HU000031750T2

(19) **HU**

(11) Lajstromszám: **E 031 750**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 14 150705**
(22) A bejelentés napja: **2008. 05. 23.**

(51) Int. Cl.: ***A61K 35/42*** *(2006.01)*
A61P 11/00 *(2006.01)*

(96) Az európai bejelentés bejelentési száma:
EP 20080150705
(97) Az európai bejelentés közzétételi adatai:
EP 2719391 A1 **2014. 04. 16.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2719391 B1 **2016. 11. 30.**

(30) Elsőbbségi adatok:
811351 **2007. 06. 08.** **US**

(72) Feltaláló(k):
Herting, Egbert, 43100 PARMA (IT)
Gopel, Wolfgang, 43100 PARMA (IT)
Chiesi, Paolo, 43100 PARMA (IT)

(73) Jogosult(ak):
CHIESI FARMACEUTICI S.p.A., 43100 Parma (IT)

(74) Képviselő:
Danubia Szabadalmi és Jogi Iroda Kft., Budapest

(54) **Eljárás pulmonális felületaktív anyag beadására**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 719 391 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
30.11.2016 Bulletin 2016/48

(51) Int Cl.:
A61K 35/42 *(2006.01)* ***A61P 11/00*** *(2006.01)*

(21) Application number: **14150705.3**

(22) Date of filing: **23.05.2008**

(54) **A method of administration of a pulmonary surfactant**

Verfahren zur Verabreichung eines Lungen-Surfactants

Procédé d'administration d'un surfactant pulmonaire

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR
Designated Extension States:
AL BA MK RS

(30) Priority: **08.06.2007 US 811351**

(43) Date of publication of application:
16.04.2014 Bulletin 2014/16

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
08758716.8 / 2 164 504

(73) Proprietor: **CHIESI FARMACEUTICI S.p.A.**
43100 Parma (IT)

(72) Inventors:
- **Herting, Egbert**
  43100 PARMA (IT)
- **Gopel, Wolfgang**
  43100 PARMA (IT)
- **Chiesi, Paolo**
  43100 PARMA (IT)

(74) Representative: **Minoja, Fabrizio**
Bianchetti Bracco Minoja S.r.l.
Via Plinio, 63
20129 Milano (IT)

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Printed by Jouve, 75001 PARIS (FR)

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Description

FIELD OF INVENTION

[0001] The present invention concerns a kit for use in preventing and/or treating respiratory distress syndrome in infants in need of such treatment through intratracheal administration of a pulmonary surfactant by a thin tube, the kit comprising said pulmonary surfactant and tube.

BACKGROUND OF THE INVENTION

[0002] The human lung is composed of a large number of small air sacs, called alveoli, in which gases are exchanged between the blood and the air spaces of the lungs. In healthy individuals, this exchange is mediated by the presence of a protein-containing surfactant complex that prevents the lungs from collapsing at the end of expiration.

[0003] Lung surfactant complex is composed primarily of lipids and contains minor amounts of various proteins. An absence of adequate levels of this complex results in malfunction of the lung. This syndrome is called Respiratory Distress Syndrome (RDS) and is the single most important cause of morbidity and mortality in pre-term infants.

[0004] RDS is mainly treated with replacement therapy whereby exogenous pulmonary surfactant preparations extracted from animal lungs, known as modified natural surfactants are administered to the human in need. For instance, modified natural surfactants used in the clinical practice are poractant alfa derived from porcine lung, and sold under the trademark of Curosurf®, beractant (Surfacten® or Survanta®), bovactant (Alveofact®), both derived from bovine lung, and calfactant derived form calf lung (Infasurf®).

[0005] Synthetic surfactants mimicking the composition of the modified natural surfactants, and known as reconstituted surfactants, have also been developed.

[0006] Exogenous pulmonary surfactants are currently administered by endotracheal instillation as suspension in a saline aqueous solution to intubated pre-term infants kept under intermittent positive pressure ventilation (IPPV).

[0007] However, IPPV is in itself an invasive procedure which frequently requires supplemental medication like treatment with sedatives, analgesic agents and catecholamines.

