PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr BLES®

bovine lipid extract surfactant

27 mg phospholipid/mL Suspension for Intratracheal Instillation

Pharmaceutical Standard: Professed

ATC Code R07AA02: Lung surfactant, natural phospholipids

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RECENT MAJOR LABEL CHANGES

Warnings and Precautions, Respiratory (8)	(TBD/end of review)
Dosage and Administration, Dosing Considerations (4.1), Administration (4.3)	(TBD/end of review)

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BLES® (bovine lipid extract surfactant suspension) is indicated for:

- rescue treatment of Neonatal Respiratory Distress Syndrome (NRDS/Hyaline Membrane Disease).

For infants with NRDS confirmed by x-ray, with arterial to alveolar oxygen ratio (Pa_{O2}/PA_{O2}) <0.22, BLES® is to be given as soon as possible after the oxygenation criteria are met.

The use of BLES® in infants less than 380 g or greater than 4460 g birth weight has not been evaluated in controlled trials.

1.1 Pediatrics

Pediatrics (neonatal age ≤ 5 days): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BLES® in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use (see 15 CLINICAL TRIALS).

Pediatrics (neonatal age > 5 days): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in infants > 5 days of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Bovine lipid extract surfactant suspension is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Use of BLES® (bovine lipid extract surfactant suspension) is contraindicated in infants with active pulmonary haemorrhage.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Administer in a highly supervised clinical setting (see WARNINGS AND PRECAUTIONS – General).
- BLES® can affect oxygenation and lung compliance rapidly. In some infants, hyperoxia may occur within minutes of administration (see WARNINGS AND PRECAUTIONS – Ophthalmologic).
- Transient episodes of bradycardia and decreased oxygen saturation may occur during dosing (see WARNINGS AND PRECAUTIONS – Respiratory).
- Administration of BLES® in small aliquots or using a slow drip method are not recommended, as these may lead to poor surfactant distribution and uneven lung compliance (see WARNINGS AND PRECAUTIONS – Respiratory).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- BLES® (bovine lipid extract surfactant suspension) is intended for **intratracheal** instillation only.
- BLES® does not require reconstitution or filtering before use. Vials are for single use only, to ensure sterility. Once at room temperature, gently invert the vial to suspend the lipid and disperse any agglomerates.
- Inspect the vial for homogeneity. It is normal for warmed vials to have an even dispersion of fine but visible flecks of lipid. Contents should appear as an off-white to light yellow suspension. If contents are a darker colour or will not disperse evenly, discard the vial. Report this and the lot number to the manufacturer.
- BLES® should be warmed to at least room temperature, but no higher than body temperature before being administered. Warming can be accomplished in the following ways (times are approximate):

Method of Warming	Refrigerated Vials	Frozen Vials
In the hand	5 min.	10 to 15 min.
On the counter	20 min.	60 min.
In a 37°C water bath	2 min.	5 min.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of BLES® is 5 mL/kg at 27 mg of phospholipids/mL, which equals 135 mg phospholipid/kg. As many as 3 subsequent doses of BLES® can be given within the first 5 days of life. See Repeat Doses for details. Table 1 suggests the total dosage for a range of birth weights.

Table 1 BLES® Dosing Chart			
Weight (grams)	Total Dose (mL)	Weight (grams)	Total Dose (mL)
600-650	3.2	1301-1350	6.8
651-700	3.5	1351-1400	7.0
701-750	3.8	1401-1450	7.2
751-800	4.0	1451-1500	7.5
801-850	4.2	1501-1550	7.8
851-900	4.5	1551-1600	8.0
901-950	4.8	1601-1650	8.2
951-1000	5.0	1651-1700	8.5
1001-1050	5.2	1701-1750	8.8
1051-1100	5.5	1751-1800	9.0
1101-1150	5.8	1801-1850	9.2
1151-1200	6.0	1851-1900	9.5
1201-1250	6.2	1901-1950	9.8
1251-1300	6.5	1951-2000	10.0

4.3 Administration

Dosing Procedures

The infant should be suctioned and allowed to recover before commencing the procedure.

INSURE (INtubate-SURfactant-Extubate) Procedure:
Ensure proper placement of the endotracheal tube (ETT) via chest auscultation and radiograph, if available (1-2 cm below the vocal cords, 1-2 cm above the carina). **Do not instill BLES® down the right mainstem bronchus.**

Draw the full dose into a syringe with a bevelled large gauge (e.g. at least 20-gauge) needle, and fit the syringe with a sterile #5 Fr feeding tube which has been cut to an appropriate length so that it will reach the distal tip of the ETT. If product is not administered to the patient immediately, invert the prepared syringe before instillation to resuspend any lipid agglomerates. Briefly disconnect the infant from the ventilator so that the feeding tube may be threaded into the ETT. Alternately, to allow simultaneous mechanical ventilation or hand bagging, pass the feeding tube through the suction valve of a closed suctioning adaptor attached to the ETT.

