

BLES[®]
(bovine lipid extract surfactant)
27 mg/~~ml~~mL Suspension for Intratracheal Instillation
Phospholipid 27 mg/mL
Surfactant associated proteins SP-B and SP-C 176-500 µg/mL

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DESCRIPTION

BLES[®] (~~bovine lipid extract surfactant~~) 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.

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COMPOSITION

Each ~~ml~~mL of suspension contains 27 mg of phospholipid and 176-500 µg of surfactant associated protein's SP-B and SP-C. ~~Contains no preservatives.~~

Inactive ingredients: 0.1 M ~~Sodium-sodium~~ chloride, 0.0015 M ~~Calcium-calcium~~ chloride, ~~Sterile sterile~~ water for ~~Irrigation-irrigation~~ and ~~Nitrogen~~nitrogen (vial head space). ~~BLES[®] contains no preservatives.~~

ACTION AND CLINICAL PHARMACOLOGY

BLES[®] (~~bovine lipid extract surfactant~~) 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.

BLES[®] 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.

The metabolic fate of BLES[®] has not been investigated.

BLES[®] 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 (FiO₂) and ventilatory requirements were significantly decreased, and there was a reduction in the severity of NRDS and its associated complications.

INDICATIONS

BLES[®] (~~bovine lipid extract surfactant~~) is indicated for rescue treatment of Neonatal Respiratory Distress Syndrome (NRDS/Hyaline Membrane Disease).

For infants with NRDS confirmed by X-ray ~~and who require mechanical ventilation~~, with arterial to alveolar oxygen ratio (PaO₂/PAO₂) <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.

DOSAGE AND ADMINISTRATION

Route of administration

~~BLES® should only be administered by the intratracheal route.~~

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Dosing Considerations: BLES® (~~bovine lipid extract surfactant~~) is intended for intratracheal instillation only, ~~after an endotracheal airway has been established.~~

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):

<u>Method of Warming</u>	<u>Refrigerated Vials</u>	<u>Frozen Vials</u>
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.

Recommended Dosage: 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.

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	10.00

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 mainstream bronchus.**

Draw the full dose into a syringe with a bevelled large gauge (e.g. at least 20-gauge) needle, and fit the ~~needle-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. ~~Discharge the syringe to fill the feeding tube with surfactant.~~ 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 H₂O, 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_{O_2}/TcP_{CO_2} readings, the oxygen saturation monitor and chest expansion. TcP_{O_2}/TcP_{CO_2} 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_{O_2} 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_{O_2} should be between 60-70 torr, Pa_{CO_2} 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_{O_2} 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_{O_2}/TcP_{CO_2} readings (as confirmed by comparison to blood gas measurements) indicate the infant should be weaned off Fi_{O_2} , ventilator rates and pressures. Blood gas readings should be 60 - 70 torr for Pa_{O_2} and 35 - 45 torr for Pa_{CO_2} . 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. Suctioning of all infants prior to dosing may lessen the chance of mucous plugs obstructing the ETT. 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 Fi_{O_2} . This increase must be at least 10% greater than the Fi_{O_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.

INCOMPATIBILITIES

This section is not applicable to BLES®, as there is no reconstitution required.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS**Serious Warnings and Precautions**

- Administer in a highly supervised clinical setting.
- BLES® can affect oxygenation and lung compliance rapidly. In some infants, hyperoxia may occur within minutes of administration.
- Transient episodes of bradycardia and decreased oxygen saturation may occur during dosing.
- 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.

General:

BLES® ~~-(bovine lipid extract surfactant)~~ is intended for intratracheal use only (See ~~see~~ 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®.

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

Monitoring and Laboratory Tests:

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

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Ophthalmologic: Hyperoxia may occur within minutes of administration of BLES®. If hyperoxia develops and oxygen saturation is in excess of 95%, Fi_{O_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®. Monitor infants 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 over distension 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 ~~see~~ Adverse Reactions, 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, 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). In 2018, 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 the patients treated with BLES® (8%) (see Post-Market Adverse Drug Reactions).~~

Monitoring and Laboratory Tests

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

INTERACTION WITH OTHER MEDICAMENTS-MEDICATIONS

There are no known drug interactions between BLES® and other substances. 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.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

~~Not applicable, as this product is used only in infants. BLES® is not indicated for pregnant or breast-feeding women.~~

ADVERSE REACTIONS

Adverse Drug Reaction Overview:- Very common adverse events occurring in $\geq 10\%$ of infants who received BLES® (~~bovine lipid extract surfactant~~), in descending order of frequency, were patent ductus arteriosus, decreased post-dose pulmonary function values, intraventricular haemorrhage of all grades, sepsis, retinopathy of prematurity, bradycardia and severe intraventricular haemorrhage.