[0008] Furthermore IPPV in pre-term infants with RDS has long been recognized to contribute to lung injury which may lead to the development of pneumothorax and/or bronchopulmonary dysplasia (BDP); and may cause reduction of mucociliary clearance, mucosal injury, and secondary infections as well as blockage of the endotracheal.

[0009] In view of the potential complications associated with intubation and mechanical ventilation, attention has been focused on different approaches of administration of exogenous surfactant.

[0010] Since long time, as a possible initial respiratory support for very low birth weight (VLBW) infants, use of early nasal Continuous Positive Airway Pressure (nCPAP), that delivers air into the lungs through specially designed nasal devices such as masks, prongs or tubes, has been introduced in neonatal intensive care.

[0011] Recently, to give exogenous surfactant without mechanical ventilation, the use of a thin gastric tube placed in the trachea supported with nCPAP has been proposed (Göpel W et al, Abstract presented at the 20th International Workshop on Surfactant Replacement, Belfast, June 2-5, 2005, page 12: Kribs, A et al. Paediatr Anaesth. 2007 Apr;17(4):364-9).

[0012] In particular, Göpel W and colleagues reported the administration of 60 mg bovine surfactant, diluted to 30 mg/ml, by a 5 Fr gastric tube in spontaneously breathing infants with a mean weight of about 1 kg.

[0013] However, to improve the clinical outcome, an initial dose higher than 60 mg/kg body weight is currently recommended. A dose higher than 60 mg/kg requires the use of a higher concentration of the surfactant preparation, in particular of at least 40 mg/ml.

[0014] Verder H et al, Pediatrics, vol 103, no. 2, February 1999, page E24, discloses the use of Curosurf® in combination with nCPAP, in the treatment of respiratory distress syndrome in newborns of less than 30-week gestation. The surfactant is administered at the dose of 200 mg/kg and at the concentration of 80 mg/ml into the trachea of the patient using a gastric tube that is removed after administration.

[0015] Kribs A et al, Paediatric Anesthesia, vol 17, no. 4, April 2007, pages 364-369, discloses the administration of the surfactant Survanta® at a dose of 100 mg/kg into the trachea of spontaneously breathing, extremely premature infants through a thin gastric tube that is removed after administration, in combination with nCPAP.

[0016] Dani C et al, Pediatrics, vol 113, no. 6, June 2004, pages E560-E563, discloses the use of Curosurf® given at the dose of 200 mg/kg via tracheal tube, in combination with nCPAP, in the treatment of respiratory distress syndrome in newborns of less than 30-week gestation.

[0017] Since viscosity increases with surfactant concentration, the administration of a concentration of at least 40 mg/ml by means of a gastric tube having a very small diameter (5 Fr. corresponds to about 1.7 mm) would only be possible with a surfactant having low viscosity. In fact high viscosities would make the passage of the surfactant through the gastric tube and the small airways more difficult and may therefore result in uneven distribution in the lungs of the pre-term infants. Theoretically, surfactants having high viscosities involve the risk of blockage of the gastric tube and of acute airway obstruction. In view of the drawbacks of the known methods for delivery of exogenous surfactant, alternative therapeutic methods for surfactant administration are needed. Such methods should provide at least identical or, preferably

improved clinical outcome, without the potential complications associated with endotracheal intubation and mechanical ventilation.

[0018] The therapeutic methods and kits disclosed herein provide a remarkable improvement over known therapies.

SUMMARY OF THE INVENTION

[0019] The present invention discloses a method for preventing and/or treating a respiratory distress syndrome in a patient in need of such treatment, said method comprising the steps of:

a) applying nasal Continuous Positive Airway Pressure (nCPAP) with a nasal device to said patient at a pressure of from 1 to 12 cm water;
b) administering a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium via a tube having a diameter comprised between 5 and 12 Fr, preferably a gastric tube, into the trachea of said patient; and
c) removing said tube at the end of the administration;

wherein the pulmonary surfactant suspension is applied at a concentration of at least 40 mg/ml and has a viscosity lower than 20 mPas.

