ЛСР-010019/08-151208

MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
INSTRUCTIONS
FOR MEDICAL USE OF THE MEDICINAL PRODUCT
SURFACTANT-BL

Marketing Authorization Number:
Trade Name: Surfactant-BL
INN:
Formulation: lyophilisate for emulsion for inhalation
Composition: 1 vial contains 25 mg of surfactant extracted from bovine lungs and representing a mixture of phospholipids and surfactant-associated proteins.
Description: White to off-white lyophilised tabletted mass or powder. Adding a 0.9% sodium chloride solution to the drug and thorough mixing result in the creamy white or off-white homogeneous emulsion, which should not contain flakes or solid particles.
Pharmacotherapeutic Group: surfactant
ATC code: R07AA30
Pharmacological Properties
Pharmacodynamics
The drug Surfactant-BL is a highly refined natural surfactant derived from bovine lungs and representing a set of substances comprising the mixture of phospholipids and surfactant associated proteins, is able to reduce the surface tension on the pulmonary alveoli surface, preventing them from collapsing and atelectasis.
The drug Surfactant-BL restores the phospholipide content on the alveolar epithelium surface, stimulates the involvement of additional pulmonary parenchyma sections in respiration, and contributes to removal of toxic substances and infectious agents from the alveolar space with sputum. The drug upregulates alveolar macrophages and suppresses the cytokine expression by polymorphonucleocytes (including eosinophils); improves mucociliary clearance and stimulates the endogenous surfactant production by Type II alveolocytes and also protects the alveolar epithelium from damage with chemical and physical agents, restores the functions of local congenital and adaptive immunity. The studies established that in case of daily inhalation administration during 10 days and during 6 months (with additional followup period for 1 month), the drug does not influence the cardiovascular system nor produces locally irritating effect, nor influences the blood composition and hematopoiesis, nor effects the biochemical blood/ urine parameters and the blood coagulation system, nor causes pathological changes in functions and structure of internal organs, nor possesses theratogenic, allergenic and mutagenic properties.

In multi-center, randomized clinical studies involving patients with pulmonary tuberculosis who underwent conventional treatment with anti-tuberculosis drugs for 2-6 months and in whom no positive changes were noticed, the efficacy assessment of the two-month inhalation course of the drug Surfactant-BL within the comprehensive treatment suggested the following: the bacteria excretion termination after the drug Surfactant-BL course discontinuation was noticed in 50% patients and in 24.0% patients in the control group. 16 weeks after the treatment initiation, 80.0% patients achieved abacillation as compared with 62.0 % in the control group; 100% patients from the main group and 68.0% patients from the control group demonstrated the reduction in infiltrative and focal changes; and cavern(s) closed in 70.0 % patients of the main group and 36.0 % patients from the comparison group. Thus, the effect in such combined treatment is achieved much quicker and in a significantly greater percentage of patients as compared with the conventional anti-TB treatment.

Pharmacokinetics:

The experiments suggested that after the single intra-tracheal introduction of the drug Surfactant-BL, its content in lungs decreases in 6-8 hours and reached the initial value 12 hours later. The drug is fully metabolized in lungs by Type II alveolocytes and alveolar macrophages and is not accumulated in the body.

Therapeutic Indications

In comprehensive treatment of pulmonary tuberculosis, both in patients with newly diagnosed tuberculosis and in those with disease recurrence, in case of infiltrative (with and without decay) or cavernous clinical form, in particular, if there is drug resistance of *Mycobacterium tuberculosis,* up to the multiple drug resistance.

Contraindications

- A trend to bloody expectoration and pulmonary hemorrhage.
- Air leakage syndrome.
- Age under 18 because the clinical trials have not been conducted in this age group and the doses are not determined.

Posology and Mode of Administration

The drug Surfactant BL is used within comprehensive treatment of patients with pulmonary tuberculosis against the background of fully deployed treatment with anti-tuberculosis drugs (ATBD), i.e. when 4-6 ATBD are selected for the patient empirically or based on data on the pathogen's drug sensitivity, which are well tolerated by the patient in the prescribed dose and combination. the drug Surfactant-BL is prescribed in multiple injections at 25 mg dose per inhalation:

- during the first 2 weeks: 5 times a week,
- during the subsequent 6 weeks: 3 times a week (in 1-2 days).

The course duration is 8 weeks: 28 inhalations; the total dose of the drug Surfactant-BL is 700 mg. Inhalations are prescribed before meals or 1.5-2 hours after meals. ATBD can be discontinued (substituted) during the treatment with the drug Surfactant-BL. The chemotherapy continues after completion of treatment with the drug Surfactant-BL.

Emulsion preparation

1. Before emulsion preparation, warm the vial with the drug Surfactant-BL in your hand for at least 1 minute.
2. Take a 3-5 mL syringe with a 18G or 19G needle of at least 50 mm long and connect the needle to the syringe. Draw up 2.5 mL warm (37 °C) 0.9% sodium chloride solution for injections into the syringe.
3. Remove the plastic cap from the drug Surfactant-BL vial containing the lyophilisate. Disinfect the rubber plug of the vial with an alcohol solution.
4. Insert the needle into the vial with lyophilisate through the center of the rubber plug (Fig. 1) and inject the sodium chloride solution slowly on the inner vial wall (Fig. 2).