Common adverse events occurring in $\geq 1\%$ and $< 10\%$ of infants who received BLES®, in descending order of frequency, were pulmonary interstitial emphysema, periventricular leukomalacia, pneumothorax, pulmonary haemorrhage, endotracheal tube complications, necrotizing enterocolitis, respiratory acidosis, convulsions, hypotension, apnoea, hydrocephalus and pneumonia.

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.

Clinical Trial Adverse Drug Reaction: Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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.

Adverse events occurring in $\geq 1\%$ of ~~instants~~ infants treated with BLES[®] are summarized by body system and in order of decreasing frequency in Table 2, below. The incidence of these events in Exosurf[®] -treated infants is provided for comparison.

Body System/event	BLES [®] N= 568	Exosurf [®] N= 565	Statistically Significant p-value
Infection			
Sepsis	28%	23%	<0.05
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%	-
Eye Disorders			
Retinopathy of prematurity	19%	20%	-
Cardiac Disorders			
Patent ductus arteriosus	44%	44%	-
Bradycardia	13%	15%	-
Vascular Disorders			
Hypotension	2%	2%	-
Respiratory Disorders			
Pulmonary interstitial emphysema	9%	17%	<0.0005
Pneumothorax	8%	12%	<0.05
Pulmonary haemorrhage	8%	7%	-
Endotracheal tube complication	6%	6%	-
Respiratory acidosis*	4%	2%	<0.05
Apnoea	2%	4%	-
Pneumonia	1%	<1%	<0.05
Gastrointestinal Disorders			
Necrotizing enterocolitis	6%	7%	-
Investigations			
Decreased pulmonary function**	39%	41%	-

* Almost all incidences of respiratory acidosis occurred at one study site.

** The term "decreased pulmonary function" covered incidences of a fall in saturation or oxygenation, or an increase in CO₂ values after dosing.

The most frequent events reported to occur in either treatment group were patent ductus arteriosus in almost half of the infants, ~~and decreased pulmonary in almost half on the infants,~~ and decreases pulmonary function (defined as incidences of a fall in saturation or oxygenation, or an increase in CO₂ value after dosing) in approximately one third of infants. These events occurred with similar frequency in either treatment group, and are anticipated complications when infants in distress and handled.

Sepsis and pneumonia occurred significantly more frequently in BLES[®] -treated infants than in those who received Exosurf[®]. Not-with-standing 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. This was not

significantly different from the incidence of pulmonary haemorrhage with Exosurf®. For the 750-1250 gram birth weight group receiving BLES®, 7 of 32 deaths (22%) were attributed to pulmonary haemorrhage.

There was a significantly 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 ventilator pressure and rate with decreased minute ventilation.

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

Table 3, 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 ~~the~~ these events in Exosurf®-treated infants is provided for comparison.

Body System/event	BLES® N= 568	Exosurf® N= 565	Statistically Significant p-value
Cardiac Disorders			
Bradycardia	11%	14%	-
Vascular Disorders			
Hypotension	2%	2%	
Respiratory System Disorders			
Endotracheal tube complication	6%	6%	-
Respiratory acidosis*	4%	2%	<0.05
Pulmonary haemorrhage	<1%	1%	-
Investigations			
Decreased pulmonary function**	39%	41%	-

*Almost all incidences of respiratory acidosis occurred at one study site.

** The term 'decreased pulmonary function' covered incidences of a fall in saturation or oxygenation, or an increase in CO₂ values after dosing.

Decreased pulmonary function (reported incidences of a fall in saturation or oxygenation, or an increase in CO₂ 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 a frequency of <1% were: acidosis; hypertension; hypotension; hypoxia; patent ductus arteriosus; pneumonia; pneumothorax; and pulmonary haemorrhage.

