of free fatty acids, and less than 1 mg/mL of SP (including SP-B, a 79-amino acid protein, and SP-C, a 35-amino acid peptide).

SURVANTA (beractant) intratracheal suspension is a sterile, preservative-free, non-pyrogenic off-white to light brown liquid supplied in single-dose glass vials for intratracheal use only. Each vial contains 4 mL (100 mg phospholipids) or 8 mL (200 mg phospholipids). Each mL of SURVANTA contains 25 mg of phospholipids. It is suspended in 0.9% sodium chloride solution and heat-sterilized. SURVANTA contains no preservatives. Sodium hydroxide or hydrochloric acid may be added to adjust the pH. The pH is approximately 6.2 to 7.6.

CLINICAL PHARMACOLOGY

Endogenous pulmonary surfactant lowers surface tension on alveolar surfaces during respiration and stabilizes the alveoli against collapse at resting transpulmonary pressures. Deficiency of pulmonary surfactant causes Respiratory Distress Syndrome (RDS) in premature infants. SURVANTA replenishes surfactant and restores surface activity to the lungs of these infants.

Activity

In vitro, SURVANTA 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 SURVANTA doses improve lung pressure-volume measurements, lung compliance, and oxygenation in premature rabbits and sheep.

Animal Metabolism

SURVANTA is administered directly to the target organ, the lungs, where biophysical effects occur at the alveolar surface. In surfactant-deficient premature rabbits and lambs, alveolar clearance of radio-labelled lipid components of SURVANTA is rapid. Most of the dose becomes lung-associated within hours of administration, and the lipids enter endogenous surfactant pathways of reutilization and recycling. In surfactant-sufficient adult animals, SURVANTA clearance is more rapid than in premature and young animals. There is less reutilization and recycling of surfactant in adult animals.

Limited animal experiments have not found effects of SURVANTA on endogenous surfactant metabolism. Precursor incorporation and subsequent secretion of saturated phosphatidylcholine in premature sheep are not changed by SURVANTA treatments.

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

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

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 $FiO_2 \geq 0.30$. Results of the studies at 28 days of age are shown in Table 1.

Table 1.

	Study 1		
	SURVANTA	Control	*P*-Value
Number 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	0.536
Death due to any cause (%)	7.6	22.8	0.001
Air Leaks[a] (%)	5.9	21.7	0.001
Pulmonary interstitial emphysema (%)	20.8	40.0	0.001

	Study 2[b]		
	SURVANTA	Control	*P*-Value

Number infants studied	91	96	
Incidence of RDS (%)	28.6	48.3	0.007
Death due to RDS (%)	1.1	10.5	0.006
Death or BPD due to RDS (%)	27.5	44.2	0.018
Death due to any cause [C](%)	16.5	13.7	0.633
Air Leaks [a](%)	14.5	19.6	0.374
Pulmonary interstitial emphysema (%)	26.5	33.2	0.298

[a]Pneumothorax or pneumopericardium
[b]Study discontinued when Treatment IND initiated
[c]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 600-1750 g 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[a]		
	SURVANTA	Control	*P*-Value
Number infants studied	198	193	
Death due to RDS (%)	11.6	18.1	0.071
Death or BPD due to RDS (%)	59.1	66.8	0.102
Death due to any cause (%)	21.7	26.4	0.285
Air Leaks[b] (%)	11.8	29.5	<0.001
Pulmonary interstitial emphysema (%)	16.3	34.0	<0.001

	Study 4		
	SURVANTA	Control	*P*-Value
Number infants studied	204	203	
Death due to 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	0.001
Air Leaks[b] (%)	11.2	22.2	0.005
Pulmonary interstitial emphysema (%)	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/APO_2), FiO_2, and mean airway pressure (MAP) during the first 48 to 72 hours of life. Significant improvements in these variables were sustained for 48-72 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 FiO_2 improved significantly.

INDICATIONS AND USAGE

SURVANTA is indicated for prevention and treatment (“rescue”) of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants.

CONTRAINDICATIONS

None

WARNINGS

SURVANTA can rapidly affect oxygenation and lung compliance within minutes of administration of SURVANTA. 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.