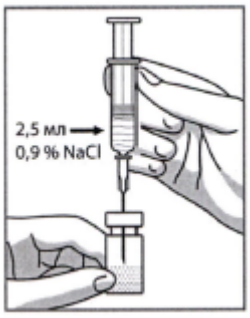

Figure 1

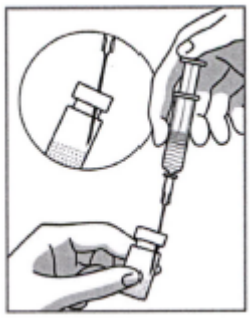

Figure 2

5. Mix the vial content immediately by circular movements for 5-10 seconds (Fig. 3). Never invert or shake the vial.

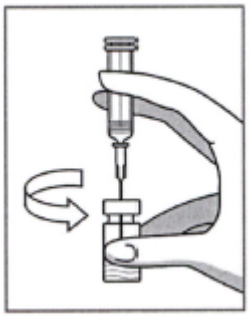

Figure 3

6. Let the vial stand for 2-3 minutes.
7. Draw up the vial content into the syringe, by placing the vial at a slight angle and the syringe needle, wit its cut to the vial wall (Fig. 4).

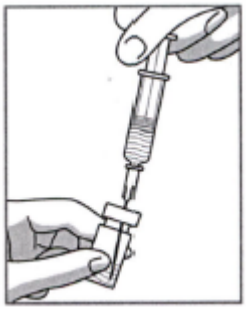

Figure 4

8. Then inject the syringe content back on the vial wall, avoiding the foam formation. Repeat the procedure 4-5 times. Never invert or shake the vial.
9. Remove the needle from the emulsion (not from the vial) so that the emulsion will not enter the syringe (Figure 5).

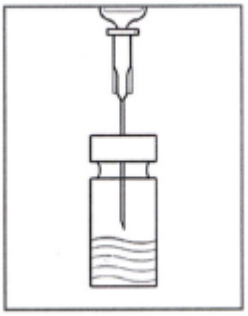

Figure 5

10. Keep the vial for approx. 1 minute motionless on a straight surface using the vial holder until the form separates (Figure 6). The ready emulsion is creamy white or off-white, and it must not contain flakes or solid particles.

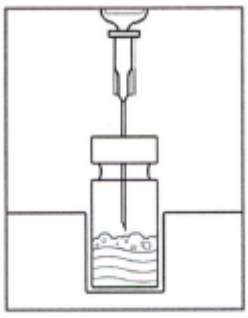

Figure 6

11. Without removing the needle from the vial with the finished emulsion, disconnect the syringe from the needle. Then take a new 18G or 19G needle of at least 50 mm long and connect it to the syringe. Draw up 2.5 mL warm (37 °C) 0.9% sodium chloride solution for injections into the syringe.

12. Disconnect the syringe from the needle with which you draw up the 0.9% sodium chloride soltion for injections and connect the syringe with the solution to the needle located in the vial with emulsion, and additionally dilute the obtained emulsion with 0.9% sodium chloride solution to 5 mL (to obtain 0.5% emulsion, 5 mg in 1 mL 0.9% sodium chloride solution). Additionally dilute the obtained emulsion with 0.9% sodium chloride solution to 5 mL (to obtain 0.5% emulsion, 5 mg in 1 mL 0.9% sodium chloride solution).

13. Slowly draw up the emulsion into the syringe leaving the foam in the vial (Fig. 7).

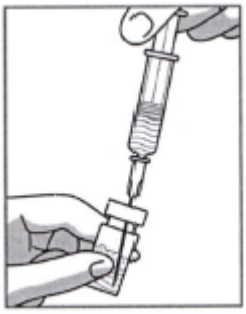

Figure 7

14. Transfer the emulsion into the nebulizer's camera, then wash the inner vial surface with 2 mL 0.9 % sodium chloride solution and also transfer them to the nebulizer.

Warning: the needle should remain in the vial during the entire procedure of the recreated emulsion preparation. After the emulsion preparation process is complete the needle must not be used anymore, it should be disposed.

The emulsion prepared for inhalations should be used during 12 hours when stored at +4 °C to +8 °C (the emulsion must not be frozen). Before use, the emulsion should be mixed slowly and warmed to 36-37 °C.

Inhalation injection: 5.0 mL obtained emulsion (25 mg) located in the nebulizer camera is used for inhalation. Inhalations are conducted 1.5-2 hours prior or 1.5-2 hors after meals. For inhalations, use mesh-nebulizers or compressor type nebulizers (e.g. Elisir from IsoMed, Russia; Borel from Flaem Nuova, Italy, or Pari Boy SX from Pari GmbH, Germany or their equivalents, which enable to spray small volumes of drugs and are fitted up with the economizer device that enables to terminate the drug supply during exhalation, which reduces the drug losses significantly). The use of economizer with the compression type nebulizers is extremely important so that the therapeutic drug dose will be injected to the patient without losses (25 mg). If the patient cannot use the entire emulsion volume because of the severe condition the 15-20 minute intervals should be made and then the inhalation should continue. If there is much sputum, it should be thoroughly expectorated before inhalation. If there is data on bronchial obstruction 30 minutes prior to inhalation of the drug Surfactant-BL emulsion, the inhalation of β_2-adrenoceptor agonist (at the physician's discretion) that reduces bronchial obstruction should be made before the inhalation. The compressor, not ultrasound nebulizers should only be used because the drug Surfactant-BL is destroyed by ultrasound. Before the drug injection the trachea bronchial tree should be thoroughly sanated, having taken efforts to improve the sputum drainage: vibromassage, postural treatment and mucolytics, which should be prescribed 3-5 days prior to the start of treatment with the drug Surfactant-BL, if there are no contraindications to their administration.