Less Common Clinical Trial Adverse Drug Reactions: Uncommon adverse events that were reported to occur in < 1% of infants treated with BLES® were:

Infections and infestations: miscellaneous infections other than pneumonia.

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

Endocrine disorders: hypercalcaemia; hypoglycaemia.

Metabolism and nutritional: acidosis; hyperkalemia.

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

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

Vascular disorders: haemorrhage; hypertension.

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

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

Hepato-biliary disorders: hepatomegaly.

Skin disorders: cellulitis.

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

General disorders: growth retardation; neonatal hypothermia.

Abnormal Hematologic and Clinical Chemistry Findings: 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 occurring occurred primarily at one study centre. Lung compliance and oxygenation should be monitored closely, as ventilation parameters may change rapidly after dosing (See ~~see~~ warning and precautions WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions: There has been an increase in the number of reported cases of pulmonary haemorrhage, including death. In 2018, two international studies reported an out-of-trend number of cases of pulmonary haemorrhage; notwithstanding, the incidence remains below that seen in the clinical trial for the patients treated with BLES[®] (8%).

Three infants at one site, who were administered very small aliquots of 1 mL at a time without rotation of the infant, 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 Serious Warning and Precaution box, small aliquot or slow-drip methods are not appropriate for the administration of BLES[®].

OVERDOSE AND TREATMENT

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

STORAGE CONDITION

BLES[®] (bovine lipid extract surfactant) 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° - 8°C) 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.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions

DOSAGE FORM AND PACKAGING AVAILABLE

BLES[®] (~~bovine lipid extract surfactant~~) 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 two or in cartons of 10 vials.

PHARMACEUTICAL INFORMATION

Drug Substance: 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.

<u>Phospholipid</u>	<u>Concentration (mol%)</u>
Phosphatidylcholine	75 - 85
Phosphatidylglycerol	12 - 17
Phosphatidylethanolamine	1 - 5
Phosphatidylinositol	10 - 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.

CLINICAL TRIALS

Study demographics and trial design: The efficacy of BLES[®] (~~bovine lipid extract surfactant~~) 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.

Commented [MA5]: The composition of BLES is provided on page 1; therefore it has been removed from this section. The heading also indicates that only the dosage form and packaging are required for this section.

Commented [MA6]: This section, Clinical trials, and Toxicology are not included in the Canadian package insert. Please confirm if we should still keep those sections for the Malaysia insert.

In order to ensure that the package insert is not overcrowded, we recommend removing these three sections.

Study #	Trial design	Route of administration, duration and dosage	Study subjects enrolled (completing)	Mean age gestational weeks (range)	Gender (% M/F)
92-001	Randomized, controlled, double-blind, multicentre, comparative. Three birth weight arms.	Intratracheal instillation Up to 4 doses within first 5 days. BLES [®] groups (B): 5 mL/kg (135 mg/kg) Exosurf [®] groups (E): 5 mL/kg (67.5 mg DPPC/kg)	<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 statistically significant 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; $p=0.0450$). 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.

Study results: Efficacy parameters were evaluated by birth weight group. Table 5 provides results for intact cardiopulmonary survival and ventilatory requirements.

	Birth Weight Arm	BLES [®]	Exosurf [®]	p-value	
Intact cardiopulmonary survival at 36 weeks post-	<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	
FiO ₂	<750 g:	pre-dose 1	0.7339	0.7451	0.7460
		4 hr post-dose 1	0.3596	0.5682	0.0000
		8 hr post-dose 1	0.3356	0.5308	0.0000
		72 hr post-last dose	0.3862	0.3617	0.5320
	750-1250 g:	pre-dose 1	0.7145	0.7346	0.3150
		4 hr post-dose 1	0.3146	0.5377	0.0000
		8 hr post-dose 1	0.2996	0.4880	0.0000
		72 hr post-last dose	0.2892	0.3323	0.0035
	>1250 g:	pre-dose 1	0.6955	0.6806	0.4401
		4 hr post-dose 1	0.3290	0.5360	0.0000
		8 hr post-dose 1	0.3252	0.5063	0.0000
		72 hr post-last dose	0.2839	0.3041	0.0360