Instill as a single bolus dose or up to three aliquots, as tolerated, with the infant supine for each aliquot. Instill each aliquot or dose over **a period of 2 to 3 seconds**. After each aliquot is instilled, the infant should be ventilated manually for 30 seconds, using pressures sufficient to achieve good chest expansion before returning the infant to the ventilator. If the infant remains on mechanical ventilation during dosing, raise the pressure by 1 to 2 cm H_2O, if necessary, to assist with emptying the ETT. Allow approximately 1-2 minutes recovery time after each aliquot. Ensure oxygen saturation readings are about 95% before commencing the next aliquot.

The volume of surfactant will rise in the ETT during administration. If the surfactant is slow to subside, interrupt administration and hand ventilate until the ETT is clear before continuing. If the surfactant fails to subside, investigate the possibility of a mucous plug. Small aliquots or a

slow drip are not recommended, as this may lead to poor surfactant distribution and uneven lung compliance.

MIST (Minimally Invasive Surfactant Therapy) Procedure:
Note: Variations of the MIST procedure detailed below have been described in the literature. A common variation is the LISA (less invasive surfactant administration) procedure that uses Magill forceps for placement. Thin catheter placement should be performed according to established protocols of the healthcare centre.

BLES® may also be administered as per MIST techniques. It is recommended that for MIST delivery the neonate is ≥ 28 weeks and / or ≥ 1000 grams, does not require intubation / mechanical ventilation and meets the criteria for surfactant administration (i.e. oxygenation requirement met). Neonates should be kept on nasal continuous positive airway pressure (NCPAP) or non-invasive positive-pressure ventilation (NIPPV) using nasal prongs or masks for the entire procedure.

To administer the dose via the MIST technique, guide a thin catheter (e.g. #5 Fr multi-access catheter) across the vocal cords to a depth of 6 cm + birth weight in kilograms as measured from the lip. This should ensure proper placement of the tip of the catheter mid-way between the vocal cords and carina. After catheter placement, keep the neonate's mouth closed for NCPAP / NIPPV delivery. Synchronize surfactant instillation with the neonate's inspiration using micro-boluses, over **a period of 1 to 3 minutes**. If unable to deliver the dose successfully using this technique in no more than three attempts, administer the dose via the INSURE method described above.

Monitoring after administration
Once instillation is complete, new mechanical ventilatory parameters need to be established according to the TcP_{O2}/TcP_{CO2} readings, the oxygen saturation monitor and chest expansion. TcP_{O2}/TcP_{CO2} readings are preferred in infants of lower gestation (less than 32 weeks), and oxygen saturation readings preferred with older infants. Monitor tidal volume closely, as sudden lung compliance may occur without much chest movement. Start at pre-instillation settings and wean the pressures (PIP/PEEP), Fi_{O2} and the ventilator rate, as indicated by the infant's status. Follow-up blood gases one hour after dosing is a standard procedure for any infant who has received BLES® (Pa_{O2} should be between 60-70 torr, Pa_{CO2} should be kept between 35-45 torr, and pH between 7.35 - 7.45). Avoid suctioning for 2 hours post-BLES®, unless absolutely necessary. Due to the immediate effect of BLES® on lung compliance and oxygenation (usually within 5 to 30 minutes), Fi_{O2} should be decreased accordingly, to prevent hyperoxia. Chest expansion should be observed closely and ventilatory pressures (PIP/PEEP) decreased accordingly. High oxygen saturation levels (>95%) or high TcP_{O2}/TcP_{CO2} readings (as confirmed by comparison to blood gas measurements) indicate the infant should be weaned off Fi_{O2}, ventilator rates and pressures. Blood gas readings should be 60 - 70 torr for Pa_{O2} and 35 - 45 torr for Pa_{CO2}. Failure to wean appropriately may result in a pneumothorax.

Infants whose ventilation becomes markedly impaired during or shortly after dosing may have mucous plugging of the ETT, particularly if pulmonary secretions were prominent prior to drug administration. In addition, surfactant may promote the movement of resident mucus. If suctioning is unsuccessful in removing the obstruction, the blocked ETT should be replaced immediately.

Repeat Doses
Neonates can receive up to 3 additional doses of BLES® within the first 5 days of life. The criteria for an additional dose are a positive response to the previous dose, and an increase in respiratory support as signalled by a gradual increase in F_{iO_2}. This increase must be at least 10% greater than the F_{iO_2} required after the initial response to the previous dose of BLES®.
All infants exhibiting respiratory deterioration should be evaluated for a patent ductus arteriosus (PDA), pneumothorax and pulmonary haemorrhage before retreatment with BLES®. The regimen for repeat doses is the same as for the initial dose. See Dosing Procedures for details.

4.4 Reconstitution

BLES® does not require reconstitution.

4.5 Missed Dose

Missed doses are not applicable to BLES® use.

5 OVERDOSAGE

No evidence of human overdose with BLES® (bovine lipid extract surfactant suspension) has been documented. Based on animal data, overdosage may result in acute airway obstruction.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of this product, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the lot number/expiry date of the product supplied.

Table 2
Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intratracheal instillation	Suspension / 27 mg per mL	Calcium chloride Sodium chloride Water for irrigation

BLES® (bovine lipid extract surfactant suspension) is a suspension for intratracheal instillation.