PRECAUTIONS

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, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with SURVANTA. SURVANTA was negative when tested in the Ames test for mutagenicity. Using the maximum feasible dose volume, SURVANTA up to 500 mg phospholipids/kg/day (approximately one-third the premature infant dose based on mg/m^2/day) was administered subcutaneously to newborn rats for 5 days. The rats reproduced normally and there were no observable adverse effects in their offspring.

ADVERSE REACTIONS

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 which were 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.

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[a]
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	< 0.001
Pulmonary interstitial emphysema	20.2	38.4	< 0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

[a] *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 and serum sodium, potassium, bilirubin, and creatinine.

More than 4300 pretreatment and post-treatment serum samples from approximately 1500 patients 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 were significantly less cerebral palsy and need for supplemental oxygen in SURVANTA infants than controls. Wheezing at the time of examination was significantly 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, and tachypnea at the time of examination. No other differences were found.

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.

DOSAGE AND ADMINISTRATION

Important Administration Instructions

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. The administration of SURVANTA is facilitated if one person administers the dose while

another person positions and monitors the infant.

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.

Administer SURVANTA intratracheally by instillation through a 5 French end-hole catheter.

Recommended Dosage

Each dose of SURVANTA is 100 mg of phospholipids/kg birth weight (4 mL/kg).

In the prevention strategy, in premature infants with evidence of surfactant deficiency, give the first dose of SURVANTA as soon as possible, preferably within 15 minutes of birth.

To treat infants with RDS confirmed by radiographic and clinical findings, give the first dose of SURVANTA as soon as possible, preferably by 8 hours of age.

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.

The need for additional doses of SURVANTA is determined by evidence of continuing respiratory distress. Radiographic confirmation of RDS should be obtained before administering additional doses to those who received a prevention dose.

Preparation of the SURVANTA Suspension

SURVANTA should be inspected visually for discoloration prior to administration. The color of SURVANTA is off-white to light brown. If settling occurs during storage, swirl the vial gently (DO NOT SHAKE) to redisperse. Do not filter SURVANTA. Some foaming at the surface may occur during handling and is inherent in the nature of the product.

SURVANTA is stored refrigerated (36°F to 46°F [2°C to 8°C]). Date and time need to be recorded in the box on front of the carton or vial, whenever SURVANTA is removed from the refrigerator. 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 24 hours of warming, and stored for future use. SURVANTA SHOULD NOT BE REMOVED FROM THE REFRIGERATOR FOR MORE THAN 24 HOURS. SURVANTA SHOULD NOT BE WARMED AND RETURNED TO THE REFRIGERATOR MORE THAN ONCE. Each single-dose vial of SURVANTA should be entered only once. Used vials with residual drug should be discarded.

SURVANTA does not require reconstitution or sonication before use.

Administration

<u>For endotracheal administration using a 5 French end-hole catheter:</u>

1. Slowly withdraw the entire contents of the vial into a plastic syringe through a large-

gauge needle (e.g., at least 20 gauge).

2. 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.

3. When administering SURVANTA using a 5 French end-hole catheter, administer in four quarter-dose aliquots. Each quarter-dose is administered with the infant in a different position:

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

4. First quarter-dose aliquot of SURVANTA suspension:

a. Position the infant appropriately in one of the four recommended positions.

b. Insert the 5-French end-hole catheter into the endotracheal tube. The tip of the catheter should protrude just beyond the end of the endotracheal tube above the infant’s carina. SURVANTA should not be instilled into a mainstem bronchus.

c. Gently inject the first quarter-dose aliquot through the catheter over 2-3 seconds.

d. After the first aliquot is instilled, remove the catheter from the endotracheal tube and manually ventilate the infant for at least 30 seconds or until clinically stable. Ventilate with sufficient oxygen to prevent cyanosis and sufficient positive pressure to provide adequate air exchange and chest wall excursion.

5. When the infant is stable, reposition the infant for instillation of the next quarter-dose.

6. Instill each remaining quarter-dose using the same procedures.

7. After instillation of the final quarter-dose, remove the catheter without flushing it. Do not suction the infant for 1 hour after dosing unless signs of significant airway obstruction occur.