Oxygen Index	< 750 g:	pre-dose 1	18.0220	15.8985	0.3149
		4 hr post dose 1	6.4249	13.6258	0.0000
		8 hr post dose 1	5.9697	12.9753	0.0001
		72 hr post last dose	6.6133	8.5459	0.1821
	750-1250 g:	pre-dose 1	15.6959	17.3776	0.0655
		4 hr post dose 1	6.2894	12.9900	0.0000
		8 hr post dose 1	5.3815	11.4025	0.0000
		72 hr post last dose	5.7925	6.6868	0.1634
	> 1250 g:	pre-dose 1	16.6848	17.0481	0.6442
		4 hr post dose 1	6.1373	12.6262	0.0000
		8 hr post dose 1	6.4682	11.0867	0.0000
		72 hr post last dose	8.1383	6.8157	0.3881

Table 5:
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-conceptual 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
	> 1250 g	112/244 (45.9%)	101/239 (42.3%)	0.4446
Secondary Endpoints	Birth Weight Arm	BLES [®] Mean (±SD)	Exosurf [®] Mean (±SD)	
Fi _{O2}	< 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)

Commented [MA7]: Table updated based on comments from Health Canada.

* 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.

BLES[®] was as effective as the comparator Exosurf[®] for intact cardiopulmonary survival at 36 weeks gestational age. BLES was as effective or more effective than Exosurf[®] for secondary endpoints. Of infants treated in the 750-1250 g arm:

- significantly more infants treated with BLES[®] were alive at discharge (p=0.0435);
- infants treated with BLES[®] had fewer air leaks (p<0.0001);
- infants treated with BLES[®] had a decreased incidence of high oxygen requirements (p=0.0234); and
- there were no significant differences in the incidences of IVH (intraventricular haemorrhage) or severe IVH/PVL (periventricular leukomalacia).

Other Studies

A published study by Lam *et al.* (2005) compared the efficacy of BLES[®] and Survanta[®] in a randomized clinical trial in premature infants with birth weights between 500 and 1,800 g who developed RDS requiring mechanical ventilation with oxygen requirements of more than 3% within the first 6 hours of life. Sixty infants were recruited, with 29 in the BLES[®] and 31 in the Survanta[®] group. The trial was not blinded due to the different administration methods recommended for each product, particularly the number of aliquots and rotations. The primary outcome was the oxygen index within 12 hr of treatment. Neonatal complications were analysed as secondary outcomes.

Both groups had significant and sustained improvements in their oxygenation index after treatment, with the BLES[®] group associated with a significantly lower oxygenation index throughout the 12-hr period compared with infants who received Survanta[®]. There was no difference in secondary outcomes, including mortality, ventilator days and occurrence of chronic lung disease. The authors attributed the difference in speed of response to the higher concentration of surfactant associated proteins in BLES[®].

In open-label trials, over 5000 infants have received BLES[®].

Long-term studies comparing BLES[®] to placebo (sham air) treatment demonstrated no significant differences in development of neurodevelopmental handicaps and allergic manifestations.

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 $\geq 1,000$ 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[®].

DETAILED PHARMACOLOGY

Twenty adult sheep were given a non-uniform pattern of lung injury by repetitive saline lavage followed by HCl instillation, until arterial PO₂ fell below 90 Torr. After the final lavage, the sheep were mechanically ventilated for 60 min before treatment with either BLES[®] (bovine lipid extract surfactant) or Survanta[®] (beractant, Abbott) which had been radiolabelled. Ten animals received 10 mL of surfactant by nebulizer, with 5 mL aliquots added as needed over a three-hour treatment

Commented [MA8]: This section was removed from the Canadian labelling documents per Health Canada's request.

period. Ten animals received instilled surfactant at a dose of 100 mg phospholipid/kg body weight, applied in three aliquots over several inspiratory breaths, while being turned.

The sheep given instilled BLES[®], aerosolized Survanta[®] and instilled Survanta[®] had significantly increased PaO₂ values and decreased A-aPO₂ values by 180 min compared with their respective pretreatment values (p<0.01). Those given aerosolized BLES[®] had no statistically significant changes in either PaO₂ or A-aPO₂ values over this treatment period. Animals given instilled BLES[®] had significantly higher PaO₂ and lower A-aPO₂ values than did the other three groups at each time point after treatment (p<0.01). Aerosolized BLES[®] values at 180 min were significantly inferior to the other treatment groups (p<0.05).