Each mL of BLES® contains 27 mg of phospholipids and 176 – 500 µg of surfactant-associated proteins SP-B and SP-C, with 0.10 M sodium chloride and 0.0015 M calcium chloride. BLES® contains no preservatives.

BLES® is available in 3 mL, 4 mL, and 5 mL sterile, single use clear glass vials, packaged individually or in cartons of 10 vials.

7 DESCRIPTION

BLES® (bovine lipid extract surfactant suspension) is extracted from bovine lung surfactant. The manufacturing process removes hydrophilic proteins, the majority of which would be surfactant-associated protein SP-A, and selects for hydrophobic phospholipids and surfactant-associated proteins SP-B and SP-C.

8 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information.

General

BLES® (bovine lipid extract surfactant suspension) is intended for intratracheal use only (see 6 DOSAGE AND ADMINISTRATION).

Use of BLES® 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.

A higher rate of sepsis has been described in those infants treated with BLES® than those in the control arm. Health professionals caring for these infants should be aware of this increased risk, take appropriate precautionary measures and be vigilant for any signs and symptoms of sepsis.

Carcinogenesis and Mutagenesis

No studies have been performed to investigate the carcinogenesis or mutagenesis of BLES®.

Immune

Long-term studies comparing BLES® to placebo (sham air) treatment demonstrated no significant differences in development of allergies.

Monitoring and Laboratory Tests

Correction of acidosis, hypotension, hypoglycemia and hypothermia is recommended prior to administration.

Ophthalmologic

Hyperoxia may occur within minutes of administration of BLES®. If hyperoxia develops and oxygen saturation is in excess of 95%, FiO_2 should be reduced until saturation is 90 to 95%, to decrease the risk of retinopathy of prematurity.

Respiratory

Vigilant clinical attention should be given to all infants prior to, during and after administration of BLES®. Infants receiving BLES® should be monitored for oxygenation with a transcutaneous oxygen probe or oxygen saturation monitor as well as occasional blood gas measurements. In addition, carbon dioxide (CO_2) levels should be monitored with transcutaneous CO_2 probe correlated with blood gas readings.

BLES® can rapidly affect oxygenation and lung compliance. If the improvement in chest expansion seems excessive, peak ventilator inspiratory pressures should be reduced

immediately, to avoid overdistension and pulmonary air leaks. Monitor tidal volume after dosing, as sudden lung compliance may occur without much chest movement.

During the dosing procedure, transient episodes of bradycardia and decreased oxygen saturation have been reported (see 9 ADVERSE REACTIONS). If these occur, the dosing procedure should be stopped and appropriate measures to alleviate the condition initiated. After stabilization, the dosing procedure can be resumed.

Administration techniques used with other surfactant products, such as slow administration or the use of small test aliquots, are not recommended with BLES®. Unlike other products that require a slow drip to prevent reflux, BLES® has a much lower viscosity and a higher protein content that promote a more rapid distribution. Slow administration may lead to uneven distribution, resulting in uneven lung compliance. If the dose fails to subside in the ETT with additional pressures recommended in the 4 DOSAGE AND ADMINISTRATION section, consider the possibility of a mucous plug.

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. After dosing, exogenous surfactant may encourage the transport of resident mucus. 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.

There has been an increase in the number of reported cases of pulmonary haemorrhage, including death (see Post-Market Adverse Drug Reactions).

8.1 Special Populations

8.1.1 Pregnant Women

BLES® is not indicated for pregnant women.

8.1.2 Breast-feeding

BLES® is not indicated for breast-feeding women.

8.1.3 Pediatrics

Pediatrics (neonatal age > 5 days): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in pediatric patients > 5 days of age.

8.1.4 Geriatrics

BLES® is not indicated for the geriatric population.

9 ADVERSE REACTIONS

9.1 Adverse Reaction Overview

In a double-blinded, comparative, multicentre clinical trial comparing the safety and efficacy of BLES® and Exosurf® Neonatal (colfosceril palmitate; Glaxo Wellcome), 568 infants received BLES® and 565 received Exosurf® for rescue treatment of NRDS. The most common adverse events in both treatment groups were patent ductus arteriosus and decreased pulmonary function (see Table 3). There were more cases in the BLES® group for respiratory acidosis, sepsis, and pneumonia, discussed in 9.2 Clinical Trial Adverse Reactions. Fatalities occurred in 1.06% of BLES® and 1.06% of Exosurf® patients; see 15 CLINICAL TRIALS for discussion of survival at 36 weeks.

Commonly observed adverse events associated with surfactant administration include bradycardia, desaturation on dosing, endotracheal tube complications, apnoea and hypotension. These would be expected to occur when handling premature infants and administering surfactant intratracheally. Many other common adverse events, such as patent ductus arteriosus, intraventricular haemorrhage, pulmonary haemorrhage, retinopathy of prematurity, pulmonary interstitial emphysema and periventricular leukomalacia are also serious complications of prematurity.

Due to the rapid effect of BLES® on lung compliance and oxygenation, infants should be monitored for respiratory parameters and any of the common adverse events.

9.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events occurring in ≥ 1% of infants treated with BLES® are summarized by body system and in order of decreasing frequency in Table 3, below. The incidence of these events in Exosurf®-treated infants is provided for comparison.