HOW SUPPLIED

SURVANTA (beractant) intratracheal suspension is supplied in 100 mg/4 mL single-dose glass vials (NDC 0074-1040-04) or 200 mg/8 mL single-dose glass vials (NDC 0074-1040-08). Each mL contains 25 mg of phospholipids suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials refrigerated at 36°F to 46°F (2°C to 8°C). Do not shake. Protect from light. Store vials in carton until ready for use. Vials are for one-time use and for only one patient. Upon opening, discard unused drug.

LITHO IN USA

AbbVie Inc.

North Chicago, IL 60064, U.S.A.

US License Number 1889

20065798 October, 2020

Principal Display Panel

NDC 0074-1040-08
8 mL One Single-Dose Vial
beractant
SURVANTA®
intratracheal suspension
200 mg/8 mL (25 mg/mL)

For Intratracheal Administration Only

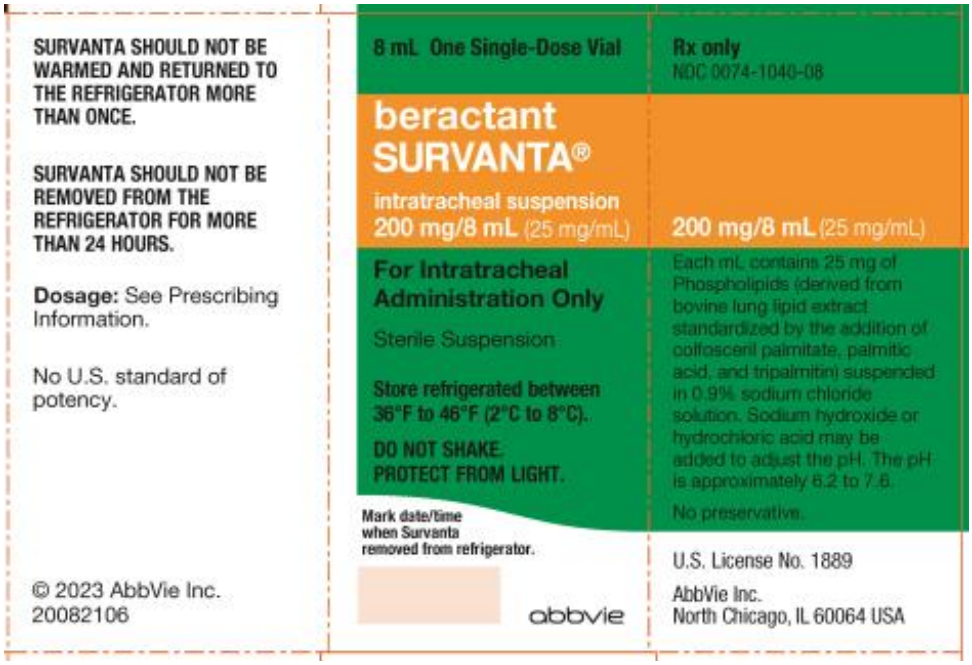
Sterile Suspension

Store refrigerated between 36°F to 46°F (2°C to 8°C).

DO NOT SHAKE.
PROTECT FROM LIGHT.

Rx only

abbvie



Principal Display Panel

NDC 0074-1040-04
4 mL One Single-Dose Vial
beractant
SURVANTA®
intratracheal suspension
100 mg/4 mL (25 mg/mL)

For Intratracheal

Administration Only

Sterile Suspension

Store refrigerated between 36°F to 46°F (2°C to 8°C).

DO NOT SHAKE.
PROTECT FROM LIGHT.