Adverse Reactions

When pulmonary tuberculosis is treated the volume of sputum increases significantly or the sputum increases that was not available before the start of inhalations after 3-5 inhalations in 60-70% patients. There is also the effect of "easy expectoration", with significant reduction in cough intensity and painfulness, and the exercise tolerance improves. These objective changes and subjective sensations are the manifestation of the direct impact of the drug Surfactant-BL and are not adverse reactions.

In rare cases, blood spitting may occur after 2-3 inhalations. In this case, the treatment with the drug Surfactant-BL should be terminated, and then inhalations should resume in 3-5 days.

Overdosage

The drug Surfactant-BL did not cause changes in animal behavior and condition when introduced to mice intravenously, intra-abdominally or subcutaneously at 600 mg/kg and when administered by inhalation to rats at 400 mg/kg. There were no animal deaths. There were no overdose cases in the clinical practice.

Drug-to-drug Interactions

The drug Surfactant-BL must not be used jointly with expectorants because the latter will remove the injected drug with the sputum. Incompatibility of the drug Surfactant-BL with any ATBD was not noted. There is no data on interactions with ATBD injected in aerosols so their co-administration should be avoided.

Special Warnings.

The use of the drug Surfactant-BL is possible to treat patients with pulmonary tuberculosis in the inpatient's department and in the day inpatient's department of an anti-TB dispensary.

Abilities to drive and use machines

The influence of treatment with the drug Surfactant-BL on the ability to drive vehicles and use machines was not studied.

Formulation: lyophilisate for emulsion for inhalation, 25 mg

25 mg in 10 mL glass vials stoppered with rubber plugs and sealed with aluminium caps.

2 vials are placed in each of cardboard packs, 5 packs together with the equal quantity of the Instructions for Use are placed into a cardboard box with the foam plastic insert.

Shelf life: 1 year. The drug must not be used after the expiry date.

Storage conditions: Keep away from direct sunlight, store at a temperature below -5° C. Keep away from children.

The opened and unused vial or any part thereof if stored in aseptic conditions at +4 - +8° C (the emulsion must not be frozen) can be used during the next 12 hours.

Dispensing conditions: at prescription.

Marketing Authorization Holder/ Manufacturer

Biosurf LLC, Russia

Manufacturing address:

St. Petersburg 197758, village of Pesochny, 70, Leningradskaya St., Letter B.

T/F: (812) 596-87-87.

Company accepting consumer complaints:

Company accepting consumer quality complaints

Biosurf LLC, Russia 197758, St. Petersburg, village of Pesochny, 70, Leningradskaya St., Letter B.

T/F: (812) 596-87-87.

Company receiving the consumer complaints on the drug safety

Nativa LLC, Russia

13, Oktyabrskaya St., Krasnogorsk, Moscow Region 143402

Tel.: (495) 644-00-59 T/F: (495) 502-16-43

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MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION
INSTRUCTIONS
FOR MEDICAL USE OF THE MEDICINAL PRODUCT

SURFACTANT-BL
lyophilisate for emulsion for endotracheal, endobronchial and inhalation administration, 75 mg

Marketing Authorization Number:
Trade Name: Surfactant-BL
Pharmaceutical Form: lyophilisate for emulsion for endotracheal, endobronchial and inhalation administration.
Composition: One vial contains **75** mg of surfactant extracted from bovine lungs and representing a mixture of phospholipids and surfactant-associated proteins.
Description: White to off-white lyophilised tabletted mass or powder. Adding 5 mL 0.9 % sodium chloride solution to the drug and slowly mixing by pipetting (draw up the suspension by the syringe with a needle from the vial and pour it back into the vial on the wall; repeat the procedure 4-5 times until complete and even emulsification is achieved, **by avoiding the foam formation),** helps obtain a homogeneous creamy white or off-white emulsion where there should be no flakes or solid particles.
Pharmacotherapeutic Group: surfactant
ATC code: R07AA30
Pharmacological Properties
Pharmacodynamics
The drug Surfactant-BL is a highly refined natural surfactant derived from bovine lungs and representing a set of substances comprising the mixture of phospholipids and surfactant associated proteins, is able to reduce the surface tension on the pulmonary alveoli surface, preventing them from collapsing and atelectasis.
The drug Surfactant-BL restores the phospholipide content on the alveolar epithelium surface, stimulates the involvement of additional pulmonary parenchyma sections in respiration, and contributes to removal of toxic substances and infectious agents from the alveolar space with sputum. The drug upregulates alveolar macrophages and suppresses the cytokine expression by polymorphonucleocytes (including eosinophils); improves mucociliary clearance and stimulates the endogenous surfactant production by Type II alveolocytes and also protects the alveolar epithelium from damage with chemical and physical agents, restores the functions of local congenital and acquired immunity.
The study established that in case of daily inhalation administration during 10 days or during 6 months and additional 1-month followup period the drug neither influences the cardiovascular system nor produces locally irritating effect nor influences the blood composition and hematopoiesis nor effects the biochemical blood/ urine parameters and the blood coagulation system, nor causes pathological changes in functions and structure of internal organs, nor possesses theratogenic, allergenic and mutagenic properties.
Endotracheal, micro-jet or bolus administration of the drug Surfactant-BL enables to greatly improve gas exchange in the pulmonary tissue in prematurely born newborns with the respiratory distress syndrome (RDS) who undergo artificial pulmonary ventilation (APV). In case of micro-jet introduction in 30-120 minutes, and in case of bolus introduction, in 10-15 minutes, the hypoxemia signs decrease; partial oxygen tension in arterial blood (PaO_2) and arterial blood hemoglobin oxigenation (SaO_2) improve, and hypercapnia decreases (partial carbon dioxide tension declines). The pulmonary tissue function restoration enables to shift to more physiological APV parameters and reduce its duration. The lethality and frequency of