[0020] Another disclosure of the present invention refers to the use of a pulmonary surfactant in the manufacture of pharmaceutical composition for administration to a patient suffering of a respiratory distress syndrome, the administration procedure comprising the steps of:

a) applying nasal Continuous Positive Airway Pressure (nCPAP) with a nasal device to said patient at a pressure of from 1 to 12 cm water;
b) administering a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium via a tube having a diameter comprised between 5 and 12 Fr, preferably a gastric tube, into the trachea of said patient; and
c) removing said tube at the end of the administration;

wherein the pulmonary surfactant suspension is applied at a concentration of at least 40 mg/ml and has a viscosity lower than 20 mPas.

[0021] The invention is directed to a kit comprising:

i) a pharmaceutical composition comprising a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium at a concentration of at least 40 mg/ml, said composition having a viscosity lower than 20 cpoise;
ii) a thin tube having a diameter comprised between 5 and 12 Fr;
iii) a device for administering the surfactant at a controlled rate; and
iv) container means for containing the dosage form, the thin tube and the device.

DEFINITION

[0022] As used herein, the term "modified natural pulmonary surfactant" means a lipid extract of minced mammalian lung which, due to the lipid extraction step used in the manufacture process, is deprived of the hydrophilic proteins SP-A and SP-D and contains variable amounts of the hydrophobic proteins SP-B and SP-C. Depending on the method of extraction, the preparation may contain non-surfactant lipids and other components.

[0023] As used herein, the term "reconstituted pulmonary surfactant" means a synthetic surfactant made of a mixture of polar lipids, primarily phospholipids and optionally other components such as neutral lipids to which have been added surfactant proteins/peptides isolated from animals or proteins/peptides manufactured through recombinant technology such as those described in WO 95/32992, or synthetic surfactant protein analogues such as those described in WO 89/06657, WO 92/22315 and WO 00/47623.

[0024] "Pharmaceutical acceptable" is a term used herein that refers to a medium that does no not produce an allergic or similar untoward reaction when administered to an infant.

[0025] As used herein, the expression "improving the clinical outcome" means a surfactant with an improved efficacy in terms of indices of activity, i.e. lung compliance, lung gas volume, blood gases and ventilator settings.

DETAILED DISCLOSURE OF THE INVENTION

[0026] The present invention discloses a method of preventing and/or treating a respiratory distress syndrome in a patient in need of such treatment, said method comprises the steps of:

a) applying nasal Continuous Positive Airway Pressure (nCPAP) with a nasal device to said patient at a pressure of about 1 to 12 cm water;
b) administering a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium via a tube having a diameter comprised between 5 and 12 Fr into the trachea of said patient; and
c) removing said tube at the end of the administration;

wherein the pulmonary surfactant suspension is applied at a concentration of at least 40 mg/ml and has a viscosity lower than 20 mPas.

[0027] Advantageously, the method is applied to preterm infants, and preferably pre-term very-low-birth-weight-infants of 24-35 weeks gestational age that are spontaneously breathing, and demonstrate early signs

of respiratory distress syndrome as indicated either by clinical signs and/or supplemental oxygen demand (fraction of inspired oxygen (FiO_2) > 30%). The treatment shall start preferably in the first 24h of life.

[0028] The method is directed to the prevention and/or treatment of the respiratory distress syndrome on the infant related to a surfactant-deficiency or dysfunction (RDS) as well as of conditions in which respiratory distress may be present that include, but are not limited to, meconium aspiration and pulmonary infection.

[0029] The method may also be useful for preventing and/or treating acute respiratory distress syndrome in children or adults.

[0030] The method comprises applying nasal Continuous Positive Airway Pressure (nCPAP) with a nasal device such as a mask, prongs, or a pharyngeal tube according to known procedures.

[0031] Preferably, a nasal mask is utilised. Any nasal mask commercially available may be used, for example those provided by The CPAP Store LLC and the CPAP Company.

[0032] Nasal CPAP is typically applied at a pressure comprised between 1 and 12 cm water, preferably 2 and 8 cm water, although the pressure can vary depending on the infant and the pulmonary condition.

[0033] The application of nCPAP is advantageously carried out to the infant prior to administering the pulmonary surfactant and continuously throughout the procedure during both the administering and the removing steps.