Rx only

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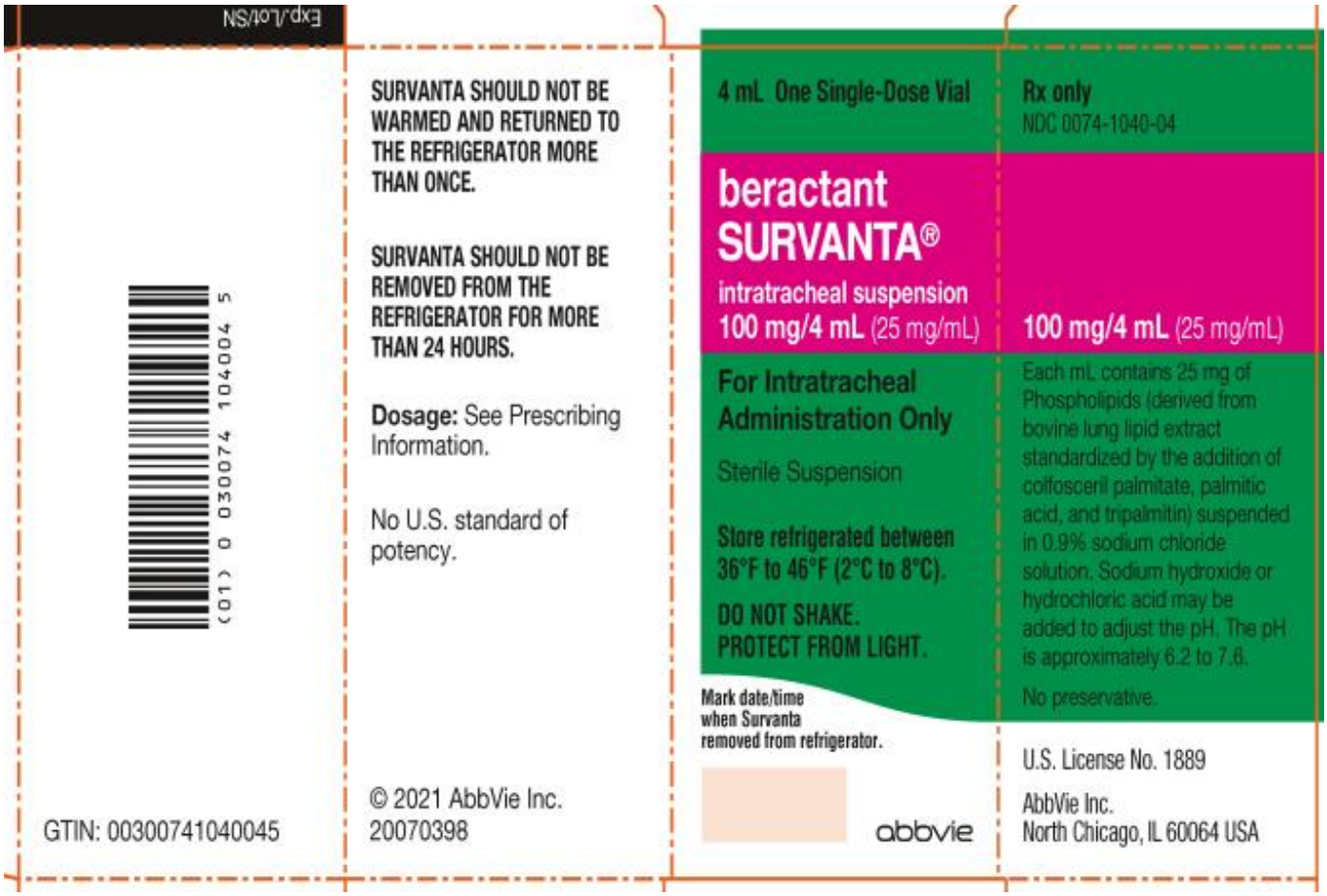

SURVANTA

beractant suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0074-1040
Route of Administration	ENDOTRACHEAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BERACTANT (UNII: S866O45PIG) (BERACTANT PHOSPHOLIPIDS - UNII:LJA7V5FCW8)	BERACTANT PHOSPHOLIPIDS	25 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
COLFOSCERIL PALMITATE (UNII: 319X2NFW0A)	
TRIPALMITIN (UNII: D133ZRF50U)	
PALMITIC ACID (UNII: 2V16EO95H1)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Product Characteristics

Color	white (off-white to light brown)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0074-1040-04	1 in 1 CARTON	07/01/1991	
1		4 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		
2	NDC:0074-1040-08	1 in 1 CARTON	07/01/1991	
2		8 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA020032	07/01/1991	

Labeler - AbbVie Inc. (078458370)

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