complications in newborns with RDS decreases significantly when the drug Surfactant-BL is used.
Early, on Day 1 of the acute respiratory distress syndrome (ARDS) development, endobronchial drug injection in adults with ARDS was also established to halve the duration of patients' stay in APV and the stay in the intensive care unit (ICU), reduce the risk of purulent septic complications, associated with prolonged APV (purulent bronchitis and ventilator-associated pneumonia), and significantly reduces lethality in case of direct and indirect lung injury. More pronounced and early effect of therapy is observed with the combined use of endobronchial administration of the drug Surfactant-BL and the alveolar "opening" maneuver.
It was found that patients with pulmonary tuberculosis who did not respond positively to treatment with anti-tuberculosis drugs (ATBD) within 2-6 months, when a two-month course of inhalations of the drug is added to the therapy regimen, 80.0% patients achieved abacillation, 100% patients demonstrated reduction or disappearance in infiltrative and focal changes of lung tissue and cavern(s) closed in 70.0% of patients. Thus, complex anti-tuberculosis chemotherapy with the addition of a course of inhalations of the drug Surfactant-BL makes it possible to obtain a positive result from treatment much quicker and in a significantly greater percentage of patients

Pharmacokinetics

The experiments suggested that after the single intra-tracheal introduction of the drug Surfactant-BL to rats, its content in lungs decreases in 6-8 hours and reaches the initial value 12 hours later. The drug is fully metabolized in lungs by Type II alveolocytes and alveolar macrophages and is not accumulated in the body.

Indications for use:

1. Treatment of respiratory distress syndrome (RDS) in newborns weighing more than 800 g at birth.
2. In comprehensive treatment of acute respiratory distress syndrome (ARDS) in adults as a result of direct or indirect lung injury.
3. In comprehensive treatment of pulmonary tuberculosis, both in patients with newly diagnosed tuberculosis and in those with disease recurrence, in case of infiltrative (with and without decay) or cavernous clinical form, in particular, if there is drug resistance of *Mycobacterium tuberculosis*, up to the multiple drug resistance.

Contraindications

I. In RDS in newborns:

1. Degree III and IV intra-ventricular hemorrhage.
2. Air leakage syndrome (pneumothorax, pneumomediastinum, interstitial emphysema).
3. Fatal developmental defects.
4. Disseminated intravascular coagulation syndrome with pulmonary hemorrhage phenomena.

II. In ARDS:

1. Gas exchange disorders related to the left ventricular heart failure.
2. Gas exchange disorders caused by bronchial obstruction
3. Age under 18 because the clinical trials have not been conducted in this age group and the doses are not determined.
4. Air leakage syndrome

III. In pulmonary tuberculosis

1. Inclination to blood spitting and pulmonary hemorrhage.
2. Age under 18 because the clinical trials have not been conducted in this age group and the doses are not determined.
3. Air leakage syndrome

Administration during pregnancy and lactation

To be administered for life indications in ARDS treatment.

Posology and Mode of Administration

1. RDS treatment in newborns.

Before the treatment start, acidosis, arterial hypotension, anemia, hypoglycaemia and hypothermia must be adjusted. It is preferable to confirm RDS in X-ray.

The drug is injected by micro-jets, by inhalation or boluses. In case of micro-jet injection, the drug Surfactant-BL emulsion is injected slowly using the syringe doser (dose of 75 mg in 2.5 mL) during 30 minutes, and by inhalation via the alveolar nebulizer, the same dose, during 60 minutes. The drug Surfactant-BL can be injected by boluses at 50 mg/kg of the body weight (at 1.7 mL/kg). The second and, if necessary, the third injection of the drug is administered in 8-12 hours, in the same doses, if the child still needs the high oxygen concentration in the supplied gas mixture (FiO_4>0.4). It should be remembered that repeated injections of the drug Surfactant-BLs are less efficient if the first administration was delayed (late).