[0034] Optionally, prior to the procedure, atropine is administered i.v. at 5 μg/kg body weight. Sedative and/or analgesic drugs can also optionally be administered.

[0035] Before administering the pulmonary surfactant, the gastric tube is placed with a Magill-forceps under direct visualization of the vocal cords of the infants by means of a laryngoscope.

[0036] After placement of the gastric tube, the laryngoscope is removed and the pulmonary surfactant is administered by instillation in the trachea at controlled rate with a suitable device.

[0037] The pulmonary surfactant in the form of suspension is administered by means of a tube having a diameter comprised between 5 and 12 Fr.

[0038] Any gastric or nasogastric tube, arterial or suction catheter of common use in hospitals can be utilised.

[0039] The tube may be made of any material, preferably of polyurethane or silicone.

[0040] Preferably a 5 Fr tube is used because it has a small diameter, but at the same time it is stiff enough to allow easy introduction with the Magill forceps. Preferably, a cm-scale is marked on the tube to allow the correct length of introduction.

[0041] If the tube has side holes, such holes should not be too far away from the catheter tip. The connector to the syringe should be small too avoid unnecessary dead space.

[0042] Preferably, the tube has a total length of about 30 cm to allow a length of about 10 cm in the oral cavity/nasopharynx and a length of about 20 cm outside for easy handling.

[0043] Suitable devices include syringes having a small dead volume, preferably of less than 0.5 ml, more preferably of less than 0.3 ml or infusion pumps.

[0044] Depending on the volume to be administered, the skilled person shall control the rate of delivering of the device in such a way as to instill the surfactant in a time comprised between 1 and 5 minutes, preferably between 1 and 3 minutes.

[0045] The pulmonary surfactant is administered as a suspension in a sterile pharmaceutically acceptable aqueous medium, preferably in a buffered physiological saline (0.9% w/v sodium chloride) aqueous solution, more preferably buffered at a pH comprised between 5.5 and 6.5.

[0046] The concentration of the surfactant is of at least 40 mg/ml, preferably comprised between 40 and 80 mg/ml.

[0047] The applied volume should be not more than 3.0 ml, preferably not more than 2 ml and, depending on the concentration of the pulmonary surfactant and dead volume the syringe.

[0048] Any modified natural or reconstituted pulmonary surfactant can be used provided that the relevant suspension in an aqueous medium has a viscosity lower than 20 mPas (1 mPas corresponds to 1 centipoise), preferably comprised between 5 and 15 mPas, more preferably between 6 and 10 mPas.

[0049] The viscosity may be determined by any known method. Preferably, the viscosity is determined according to the method reported in Example 1.

[0050] In particular, it has been found that, due to its low viscosity, the modified natural pulmonary surfactant known as poractant alfa is particularly suitable for administration by a gastric tube.

[0051] In particular its low viscosity allows administering the surfactant at a concentration of at least 40 mg/ml.

[0052] Poractant alfa formulated as a sterile suspension in a saline (0.9% w/v sodium chloride) aqueous solution at a concentration of 80 mg/ml is commercially available under the trademark of Curosurf®.

[0053] To achieve a concentration of 40 mg/ml or others comprised in the range of 40 to 80 mg/ml, Curosurf® can be diluted with a suitable volume of saline aqueous solution.

[0054] Advantageously, the dose of the pulmonary surfactant to be administered is equal to or higher than 80 mg *per* kg body weight, preferably comprised between 100 and 200 mg *per* kg body weight. The preferred dose is 100 mg *per* kg body weight.

[0055] The dose of the pulmonary surfactant to be administered varies with the size and maturity of the patient, as well as with the severity of the patient's condition. The skilled persons will be readily able to determine these factors and to adjust the dosage administered via the thin tube.

[0056] After administration of pulmonary the surfactant, the thin tube is removed.

[0057] However, the patient may receive a second dose of pulmonary surfactant, depending on the severity of the individual condition and on the response to the first surfactant treatment. In particular, if the needed FiO_2 is higher than 40%, the surfactant can be instilled by the thin tube, otherwise if the needed FiO_2 exceeds 60%, the surfactant can be instilled by endotracheal intubation under mechanical ventilation.