PaCO₂ values following instillation of BLES[®] were significantly lower than the pretreatment values from 60 min after treatment (p<0.05) through to 180 min (p<0.01). PaCO₂ values for aerosolized Survanta[®] were significantly lower than the pretreatment values (p<0.01), whereas PaCO₂ values were significantly higher following instilled Survanta[®], and did not change significantly over time for the aerosolized BLES[®]. Animals given instilled BLES[®] or aerosolized Survanta[®] had significantly lower PaCO₂ values than did the animals given either instilled Survanta[®] or aerosolized BLES[®] at any time point after treatment (p<0.05).

Three hours after treatment, the proportion of the recovered surfactant present in the airways relative to lung tissue was greater for animals treated with BLES[®] than those treated with Survanta[®] (p<0.05).

Total phospholipid recovery was significantly higher in lavage isolated from the instilled groups compared with the aerosolized groups. The total quantity of protein present in the alveolar lavage was similar for all four treatment groups. The mean small aggregate/large aggregate (SA/LA) of animals given instilled BLES[®] was significantly lower than that of animals receiving instilled Survanta[®] (p<0.05). Animals treated with aerosolized BLES[®] had a significantly higher SA/LA than did aerosolized Survanta[®] animals (p<0.05).

In conclusion, instilled BLES[®] resulted in the greatest improvement in lung function. Viscosity measurements of each preparation using an Ostwald viscometer, showed Survanta[®] to have a viscosity eight times that of BLES[®]. It also was noted that BLES[®] contains significantly more surfactant associated proteins than does Survanta[®]. These factors may have influenced the distribution of each surfactant, as it was observed that there was acute deterioration in ventilator parameters after instillation of Survanta[®].

TOXICOLOGY

Acute Toxicity: No acute toxicity studies have been conducted with BLES[®] (bovine lipid extract surfactant).

Long-Term Toxicity: In a 17-day intratracheal toxicity study, four groups of male and female western cross lambs were administered BLES[®] 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 BLES[®]. Two animals given BLES[®] died during the second dosing (Study Day 3) from apparent volume overload (drowning). Further doses of BLES[®] were administered in aliquots spread over several hours. No other consistent adverse pharmacologic, toxicologic or behavioural clinical signs were noted from treatment with BLES[®] or vehicle control.

A localized 2 cm mass (abscess) was observed near the trachea of one lamb in the BLES® group; no definitive relationship to treatment was established.

In summary, intratracheal administration of 270 mg/kg BLES® 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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No studies have been performed to investigate the carcinogenesis, mutagenesis or impairment to fertility of BLES®.

Immunogenicity: Animal studies for assessing immunogenicity have not been performed.

SHELF-LIFE

BLES® has a shelf life of 36 months when stored frozen below -10°C. Alternately, BLES® may be stored refrigerated (2° - 8°C) upon receipt, for up to 10 months ([see STORAGE CONDITIONS](#)).

REGISTRATION NUMBER

BLES® (bovine lipid extract surfactant) 27 mg/ml Suspension for Intratracheal Instillation
-MAL18116081AZ

NAME AND ADDRESS OF MANUFACTURER

BLES Biochemicals Inc.
60 Pacific Court, Unit 8
London, Ontario
Canada N5V 3K4
Tel: 519-457-2537
Fax: 519-457-7470
Email: info@blesbiochem.com
[Website: blesbiochem.com](http://blesbiochem.com)

NAME AND ADDRESS OF PRODUCT REGISTRATION HOLDER

Averroes Pharmaceutical Sdn. Bhd 03-08-01 & 03-09-01,
Block 3, Presint Alami, Worldwide Business Centre II,
Persiaran Akuatik, Seksyen 13,
40100 Shah Alam, Malaysia
Tel: +603 5511 1433
Fax: +603 5511 1431

DATE OF REVISION OF PACKAGE INSERT

~~14th October 2020~~ [30 January 2023](#)