In case of a severe RDS (type 2 RDS, which often develops in full-term babies as a result of meconium aspiration, intrauterine pneumonia, sepsis), a greater dose of the drug Surfactant-BL, 100 mg/kg, should be used. The drug is repeatedly administered with the 8-12 hour interval, and if necessary, during several days.

The early beginning of treatment with the drug Surfactant-BL, within two hours after birth, if RDS diagnosis was established, but not less than Day 1 after birth, is an important efficacy factor of the drug Surfactant-BL administration, in comprehensive treatment of RDS.

The use of high frequency oscillatory APV enhances the efficacy of treatment with the drug Surfactant-BL significantly and reduces the frequency of adverse reactions.

Emulsion preparation:

the emulsion for endotracheal, endobronchial or inhalation administration is prepared immediately before use, using 0.9% of sodium chloride solution for injections.

1. Before emulsion preparation, warm the vial with Surfactant-BL in your hand for at least 1 minute.
2. Take a 3-5 mL syringe with a 18G or 19G needle of at least 50 mm long and connect the needle to the syringe. Draw up 2.5 mL warm (37 °C) 0.9% sodium chloride solution for injections into the syringe.
3. Remove the plastic cap from the drug Surfactant-BL vial containing the lyophilisate. Disinfect the rubber plug of the vial with an alcohol solution.
4. Insert the needle into the vial with lyophilisate through the center of the rubber plug (Fig. and inject the sodium chloride solution slowly on the inner vial wall (Fig. 2).

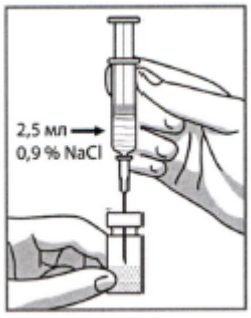

Figure 1

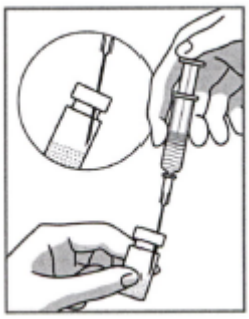

Figure 2

5. Mix the vial content immediately by circular movements for 5-10 seconds (Fig. 3). Never invert or shake the vial.

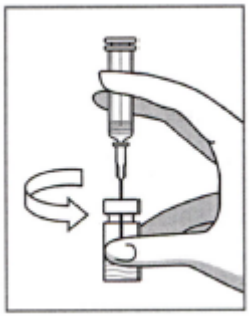

Figure 3

6. Let the vial stand for 2-3 minutes

7. Draw up the vial content into the syringe, by placing the vial at a slight angle and the syringe needle, wit its cut to the vial wall (Fig. 4).

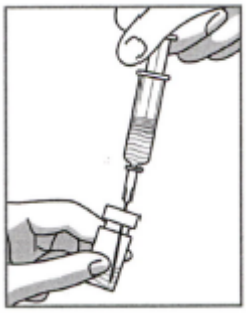

Figure 4

8. Then inject the syringe content back on the vial wall, avoiding the foam formation. Repeat the procedure 4-5 times. Never invert or shake the vial.

9. Remove the needle from the emulsion (not from the vial) so that the emulsion will not enter the syringe (Figure 5).

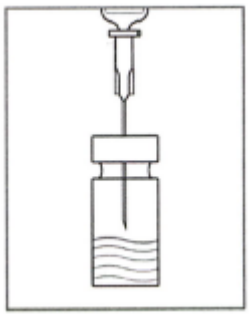

Figure 5

10. Keep the vial for approx. 1 minute motionless on a straight surface using the vial holder until the form separates (Figure 6). The ready emulsion is creamy white or off-white, and it must not contain flakes or solid particles.

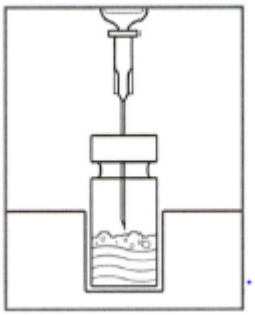

Figure 6

11. Slowly draw up the emulsion into the syringe leaving the foam in the vial (Fig. 7).

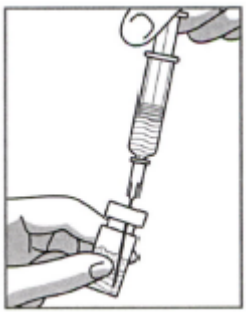

Figure 7

Warning: the syringe and the needle should remain in the vial during the entire procedure of the recreated emulsion preparation. After the emulsion preparation process is complete the needle must not be used anymore, it should be disposed.