Table 3
Adverse Events in ≥ 1% of Infants Treated with BLES® Compared with Infants Treated with Exosurf®

Body System / Event	**BLES®** **N = 568** **(%)**	**Exosurf®** **N = 565** **(%)**
Cardiac Disorders		
Patent ductus arteriosus	44%	44%
Bradycardia	13%	15%
Eye Disorders		
Retinopathy of prematurity	19%	20%
Gastrointestinal Disorders		
Necrotizing enterocolitis	6%	7%
Infections		
Sepsis	28%	23%

Table 3 Adverse Events in ≥ 1% of Infants Treated with BLES® Compared with Infants Treated with Exosurf®		
Body System / Event	**BLES® N = 568 (%)**	**Exosurf® N = 565 (%)**
Investigations		
Decreased pulmonary function *	39%	41%
Nervous System Disorders		
Intraventricular haemorrhage, total	29%	29%
Intraventricular haemorrhage, Grades III and IV	12%	11%
Periventricular leukomalacia	8%	7%
Convulsion	2%	1%
Hydrocephalus	1%	<1%
Respiratory Disorders		
Pulmonary interstitial emphysema	9%	17%
Pneumothorax	8%	12%
Pulmonary haemorrhage	8%	7%
Endotracheal tube complication	6%	6%
Respiratory acidosis **	4%	2%
Apnoea	2%	4%
Pneumonia	1%	<1%
Vascular Disorders		
Hypotension	2%	2%

The most frequent events reported to occur in either treatment group were patent ductus arteriosus and decreased pulmonary function (defined as incidences of a fall in saturation or oxygenation, or an increase in CO_2 values after dosing); these events occurred with similar frequency in either treatment group, and are anticipated complications when infants in distress are handled.

Sepsis and pneumonia occurred more frequently in BLES® -treated infants than in those who received Exosurf®. Notwithstanding this higher incidence of sepsis, death due to infections was comparable between the two arms of the study.

Although the incidence of pulmonary haemorrhage was low (<1%) within the first two hours after dosing, it was observed to increase to 8% before discharge from intensive care. For the 750 - 1250 gram birth weight group receiving BLES®, 7 of 32 deaths (22%) were attributed to pulmonary haemorrhage.

There was a greater incidence of respiratory acidosis following treatment with BLES®. All incidences of respiratory acidosis occurred within two hours of dosing, and almost all incidences following either surfactant occurred at one study centre, perhaps due to too rapid weaning of the ventilatory pressure and rate with decreased minute ventilation.

Fewer infants who received BLES® developed pulmonary interstitial emphysema or pneumothorax than did those who were treated with Exosurf®. This may reflect the increased ventilatory requirements of infants who received Exosurf®. Thus, a reduction in ventilatory pressure following treatment with BLES® may protect infants from pulmonary air leaks.

Table 4, below, summarizes the adverse events that were reported to occur within two hours post-dose, in ≥ 1% of infants treated with BLES®. The incidence of these events in Exosurf® - treated infants is provided for comparison.

Table 4
Adverse Events within Two Hours of Dosing in ≥ 1% of Infants Treated with BLES® or Exosurf®

Body System / Event	**BLES®** **N = 568** **(%)**	**Exosurf®** **N = 565** **(%)**
Cardiac Disorders		
Bradycardia	11%	14%
Investigations		
Decreased pulmonary function*	39%	41%
Respiratory System Disorders		
Endotracheal tube complications	6%	6%
Respiratory acidosis**	4%	2%
Pulmonary haemorrhage	<1%	1%

* The term "decreased pulmonary function" covered incidences of a fall in saturation or oxygenation, or an increase in CO_2 values.
** Almost all incidences of respiratory acidosis occurred at one study site.

Decreased pulmonary function (reported incidences of a fall in saturation or oxygenation, or an increase in CO_2 values), bradycardia and endotracheal tube complications occurred with the same frequency in each treatment group, and are commonly associated with handling and treatment of premature infants. As discussed above, respiratory acidosis occurred, for the most part, at one site and may have been due to inadequate monitoring of lung compliance at that site.

Other adverse events that were reported to occur within two hours after administration of BLES®, but at a frequency of <1% were: acidosis; hypertension; hypotension; hypoxia; patent ductus arteriosus; pneumonia; pneumothorax; and pulmonary haemorrhage.

9.3 Less Common Clinical Trial Adverse Reactions

Uncommon adverse events that were reported to occur in < 1% of infants treated with BLES® were:

Blood and lymphatic system: neonatal coagulation disorder, neonatal jaundice; thrombocytopenia.

Cardiac disorders: cardiac arrest; cardiomegaly; cor pulmonale; hypertrophic cardiomyopathy; pneumopericardium; pulmonary oedema; pulmonary valve stenosis; supraventricular tachycardia.

Endocrine disorders: hypercalcaemia; hypoglycaemia.

Gastrointestinal disorders: enteritis; gastrointestinal haemorrhage; gastrointestinal reflux; ileus; intestinal perforation; pneumoperitoneum.

General disorders: growth retardation; neonatal hypothermia.