[0058] Said second dose may be equal to, higher or lesser than the first dose, depending on the needs and response of the patient.

[0059] The present invention is directed to a kit comprising: a) a pharmaceutical composition comprising a pulmonary surfactant suspended in a pharmaceutically acceptable aqueous medium at a concentration of at least 40 mg/ml, said composition having a viscosity lower than 20 centipoise; b) a thin tube having a diameter comprised between 5 and 12 Fr; c) a device for administering the surfactant at a controlled rate; and d) container means for the dosage form, the thin tube and the device.

[0060] The pulmonary surfactant is preferably poractant alfa.

[0061] The composition described herein is typically prepared by combining the pulmonary surfactant with a suitable volume of a pharmaceutically acceptable aqueous medium, preferably a saline aqueous solution, to form a substantially homogeneous aqueous suspension at the desired concentration.

[0062] Advantageously, the pharmaceutical composition is sterile and is supplied as a single-use glass vial.

[0063] Otherwise, in a particular embodiment, the sterile pharmaceutical composition may be supplied directly in the device used for administering the surfactant at a controlled rate.

[0064] The composition can be sterilized according to known methods.

[0065] The following examples illustrate the invention in more detail.

EXAMPLES

Example 1 - Viscosity measurement of a suspension of poractant alfa in a physiological saline aqueous solution

[0066] Rheological measurements are carried out at 25°C with a rheometer SR 200 (Rheometric Scientific) and 40 parallel plate geometry using different batches of Curosurf®, i.e. of poractant alfa suspended in physiological saline aqueous solution at a concentration of 80 mg/ml.

[0067] The instrument is calibrated to a gap of 0.7 mm.

[0068] The shear rate is varied between 0 and 500 s^{-1}.

[0069] For all batches Curosurf®, the viscosity (η) approaches a well-reproducible asymptotic value (max Shear Rate 500 s^{-1}) comprised between 6 and 10 mPas (1 mPas = 1 centipoise).

Example 2 - Administration of 100 mg/kg dose poractant alfa by gastric tube in very-low-birth-weight infants

Protocol of the study

[0070] In a preliminary observational study no differences between infants after surfactant application without intubation and infants with standard treatment are observed, despite the fact that infants treated with surfactant application without intubation are significantly smaller.

[0071] The primary objective of the following study is to demonstrate that the treatment of very-low-birth-weight (VLBW) infants with intratracheal instillation of a pulmonary surfactant is able to reduce the frequency of mechanical ventilation.

[0072] Secondary objectives of the study are to demonstrate that the proposed method:

- is associated with a reduced duration and intensity of mechanical ventilation; and
- is associated with a reduced incidence of bronchopulmonary dysplasia (BDP),

while being at least equivalent to standard treatment with regard to the secondary outcome measures death, intraventricular hemorrhage grade III and IV (IVH), and periventricular leukomalacia (PVL).

Design:

[0073] Prospective, randomized multi-center trial.

Study population:

[0074] Inclusion criteria:

- gestational age 26+0 - 28+6 weeks,
- birth weight below 1500 gram
- Age 0-12 hours
- Informed consent

[0075] Exclusion criteria:

- Mechanical ventilation
- Participation in other studies

Intervention:

[0076] Control-group:

- CPAP if FiO_2 exceeds 0.25
- all other therapies according to local standards.

[0077] Intervention group:

- CPAP if FiO_2 exceeds 0.25
- intratracheal surfactant via a gastric feeding tube if FiO_2 exceeds 0.3 (to keep oxygen saturation above 85%) and Silverman-score >4
- all other therapies according to local standards.