Drug administration

Micro-jet introduction The child is pre-intubated and the sputum is aspirated from the respiratory tract and endotracheal tube (ET). The correct location and the conformity of ET size to the tracheal diameter is important because if there is a major leakage of emulsion past ET (over 25 % in the respiratory monitor or by auscultation) and also in case of selective intubation

to the right bronchus or the ET high standing, the treatment efficacy with the drug Surfactant-BL reduces significantly or becomes useless.
As soon as the child's respiratory cycle is synchronized with APV, the prepared emulsion of the drug Surfactant-BL is injected via a catheter introduced via the adapter with the additional lateral entrance into the endotracheal tube, so that the lower end of the catheter will not reach the lower edge of the endotracheal tube by 0.5 cm. The injection is carried out using the syringe doser for 30 minutes, without interrupting APV, without depressurizing of the breathing system. For even distribution of surfactant in different divisions of lungs during the drug administration, if the child's condition severity allows so, the first half of the dose is administered when the child lies on the left side, and the second half of the dose, when the child lies on the right side. When the administration is nearing completion, 0.5 mL of 0.9% sodium chloride solution is drewn up into the syringe, and the introduction continues, in order to replace the drug residues from the catheter. It is advisable to conduct the tracheal sanation during 2-3 hours after the drug Surfactant-BL introduction.
Inhalation administration of the drug Surfactant-BL is carried out using the alveolar nebulizer included into the breathing system of APV drug synchronized with the inhalation, as close as possible to the endotracheal tube, to reduce the drug losses. If there is no such opportunity, it is preferable to use a micro-jet or bolus administration method. To receive an aerosol and to inject the drug, the ultrasound nebulizers **must not be used** because the drug Surfactant-BL is destroyed when the emulsion is treated with ultrasound. The compressor type nebulizers should be used.
Bolus administration of the drug Surfactant-BL Before the drug administration, just as in case with micro-jet introduction, the central circulatory dynamics is stabilized, hypoglycaemia, hypothermia and metabolic acidosis are adjusted. It is preferable to confirm RDS in X-ray. The child is intubated and the sputum is aspirated from the respiratory tract ET. Immediately prior to the drug Surfactant-BL administration, the child may be temporarily shifted to manual ventilation with the Ambou-type self-expanding bag. If necessary, the child is sedated. The prepared emulsion of the drug Surfactant-BL (30 mg/mL) is used at 50 mg/kg in 1.7 mL/kg volume. For instance, 75 mg (50 mg/kg) in the volume of 2.5 mL is injected to a child weighing 1,500 g. The drug is injected by boluses during 1-2 minutes via the catheter placed into an endotracheal tube; the child is turned to the left side slowly and the first half of the dose is injected, then the child is turned to the right side and the second dose half is injected. The administration ends with the forced manual ventilation for 1-2 minutes, with the inhaled oxygen concentration that is equal to the initial indicator in APV device or manual ventilation using the Ambou-type self-extending bag. SaO_2 must be monitored; control over blood gases before and after the drug Surfactant-BL administration is desirable. Then the child is transferred to the auxiliary ventilation or forced APV, and the ventilation parameters are adjusted. Bolus administration of the drug enables to quickly bring the treatment dose to the alveolar space and avoid inconveniences and adverse reactions typical of the micro-jet administration.
A half of dose is administered by boluses to the full-term newborns weighting over 2.5 kg, with the severe Type 2 RDS, because of the large emulsion volume, and the second half of the dose is administered in micro-jets. Bolus administration may be used for preventive administration of Surfactant-BL. In the future, depending on the baseline condition and the treatment efficacy, the child may be extubated with potential transfer to non-invasive lung ventilation method, with maintenance of the continuous positive airway pressure (CPAP).

2. ARDS treatment in adults

Treatment with the drug Surfactant-BL is carried out by endobronchial bolus administration using fibrobronchoscope. The drug is administered at 12 mg/kg/day. The dose is divided into two administrations of 6 mg/kg in 12-16 hours. It may take multiple injections of the drug (4-6 injections) to reach the steady gas exchange improvement (PaO_2/FiO_2increase to over 300 mm

Hg), increase in lung airness at thoracic X-ray and the possibility to conduct APV with FiO_4 < 0.4. In most cases, the drug Surfactant-BL course duration does not exceed 2 days. In 10-20% patients, the drug administration is not accompanied with the gas exchange normalization, first of all, in those patients in whom the drug is administered to treat the advanced multi-organ insufficiency (MOI). If the oxigenation does not improve during 2 days, the drug administration stops.

The drug administration commencement time is the most important efficacy factor in the drug Surfactant-BL administration in comprehensive ARDS treatment. It should begin during the first day (preferably, first hours) after PaO_2/FiO_2decline below 250 mm Hg

The drug can be administered for prevention when there is a threat of ARDS development in patients with chronic lung diseases, in particular, those with chronic obstructive pulmonary disease (COPD) and also before the extended thoracic surgeries at 6 mg/kg/day, or 3 mg/kg in 12 h.

Emulsion preparation

Before administration, the drug Surfactant-BL (75 mg in vial) is diluted in the same way as for newborns in 2.5 mL 0.9% sodium chloride solution. The obtained emulsion that must not contain flakes or solid particles is additionally diluted with 0.9% sodium chloride solution to 5 mL (15 mg in 1 mL).

Drug administration

Endobronchial administration is the most appropriate way of drug delivery. The drug Surfactant-BL administration is preceded by thorough sanation bronchoscopy conducted under a standard technique. At the end of the procedure, the equal quantity of drug emulsion is administered into each lung. The best effect is achieved when the emulsion is administered into each segmentary bronchus. The volume of administered emulsion is determined by the drug dose.