Hepato-biliary disorders: hepatomegaly.

Infections and infestations: miscellaneous infections other than pneumonia.

Metabolism and nutritional: acidosis; hyperkalemia.

Nervous system disorders: abnormal electroencephalogram; cerebral infarction; encephalopathy; ependymitis; meningitis.

Renal and urinary disorders: anuria; hydronephrosis; hydroureter; nephrocalcinosis.

Respiratory disorders: asphyxia; bronchopulmonary dysplasia; hypoxia; pulmonary hypertension.

Skin disorders: cellulitis.

Vascular disorders: haemorrhage; hypertension.

9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Laboratory values were not collected in clinical trials. However, respiratory acidosis was reported as an adverse event in 4% of infants receiving BLES® and 2% of those receiving Exosurf® ($p<0.05$). Respiratory acidosis occurred primarily at one study centre. Lung compliance and oxygenation should be monitored closely, as ventilation parameters may change rapidly after dosing (see 8 WARNINGS AND PRECAUTIONS).

9.5 Clinical Trial Adverse Reactions (Pediatrics)

Adverse events associated with BLES® use in the indicated pediatric population are described above (see 9.2 Clinical Trial Adverse Reactions). Adverse event data are not available for pediatric population > 5 days postnatal age.

9.6 Post-Market Adverse Reactions

In 2019, two international studies reported an out-of-trend number of cases of pulmonary haemorrhage, including death; notwithstanding, the incidence remains below that seen in the clinical trial for patients treated with BLES® (8%).

Three infants at one site, who were administered very small aliquots of 1 mL at a time, developed pulmonary haemorrhage, intraventricular haemorrhage and/or periventricular leukomalacia, and died. The very small doses may have led to uneven surfactant distribution and uneven lung compliance. As noted in 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, small aliquot or slow-drip methods are not appropriate for the administration of BLES®.

10 DRUG INTERACTIONS

10.1 Overview

There are no known drug interactions between BLES® and other substances, including alcohol. BLES® is not known to interfere with laboratory results.

Clinical experience with BLES® has shown it to be safe and effective when used with nitric oxide therapy, high frequency oscillation and extracorporeal membranous oxygenation.

10.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

10.3 Drug-Food Interactions

Interactions with food have not been established.

10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Bovine lipid extract surfactant suspension restores surfactant activity in neonates with respiratory distress syndrome (NRDS), thereby improving gaseous exchange by decreasing alveolar surface tension and promoting lung compliance in the infant with NRDS.

Bovine lipid extract surfactant suspension is an extract of natural bovine surfactant which contains numerous phospholipids, with dipalmitoylphosphatidylcholine (DPPC) being the most abundant. It also includes hydrophobic surfactant-associated proteins SP-B and SP-C, which facilitate their dispersion. When administered intratracheally, BLES® is rapidly adsorbed, forming an active phospholipid monolayer at the air-fluid interface.

11.2 Pharmacodynamics

Bovine lipid extract surfactant suspension can have an immediate effect on lung compliance, usually within 5 to 30 minutes after treatment with a single dose. Clinical experience with BLES® has shown that BLES® significantly improved gas exchange and lung compliance by the 4-hour time-point. Fraction of inspired oxygen (FiO_2) and ventilatory requirements were significantly decreased, and there was a reduction in the severity of NRDS and its associated complications.

11.3 Pharmacokinetics

The metabolic fate of bovine lipid extract surfactant suspension has not been investigated.

12 STORAGE, STABILITY AND DISPOSAL

BLES® (bovine lipid extract surfactant suspension) has a shelf life of 36 months when stored frozen below -10°C. Do not use past expiry date on label. Store vials in cartons until ready for use. Frozen product may have two excursions to 2°–8°C for a combined maximum of two weeks.

Alternately, BLES® may be stored refrigerated (2°– 8ºC) upon receipt, for up to 10 months. In the space provided on the vial labelling, record the new expiry date of up to 10 months from the day it is received. Refrigerated vials should not be returned to the freezer.

An unopened vial warmed to room temperature for less than 6 hours, may be returned to its previous storage condition a maximum of 2 times. In the space provided on the vial labelling, record the number of times the vial has been warmed and returned to storage.

There are no special disposal considerations for BLES®.

13 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

14 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Bovine lipid extract surfactant

Bovine lipid extract surfactant is an extract of bovine pulmonary surfactant that contains numerous phospholipids and hydrophobic surfactant associated proteins SP-B and SP-C.

The phospholipids are present in the drug product in the following ratio, expressed as a percent of the total phospholipid concentration.

Phospholipid	Concentration (mol%)
Phosphatidylcholine	75 - 85
Phosphatidylglycerol	12 - 17
Phosphatidylethanolamine	1 - 5
Phosphatidylinositol	0 - 2
Phosphatidylserine	0 - 2
Sphingomyelin	0 - 5
Lyso-phosphatidylcholine	0 - 2.5
Lyso-bis-phosphatidic acid	0 - 2.4

The hydrophobic proteins are surfactant-associated proteins SP-B and SP-C present at 6.5 - 18.5 µg/mg phospholipid.