[0078] Intervention:

- Surfactant is given at a dose of 100 mg surfactant per kg body weight via a thin (gastric) tube into the trachea of the spontaneously breathing infant.
- CPAP is applied continuously during the procedure (nasal IPPV may be applied).
- Optional use of atropin (5 μg/kg body weight i.v.) prior to the procedure.
- As many doctors will not use sedation for intubation in the delivery suite or in the first hours/minutes of life, sedation/analgesia is not mandatory and at the discretion of the individual neonatologist.
- The gastric tube is placed with a Magill-forceps under direct visualization of the vocal cords by means of a laryngoscope.
- After placement of the gastric tube, the laryngoscope is removed and surfactant (100 mg/kg body weight) is instilled into the trachea during 1-5 minutes.
- Thereafter, the gastric tube is removed.
- Close observation of the child during the procedure is mandatory.
- Surfactant administration can be repeated if FiO_2 exceeds 0.4.
- Intubation and intratracheal surfactant administration should be considered if FiO_2 exceeds 0.6 or the child suffers from severe respiratory distress.
- All other treatments according to local standards.

[0079] Primary Outcome Measure:

- Intubation and mechanical ventilation between the 25. and 72. hour of life
- or
- FiO_2 >0.6 (to keep oxygen saturation above 85%) between the 25. and 72. hour of life
- or
- pCO_2 > 65 mm Hg for more than two hours between the 25. and 72. hour of life.

Sample size:

[0080] Based on current multi-center study data, we expect a frequency of the primary outcome measure in the control group of 60% vs. 40% in the intervention group. Since 50% of the infants are randomized to the control group, a total of 210 infants (105 in each group) will be necessary to test the primary hypothesis (p=0,05; beta-error 0,2; 2-sided). Since the participating centers are treating 250 patients/year who are eligible for the study and we calculated a 60% inclusion rate, a period of 30 months would be sufficient to test the primary hypothesis.

Secondary outcomes:

[0081] Ventilation rate, IVH, PVL, BPD, death, operation due to retinopathy (ROP), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intestinal perforation, hydrocephalus and ventricular-peritoneal-shunt, number of surfactant doses, total surfactant (mg/kg bodyweight), days on assisted ventilation, days on supplemental oxygen, duration of hospitalization, weight gain per day, pneumothorax, other complications of prematurity (same definitions as for the genetic study).

Methods against bias:

[0082] Infants are randomized prior to intubation. To avoid the possible bias that infants in the intervention group are not intubated although they meet local intubation criteria, we defined a combined primary endpoint using a FiO_2 >0.6 to gain a saturation > 85% and/or pCO_2 > 65 mm Hg for more than two hours during the 25-72 hour of life as an indicator for treatment failure. FiO_2-levels and pCO_2 levels are observed and documented by nurses. Blinding and a sham procedure in the control group are not possible.

Claims

1. A kit for use in the prevention and/or treatment of a respiratory distress syndrome comprising:

   a) a pharmaceutical composition comprising from 40 to 80 mg/ml of a pulmonary surfactant suspended in not more than 3.0 ml of a pharmaceutically acceptable aqueous medium in an unit dosage form, said composition having a viscosity lower than 20 mPas;
   b) a thin tube having a diameter of 5 Fr;
   c) a syringe for administering the surfactant at a controlled rate having a dead volume of less than 0.5 ml; , and
   d) container means for containing the dosage form, the thin tube and the syringe.

2. The kit for use as claimed in claim 1, wherein the thin tube is selected from the group consisting of gastric tube, nasogastric tube, and arterial or suction catheter.

3. The kit for use as claimed in claim 1 or 2, wherein pharmaceutically acceptable aqueous medium is a buffered physiological saline aqueous solution.

4. The kit for use as claimed in claim 3 wherein the pharmaceutical composition is sterile.

5. The kit for use as claimed in claim 4, wherein the unit dosage form is a single-use glass vial.

6. The kit for use as claimed in claim 5, wherein the sterile pharmaceutical composition is supplied directly in the device used for administering the surfactant at a controlled rate.

7. The kit for use as claimed in claim 1, wherein the volume of the pharmaceutically acceptable aqueous medium is not more than 2 ml.

8. The kit for use as claimed in any of the preceding claims, wherein the pharmaceutical composition has a viscosity comprised between 5 and 15 mPas.

9. The kit for use as claimed in claim 8, wherein the viscosity is comprised between 6 and 10 mPas.

10. The kit for use as claimed in claim 9, wherein the pulmonary surfactant is poractant alfa.

11. The kit for use as claimed in claim 1, wherein the respiratory distress syndrome is the infant respiratory distress syndrome (IRDS).