The combination of endobronchial drug administration and the alveolar "opening" maneuver is the most efficient metod of the drug Surfactant-BL administration in ARDS treatment, provided that segmental administration of the drug is conducted immediately before the alveolar "opening" maneuver. The bronchial sanation and administration of the drugs increasing the sputum discharge should be avoided during 2-3 days after the drug administration.

Use of intra-tracheal instillation is indicated if bronchoscopy is impossible. The emulsion is prepared under the above mentioned method. Before the drug administration, it is necessary to thoroughly sanate the trancheobronchial tree, having taken efforts to improve the sputum drainage (vibromassage, postural treatment). The emulsion is injected via the catheter installed into the endotracheal tube so that the catheter end will be located below the endotracheal tube opening, but necessarily above the carina of trachea. The emulsion should be introduced in two runs, by halving the dose, at 10 minute interval. In this case, the alveolar "opening" maneuver can be carried out after instillation.

3. Pulmonary tuberculosis treatment

The pulmonary tuberculosis treatment is carried out by multiple inhalations of the drug Surfactant BL drug as part of **comprehensive treatment** against the background of fully deployed treatment with anti-tuberculosis drugs (ATBD), i.e. when 4-6 ATBD are selected for the patient empirically or based on data on the pathogen's drug sensitivity, which are well tolerated by the patient in the prescribed dose and combination. It is in this case that the emulsion of the drug Surfactant-BL in inhalations at 25 mg/administration is prescribed to a patient.

- during the first 2 weeks: 5 times a week,
- during the subsequent 6 weeks: 3 times a week (in 1-2 days).

The course duration is 8 weeks: 28 inhalations; the total dose of the drug Surfactant-BL is 700 mg. Anti-tuberculosis drugs can be discontinued (substituted) during the treatment with the drug

Surfactant-BL. The chemotherapy continues after completion of treatment with the drug Surfactant-BL.

Emulsion preparation: Before use, the drug Surfactant-BL (75 mg in vial) is diluted in the same way as for newborns in 2.5 mL 0.9% sodium chloride solution. The obtained emulsion that must not contain flakes or solid particles is additionally diluted with 0.9% sodium chloride solution to 6 mL (12.5 mg in 1 mL). Then transfer 2.0 mL of the obtained emulsion to the nebulizer camera and add 3.0 mL more of 0.9% sodium chloride solution to the emulsion while mixing slowly. Thus, there are 25 mg of the drug Surfactant-BL in 5.0 mL emulsion in the nebulizer camera. This is the dose for inhalation to one patient. Thus, 1 vial of the drug Surfactant-BL contains three doses for inhalations to three patients. The emulsion prepared for inhalations should be used during 12 hours when stored at +4 °C to +8 °C (the emulsion must not be frozen). Before use, the emulsion should be mixed slowly and warmed to 36-37 °C.
Inhalation administration: 5.0 mL obtained emulsion (25 mg) located in the nebulizer camera is used for inhalation. Inhalations are conducted 1.5-2 hours prior or 1.5-2 hours after meals. The inhalations are performed using compressor type nebulizers, such as Borel from Flaem Nuova, Italy, or Pari Boy SX from Pari GmbH, Germany, or their equivalents that enable to pulverize small volumes of drugs and fitted up with the economizer device that enables to stop the drug supply during exhalation, which will reduce the drug losses significantly. The use of economizer is extremely important so that the therapeutic drug dose will be injected to the patient without losses (25 mg). If the patient cannot use the entire emulsion volume because of the severe condition the 15-20 minute intervals should be made and then the inhalation should continue. If there is much sputum, it should be thoroughly expectorated before inhalation. If there is data on bronchial obstruction, 30 minutes before inhalation of the drug Surfactant-BL emulsion it is necessary to make a preliminary inhalation of β_2-adrenoceptor agonist (at the physician's discretion) that reduces the bronchial obstruction. The compressor, not ultrasound nebulizers should only be used because the drug Surfactant-BL is destroyed by ultrasound. Before the drug injection the trachea bronchial tree should be thoroughly sanated, having taken efforts to improve the sputum drainage: vibromassage, postural treatment and mucolytics, which should be prescribed 3-5 days prior to the start of treatment with Surfactant-BL, if there are no contraindications to their administration.

Adverse Reactions

1. In RDS in newborns:

In case of micro-jet and bolus administration of the emulsion of the drug Surfactant-BL, the ET obturation with the drug or the emulsion regurgitation may occur. This problem may arise if the Emulsion Preparation section of the Instruction is not complied with (the use of 0.9 % sodium chloride solution at below 37 C, heterogeneous emulsion), in case of rigid chest, the child's high activity accompanied with coughing, weeping, if ET size does not conform to the tracheal internal diameter, selective intubation, the drug Surfactant-BL introduction into one bronchus or if these factors combine. If all of these factors are eliminated or excluded it is necessary to increase the peak inhalation pressure (P_{peak}) to the child who undergoes the instrumental APV. If a child has signs of the respiratory duct obturation, when the child is not in artificial ventilation, it is necessary to make several respiratory cycles using manual ventilation with increased pressure to push the drug in-depth. If the aerosol drug administration method is used such phenomena are not observed. The physical and instrumental monitoring of circulatory dynamics and SaO_2 is mandatory. Pulmonary hemorrhage is possible, usually during 1-2 days after the drug administration to prematurely delivered newborns, with low or extremely low body weight at birth. Prevention of pulmonary hemorrhage consists in early diagnosis and adequate treatment of the functioning arterial duct. If partial oxygen tension in blood increases quickly and significantly retinopathy may develop. The oxigen concentration in the inhaled mixture should be reduced as quickly as possible to the safe value, by maintaining the target value of SaO2