Product Characteristics

Phospholipids and hydrophobic proteins SP-B and SP-C are isolated from bovine lung surfactant, then suspended in a sodium chloride and calcium chloride solution, which is heat sterilized in single-use vials.

Viral Inactivation

Not applicable.

15 CLINICAL TRIALS

15.1 Trial Design and Study Demographics

The efficacy of BLES® (bovine lipid extract surfactant suspension) is supported by the results of a Phase III pivotal trial, Study No. 92-001, comparing the safety and efficacy of BLES® with Exosurf® Neonatal (colfosceril palmitate; Glaxo Wellcome) in the rescue treatment of neonates with respiratory distress syndrome. Exosurf® was chosen as the comparator because it was the only approved exogenous surfactant therapy available in Canada at that time.

This 10 centre double-blinded randomized controlled trial involved 1133 infants. Infants were stratified into weight groups of <750 grams (n=180), 750-1250 grams (n=455) and >1250 grams

(n=499). Infants could receive up to four doses of surfactant, as required, within the first five days of life.

Table 5
Summary of Patient Demographics for Treatment of NRDS with BLES® and Exosurf®

Study #	Trial design	Dosage, route of administration and duration	Study subjects enrolled (completing)	Mean age gestational weeks (range)	Gender (% M/F)
92-001	Randomized, controlled, double-blind, multicentre, comparative. Three birth weight arms.	BLES® groups (B): 5 mL/kg (135 mg/kg) Exosurf® groups (E): 5 mL/kg (67.5 mg DPPC/kg) Intratracheal instillation (INSURE method) Up to 4 doses within first 5 days.	<750 g B: 92 (46) E: 88 (34) 750-1250 g B: 223 (191) E: 231 (181) >1250 g B: 253 (243) E: 246 (236)	<750 g B: 25 (21-30) E: 25 (21-30) 750-1250 g B: 27 (23-33) E: 27 (23-32) >1250 g B: 32 (25-39) E: 33 (27-41)	<750 g B: 46/54 E: 50/50 750-1250 g B: 58/42 E: 60/40 >1250 g B: 66/34 E: 64/36

Infants with NRDS were enrolled in three birth weight arms and randomized to receive BLES® or Exosurf®. There were no differences between treatment groups for demographic variables or pre-dose complications, except a significantly greater incidence of prolonged rupture of the membranes (PROM) in BLES®-treated infants weighing 750-1250 g compared with those receiving Exosurf® (26% and 18%, respectively). Because both treatment groups had a similar severity of hyaline membrane disease prior to treatment, as measured by ventilation parameters, age of intubation and age of first treatment, this increased incidence of PROM was considered not likely to have affected the study outcomes.

15.2 Study Results

Efficacy parameters were evaluated by birth weight group. Table 6 provides results for intact cardiopulmonary survival and ventilatory requirements.

Table 6
Results of Study # 92-001: Comparison of Outcomes for BLES® and Exosurf® in Rescue Treatment of NRDS

Primary Endpoint	Birth Weight Arm	BLES®	Exosurf®	p-value*
Intact cardiopulmonary survival at 36 weeks post-conceptional age	< 750 g	10/48 (20.8%)	6/36 (16.7%)	1.0000
	750-1250 g	87/194 (44.8%)	78/187 (41.7%)	0.6307
	> 1250g	112/244 (45.9%)	101/239 (42.3%)	0.4446

Table 6 Results of Study # 92-001: Comparison of Outcomes for BLES® and Exosurf® in Rescue Treatment of NRDS			
Secondary Endpoints	**Birth Weight Arm**	**BLES® Mean (±SD)**	**Exosurf® Mean (±SD)**
F_{iO_2}	< 750 g: pre-dose 1	0.7339 (0.2225)	0.7451 (0.2411)
	4 hr post dose 1	0.3596 (0.2154)	0.5682 (0.2713)
	8 hr post dose 1	0.3356 (0.1887)	0.5308 (0.2817)
	72 hr post last dose	0.3862 (0.2243)	0.3617 (0.1900)
	750-1250 g: pre-dose 1	0.7145 (0.2135)	0.7346 (0.2128)
	4 hr post dose 1	0.3146 (0.1865)	0.5377 (0.2374)
	8 hr post dose 1	0.2996 (0.1620)	0.4880 (0.2338)
	72 hr post last dose	0.2892 (0.1145)	0.3323 (0.1749)
	> 1250 g: pre-dose 1	0.6955 (0.2107)	0.6806 (0.2160)
	4 hr post dose 1	0.3290 (0.1788)	0.5360 (0.2330)
	8 hr post dose 1	0.3252 (0.1834)	0.5063 (0.2313)
	72 hr post last dose	0.2839 (0.0945)	0.3041 (0.1157)
Oxygen Index	< 750 g: pre-dose 1	18.0220 (17.8002)	15.8985 (9.1605)
	4 hr post dose 1	6.4249 (7.2556)	13.6258 (11.2144)
	8 hr post dose 1	5.9697 (5.7121)	12.9753 (13.3296)
	72 hr post last dose	6.6133 (4.9333)	8.5459 (8.6711)
	750-1250 g: pre-dose 1	15.6959 (8.1102)	17.3776 (10.7439)
	4 hr post dose 1	6.2894 (7.9001)	12.9900 (17.0293)
	8 hr post dose 1	5.3815 (4.2476)	11.4025 (10.7463)
	72 hr post last dose	5.7925 (4.5380)	6.6868 (5.3723)
	> 1250 g: pre-dose 1	16.6848 (8.5005)	17.0481 (8.9031)
	4 hr post dose 1	6.1373 (5.7382)	12.6262 (9.9566)
	8 hr post dose 1	6.4682 (5.4018)	11.0867 (7.8351)
	72 hr post last dose	8.1383 (10.4309)	6.8157 (4.2723)

* Adjusted, two-sided p-value. Data analyzed by logistic regression. Missing data was handled according to the intention to treat principle without using imputation technique.