12. The kit for use as claimed in claim 1, wherein the respiratory distress syndrome is due to meconium aspiration or a pulmonary infection.

Patentansprüche

1. Kit zur Verwendung bei der Prävention und/oder Behandlung eines Atemnotsyndroms, umfassend:

   a) eine pharmazeutische Zusammensetzung, umfassend 40 bis 80 mg/ml eines pulmonalen Surfactant suspendiert in nicht mehr als 3,0 ml eines pharmazeutisch annehmbaren wässrigen Mediums, in einer Einheitsdosierungsform, wobei die Zusammensetzung eine Viskosität von niedriger als 20 mPas hat;
   b) einen dünnen Schlauch mit einem Durchmesser von 5 Fr;
   c) eine Spritze zur Verabreichung des Surfactants mit einer kontrollierten Rate, die ein Totvolumen von weniger als 0,5 ml hat, und
   d) Behältermittel zum Aufnehmen der Dosierungsform, des dünnen Schlauchs und der Spritze.

2. Kit zur Verwendung gemäß Anspruch 1, wobei der dünne Schlauch aus der Gruppe, bestehend aus Magenschlauch, transnasaler Magensonde und arteriellem Katheter oder Saugkatheter, ausgewählt ist.

3. Kit zur Verwendung gemäß Anspruch 1 oder 2, wobei das pharmazeutisch annehmbare wässrige Medium eine gepufferte physiologische wässrige Kochsalzlösung ist.

4. Kit zur Verwendung gemäß Anspruch 3, wobei die pharmazeutische Zusammensetzung steril ist.

5. Kit zur Verwendung gemäß Anspruch 4, wobei die Einheitsdosierungsform eine Glasphiole zur Einmalverwendung ist.

6. Kit zur Verwendung gemäß Anspruch 5, wobei die sterile pharmazeutische Zusammensetzung direkt in die Vorrichtung geleitet wird, die zur Verabreichung des Surfactants mit kontrollierter Rate verwendet wird.

7. Kit zur Verwendung gemäß Anspruch 1, wobei das Volumen des pharmazeutisch annehmbaren wässrigen Mediums nicht mehr als 2 ml ist.

8. Kit zur Verwendung gemäß einem der vorangehenden Ansprüche, wobei die pharmazeutische Zusammensetzung eine Viskosität hat, die zwischen 5 und 15 mPas liegt.

9. Kit zur Verwendung gemäß Anspruch 8, wobei die Viskosität zwischen 6 und 10 mPas liegt.

10. Kit zur Verwendung gemäß Anspruch 9, wobei das pulmonale Surfactant Poractant alfa ist.

11. Kit zur Verwendung gemäß Anspruch 1, wobei das Atemnot-syndrom das Säuglingsatemnotsyndrom (infant respiratory distress syndrome, IRDS) ist.

12. Kit zur Verwendung gemäß Anspruch 1, wobei das Atemnot-syndrom durch Meconiumaspiration oder pulmonale Infektion bedingt ist.

Revendications

1. Kit pour son utilisation dans la prévention et/ou le traitement d'un syndrome de détresse respiratoire, comprenant :

   a) une composition pharmaceutique comprenant de 40 à 80 mg/ml d'un agent tensioactif pulmonaire mis en suspension dans pas plus de 3,0 ml d'un milieu aqueux pharmaceutiquement acceptable dans une forme posologique unitaire, ladite composition possédant une viscosité inférieure à 20 mPas ;
   b) un tube mince possédant un diamètre de 5 Fr ;
   c) une seringue pour l'administration de l'agent tensioactif à un débit contrôlé, possédant un volume mort inférieur à 0,5 ml ; et

d) un moyen faisant office de récipient pour contenir la forme posologique, le tube mince et la seringue.

2. Kit pour son utilisation selon la revendication 1, dans lequel le tube mince est choisi parmi le groupe constitué par un tube gastrique, un tube nasogastrique et un cathéter artériel ou d'aspiration.

3. Kit pour son utilisation selon la revendication 1 ou 2, dans lequel le milieu aqueux pharmaceutiquement acceptable est une solution saline physiologique aqueuse tamponnée.