within 86%-93 %. Some newborns have short-term hyperemia of skin, which require adequacy assessment of the APV parameters, to rule out hypoventilation resulting from the transitory obstruction of the respiratory duct. In the first minutes after the micro-jet and bonus introduction of the drug Surfactant-BL, the large-bubble rales at inhalation may be auscultated in lungs. During 2-3 hours after the use of the drug Surfactant-BL, bronchial sanation should be avoided. In children with intranatal respiratory infection, the drug introduction may increase the sputum discharge because of the mucociliary clearance activation, which may require their sanation in a shorter term.

2. In ARDS in adults

So far, no specific adverse reactions were observed in treatment of ARDS of different origin with the drug Surfactant-BL.

If the endobronchial administration is used the gas exchange may deteriorate for 10 to 60 minutes, in connection with the bronchoscopy procedure. When SaO_2 drops below 90%, it is necessary to temporarily increase the positive pressure at the end of exhalation (PPEE) and the oxygen concentration in the gas mixture supplied to the patient (FiO_2). No gas exchange deterioration was observed when the endobronchial administration of the drug Surfactant-BL was combined with the alveolar "opening" maneuver.

3. Pulmonary tuberculosis

When pulmonary tuberculosis is treated the volume of sputum increases significantly or the sputum increases that was not available before the start of inhalations after 3-5 inhalations in 60-70% patients There is also the effect of "easy expectoration", with significant reduction in cough intensity and painfulness, and the exercise tolerance improves. These objective changes and subjective sensations are the manifestation of the direct impact of the drug Surfactant-BL and are not adverse reactions.

In rare cases, blood spitting may occur after 2-3 inhalations. In this case, the treatment with the drug Surfactant-BL should be interrupted, and then inhalations should resume in 3-5 days.

Overdosage

The drug Surfactant-BL did not cause changes in animal behavior and condition when introduced to mice intravenously, intra-abdominally or subcutaneously at 600 mg/kg and when administered by inhalation to rats at 400 mg/kg. There were no animal deaths. In case of clinical use, overdose cases were not observed.

Drug-to-drug Interactions

The drug Surfactant-BL must not be used jointly with expectorants because the latter will remove the injected drug with the sputum.

Special Warnings.

The use of the drug Surfactant-BL for treatment of critical states in newborns and adults is only possible in a specialized resuscitation unit, and for pulmonary tuberculosis treatment, in an inpatient department and a specialized anti-tuberculosis dispensary.

1. RDS treatment in newborns:

Before the drug Surfactant-BL administration, it is necessary to stabilize central circulatory dynamics and to correct the metabolic acidosis, hypoglycaemia and hypothermia, which have negative implications for the drug efficacy. It is preferable to confirm RDS in X-ray.

2. ARDS treatment in adults

The drug should be used as part of ARDS comprhensive treatment, including reasonable respiratory support, antibiotic treatment, support of adequate circulatory dynamics and water/ electrolyte balance.

The issue of the drug Surfactant-BL administration in ARDS combined with the Multiple organ dysfunction syndrome (MODS) should be resolved on a case-by-case basis, depending on the possibility to adjust other MODS components.

Immediately after the drug Surfactant-BL administration, the recommendation is to conduct the alveolar "opening" maneuver, and if it is impossible because of the patient's condition, to conduct the one-off pulmonary inflation with the double respiratory volume.

3. Pulmonary tuberculosis treatment

In rare cases, blood spitting may occur after 2-3 inhalations. In this case, the treatment with the drug Surfactant-BL should be interrupted, and then inhalations should resume in 3-5 days.
Incompatibility of the drug Surfactant-BL with any anti-tuberculosis drugs was not noted. There is no data on interactions with anti-tuberculosis drugs injected in aerosols so their co-administration should be avoided.

Abilities to drive and use machines

The influence of treatment with the drug Surfactant-BLs on the ability to drive vehicles and use machines was not studied.

Formulation:

Lyophilisate for emulsion for endotracheal, endobronchial and inhalation administration, 75 mg
75 mg in 10 mL glass vials stoppered with rubber plugs and sealed with aluminium caps.
2 vials are placed in each of cardboard packs, 5 packs together with the equal quantity of the Instructions for Use are placed into a cardboard box with the foam plastic insert.

Expiration Date:

1 year
Do not use after the expiration date.

Storage Conditions:

Keep away from direct sunlight, store at a temperature not exceeding -5°C.
Keep out of reach of children.
If the emulsion in the open vial is not fully used then during storage at aseptic conditions at +4 - +8 °C (do not freeze the emulsion), it can be used within 12 hours after its preparation.

Prescription Status

By prescription. To be used in the inpatient department.

Marketing Authorisation Holder/ Manufacturer

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Company accepting consumer quality complaints

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