The endpoints were selected based on relevancy to the clinical benefit of surfactant therapy. All patients randomized to treatment were included in the efficacy analyses. The three birth weight arms were analyzed separately due to the difference in maturity of the lungs usually found in these birth weights. The testing plan also investigated the interaction effect between birth weight and assigned treatment. In addition, hospital centres were controlled for in the analyses of the outcome variables. A P-value of less than 0.05 was accepted as significant.

Administration via MIST:
In a published retrospective cohort study by Bhattacharya *et al*. (2019) the safety, efficacy, and procedural details pertaining to the delivery of BLES® via the minimally invasive surfactant therapy (MIST) technique were reviewed in infants born at ≥ 28 weeks and / or with a birth weight ≥ 1,000 grams with respiratory distress syndrome. The study spanned more than two years and examined data from 43 infants that had undergone the MIST technique at the London Health Sciences Centre, with successful surfactant instillation seen in 41 neonates (95.3%). No serious adverse events were reported. Intubation and positive pressure ventilation were avoided in 35 neonates (85.3%). The authors concluded that MIST can be successfully performed with higher dosing volume surfactants such as BLES®.

16 MICROBIOLOGY

No microbiological information is required for this drug product.

17 NON-CLINICAL TOXICOLOGY

17.1 General Toxicology

Acute Toxicity
No acute toxicity studies have been conducted with bovine lipid extract surfactant suspension.

Long-Term Toxicity
In a 17-day intratracheal toxicity study, four groups of male and female western cross lambs were administered bovine lipid extract surfactant suspension or vehicle control by intratracheal instillation every other day for a total of 5 doses. Another four males and four females received no treatment.

Dyspnea was commonly observed during dosing with both the vehicle control and bovine lipid extract surfactant suspension. Two animals given bovine lipid extract surfactant suspension died during the second dosing (Study Day 3) from apparent volume overload (drowning). Further doses of bovine lipid extract surfactant suspension were administered in aliquots spread over several hours. No other consistent adverse pharmacologic, toxicologic or behavioural clinical signs were noted from treatment with bovine lipid extract surfactant suspension or vehicle control.

A localized 2 cm mass (abscess) was observed near the trachea of one lamb in the bovine lipid extract surfactant suspension group; no definitive relationship to treatment was established.
In summary, intratracheal administration of 270 mg/kg bovine lipid extract surfactant suspension in a volume of 10 mL/kg once every other day for a total of 5 doses beginning 24-48 hr after birth produced no distinct or definitive signs of systemic toxicity.

17.2 Carcinogenicity

- The carcinogenic potential of bovine lipid extract surfactant suspension has not been evaluated.

17.3 Genotoxicity

- The genotoxic potential of bovine lipid extract surfactant suspension has not been evaluated.

17.4 Reproductive and Developmental Toxicology

- Impairment to reproductive potential has not been evaluated for bovine lipid extract surfactant suspension.

17.5 Special Toxicology Studies

- Animal studies assessing the immunotoxicity of bovine lipid extract surfactant suspension have not been performed.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BLES®
bovine lipid extract surfactant suspension

This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about the medical condition and treatment and ask if there is any new information about **BLES®**.

Serious Warnings and Precautions

- **BLES® should only be given in a properly resourced clinical setting.**
- **BLES® can affect oxygen intake and lung expansion rapidly. In some cases, excess oxygen may enter the lungs minutes after administration.**
- **While BLES® is being administered, the baby's heart rate may slow down and less oxygen may enter the lungs for a short period of time.**
- **It is not recommended to give BLES® slowly or in small doses as this may lead to uneven spreading in the lungs.**

What is BLES® used for?

- BLES® is used to treat or "rescue" premature babies with Neonatal Respiratory Distress Syndrome (NRDS).

How does BLES® work?

BLES® is an extract of a natural substance (lung surfactant) necessary for effective breathing. Babies with NRDS who lack their own surfactant may have trouble absorbing enough oxygen when they breathe. BLES® spreads through the lungs, allowing the lungs to expand properly and oxygen to enter the blood more easily. This will lower the baby's need for extra oxygen under pressure.

What are the ingredients in BLES®?

Medicinal ingredients: phospholipids (natural fats) and proteins found in cow lung surfactant.
Non-medicinal ingredients: calcium chloride (salt), sodium chloride (salt) and water.