4. Kit pour son utilisation selon la revendication 3, dans lequel la composition pharmaceutique est stérile.

5. Kit pour son utilisation selon la revendication 4, dans lequel la forme posologique unitaire est un flacon en verre à usage unique.

6. Kit pour son utilisation selon la revendication 5, dans lequel la composition pharmaceutique stérile est alimentée directement dans le dispositif utilisé pour l'administration de l'agent tensioactif à un débit contrôlé.

7. Kit pour son utilisation selon la revendication 1, dans lequel le volume du milieu aqueux pharmaceutiquement acceptable n'est pas supérieur à 2 ml.

8. Kit pour son utilisation selon l'une quelconque des revendications précédentes, dans lequel la composition pharmaceutique possède une viscosité comprise entre 5 et 15 mPas.

9. Kit pour son utilisation selon la revendication 8, dans lequel la viscosité est comprise entre 6 et 10 mPas.

10. Kit pour son utilisation selon la revendication 9, dans lequel l'agent tensioactif pulmonaire est le poractant alfa.

11. Kit pour son utilisation selon la revendication 1, dans lequel le syndrome de détresse respiratoire représente le syndrome de détresse respiratoire du nouveau-né (IRDS).

12. Kit pour son utilisation selon la revendication 1, dans lequel le syndrome de détresse respiratoire est dû à une aspiration de méconium ou à une infection pulmonaire.

REFERENCES CITED IN THE DESCRIPTION

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Szabadalmi igénypontok

1. Készlet légzési distressz szindróma megelőzésében és/vagy kezelésében történő alkalmazásra, amely készlet tartalmazza a következőket:

a) gyógyszerészeti készítmény, amely tartalmaz 40-80 mg/ml pulmonális felületaktív anyagot szuszpendálva nem több, mint 3,0 ml gyógyszerészetileg elfogadható vizes közegben egységdózis formában, a készítmény kisebb, mint 20 mPas viszkozitással rendelkezik;

b) 5 Fr átmérőjű vékony cső;

c) fecskendő a felületaktív anyag szabályozott sebességű beadására, amely kisebb, mint 0,5 ml holttérfogattal rendelkezik; és

d) tárolóeszköz a dózisforma, a vékony cső és a fecskendő tárolására.

2. Készlet alkalmazásra az 1. igénypont szerint, ahol a vékony cső a következők alkotta csoportból választott: gyomorcső, orr-gyomor cső és artériás vagy szívó kateter.

3. Készlet alkalmazásra az 1. vagy 2. igénypont szerint, ahol a gyógyszerészetileg elfogadható vizes közeg pufferolt, fiziológiás sós vizes oldat.

4. Készlet alkalmazásra a 3. igénypont szerint, ahol a gyógyszerészeti készítmény steril.

5. Készlet alkalmazásra a 4. igénypont szerint, ahol az egységdózisforma egyszer használatos üvegfiola.

6. Készlet alkalmazásra az 5. igénypont szerint, ahol a steril gyógyszerészeti készítmény közvetlenül van biztosítva az eszközben, amely a felületaktív anyag szabályozott sebességű beadására alkalmazott.

7. Készlet alkalmazásra az 1. igénypont szerint, ahol a gyógyszerészetileg elfogadható vizes közeg térfogata nem nagyobb, mint 2 ml.

8. Készlet alkalmazásra az előző igénypontok bármelyike szerint, ahol a gyógyszerészeti készítmény viszkozitása 5 és 15 mPas közötti.

9. Készlet alkalmazásra a 8. igénypont szerint, ahol a viszkozitás 6 és 10 mPas közötti.

10. Készlet alkalmazásra a 9. igénypont szerint, ahol a pulmonális felületaktív anyag poracsant alfa.

11. Készlet alkalmazásra az 1. igénypont szerint, ahol a légzési distressz szindróma újszülött légzési distressz szindróma (IRDS).

12. Készlet alkalmazásra az 1. igénypont szerint, ahol a légzési distressz szindróma mekónium belégzés vagy pulmonális fertőzés következménye.