BLES® comes in the following dosage forms:

BLES® is a suspension that contains 27 milligrams of phospholipids and 0.2 to 0.5 milligrams of surfactant proteins SP-B and SP-C per milliliter.

Do not use BLES® if:

- The infant's lungs may be bleeding.

To help avoid side effects, talk to your healthcare professional about BLES® use. Talk about any health conditions or problems, including:

- BLES® should only be given by healthcare professionals experienced in treating premature babies with Neonatal Respiratory Distress Syndrome. During and after receiving a dose, the baby will need to be monitored closely for any clinical changes.

- There is an increased risk of infections in babies treated with BLES®.
- Studies to show whether BLES® is linked to the development of cancer or genetic mutations have not been performed.
- Studies have shown that BLES® is not expected to cause allergies.
- Before giving BLES®, healthcare professionals should correct high acidity in the blood, low blood pressure, low blood sugar, and low body temperature in the baby.
- Excess oxygen may enter in the lungs after BLES® is given. If this happens, the healthcare professionals will adjust the oxygen intake level to prevent risk of abnormal blood vessel growth in the eye.
- Babies should be monitored closely for oxygen requirements before, during, and after BLES® is given as it can cause oxygen to enter the blood very quickly.
- While BLES® is being administered, the baby's heart rate may slow down and less oxygen may enter the lungs for a short period of time. If this occurs, the healthcare professional should stop giving BLES® and correct the condition before proceeding.
- BLES® should not be given slowly or in small doses. Unlike other surfactants, BLES® has a "thin" consistency and therefore it travels down into the lungs much more rapidly. If given slowly, BLES® may not spread into the lungs evenly.
- If the baby's breathing grows shallow after BLES® is administered, liquid from the lungs may have formed a plug in the baby's airway. If suctioning of the airway is unsuccessful, the blocked tube should be replaced immediately. There is a reduced chance of this plug forming if the baby is suctioned before giving BLES®.
- In 2019, two international studies reported a higher than usual number of cases of bleeding in the lungs, including death; however, the total number of cases is less than the number seen during clinical testing.

The following may interact with BLES®:
- There are no known interactions between BLES® and other drugs.

How to take BLES®:
BLES® is given to babies within several hours of birth by healthcare professionals.

Usual dose:
For each kilogram of birth weight, the baby may receive 135 milligrams of phospholipid. If more than one dose is needed, the dose may be repeated up to three times in the first five days of life.

Overdose:
There is no record of an overdose having been given. Although it is possible that too much BLES® could block the baby's airway, it can be removed by suction.

If you think the baby may have been given too much BLES®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using BLES®?

These are not all the possible side effects the baby may feel when taking BLES®. If the baby experiences any side effects not listed here, contact your healthcare professional.

BLES® is given to babies within several hours of birth by healthcare professionals who will monitor the baby for any side effects. Because the baby's breathing will be interrupted during dosing, the baby may require more oxygen for a short while.

The baby will receive surfactant as soon as possible after birth. Complications that develop may be due to the baby's prematurity rather than this treatment. If you should have any concerns or questions about the baby's condition after a dose, consult with the healthcare professionals who are monitoring the baby.

Serious side effects and what to do about them			
Symptom / effect	Report the event to the healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Decreased pulmonary function: low level of oxygen entering the lungs. This lasts for a very short time after BLES® has been administered.	X		
Intraventricular haemorrhage: bleeding in the brain leading to increased pressure in the head.		X	
Patent ductus arteriosus: increased blood pressure in the lungs causing the lungs and the heart to increase in size.		X	
Retinopathy of prematurity: abnormal growth of blood vessels in the eyes.		X	
Sepsis: severe infection in the body leading to fever and inflammation.		X	
COMMON Airways obstruction: liquid plug formation in the surfactant administration tube leading to shortening of breath. This tube is removed after BLES® has been given.	X		
Bradycardia: slow heart rate.		X	
Necrotizing enterocolitis: infection and inflammation in the intestine.		X	
Periventricular leukomalacia: brain injury in areas of brain tissue that may cause mental and physical impairments.		X	

Pneumothorax: a collapsed lung occurs when air leaks into the space between your lung and chest wall leading to chest pain and shortness of breath.		X	
Pulmonary haemorrhage: coughing up blood and shortness of breath.		X	
Pulmonary interstitial emphysema: collection of air outside the air sacs of the lung causing breathing difficulty.		X	
RARE Apnoea: interruption or lack of breathing.		X	
Convulsion: rapid shaking or seizure like movement.		X	
Hydrocephalus: build-up of fluid in the brain that may cause bulges on the head.		X	
Hypotension: low blood pressure that may cause dizziness or fainting.		X	
Pneumonia: inflammation in the air sacs in the lungs that may cause coughing, fever and difficulty breathing.		X	
Respiratory acidosis: inability of the lungs to remove carbon dioxide, leading to increased acidity of the blood.		X	

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
BLES® is stored either frozen or refrigerated at the hospital.

If you want more information about BLES®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; by contacting the sponsor, BLES Biochemicals Inc., at info@blesbiochem.com or by calling 1-519-457-2537.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

This leaflet was prepared by BLES Biochemicals Inc.

Last Revised: September 29, 2021