ALVEOFACT® 45 mg/ml

1. Name of the Medicinal Product

Alveofact® 45 mg/ml
54 mg, powder and solvent for preparation of a suspension

2. Qualitative and Quantitative Composition

Active substance: Phospholipid fraction from bovine lung (surfactant)
1 vial with 54 mg contains 50.76 to 60.00 mg of a phospholipid fraction from bovine lung (powder), equivalent to a content of 66 µmol or 54 mg total phospholipids as freeze-dried powder.
For a full list of excipients see section 6.1

3. Pharmaceutical Form

Powder and solvent for preparation of a suspension

4. Clinical Particulars

4.1 Therapeutic Indications

Alveofact® is indicated for treatment of respiratory distress syndrome (RDS) in premature neonates.
Alveofact® is also indicated for preventive use in premature neonates with a high risk of respiratory distress syndrome (RDS).

4.2 Posology and method of Administration

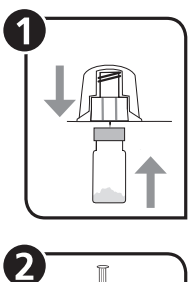
Alveofact® should be administered by or under the supervision of clinicians experienced in intubation, ventilator management and general care of premature infants.
Each dose of Alveofact® is 54 mg of total phospholipids per kg body weight (1.2 ml per kg body weight)
Prevention: A single dose of Alveofact® and application within the first hour after birth are recommended.
Treatment: Alveofact® should be administered early in the course of RDS i.e preferably less than 6 hours of age.
Treatment with Alveofact® is given only by endotracheopulmonary instillation. A ready prepared catheter (e.g. umbilical catheter or gastric tube) is inserted through the positioned tracheal tube and the catheter opening positioned at the level of the tip of the tube. Using a syringe, the single dose of 1.2 ml Alveofact® per kg body weight (corresponding to 54 mg total phospholipids per kg body weight) is administered as an intratracheal bolus via this catheter.
Additional injections of air are used to help ensure that instillation is complete. Upon removal of the catheter the patient is reconnected to the respirator. To promote the equal distribution of Alveofact®, the patient may be gently turned from side to side every few seconds.

Duration of treatment
Depending on the need for ventilation and on the initial dose, the following dosing scheme should be applied:
- Initial dose 54 mg :
  up to three subsequent applications of 54 mg,
- Initial dose 108 mg:
  up to one dose of 108 mg or up to two doses of 54 mg.

The total dose should not exceed 216 mg total phospholipids per kg body weight within the first 2 days of life.

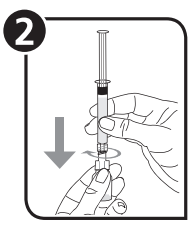
Instruction for reconstitution of the powder:
There are two options:
Option 1 – with vial adapter
Option 2 – with cannula

<u>Option 1 – with vial adapter</u>
Remark: The syringe and vial adapter remain connected to the vial throughout the reconstitution procedure and are also used for withdrawing the ready-to-use suspension.



Remove the foil from the packaging of the vial adapter.

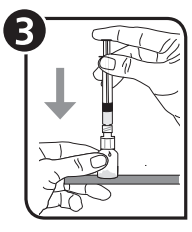
Remove the cap of the vial and press the adapter onto the vial until the vial adapter audibly clicks into place.



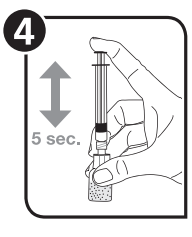
Remove the vial with the adapter from the plastic wrapping.

Twist the plastic cap off the syringe.

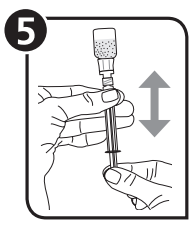
Then place the Luer lock adapter of the syringe on the vial adapter and fix it in place with a twisting motion.



Add the solvent to the vial

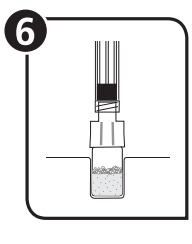


Then swirl **it for 5 seconds and shake it gently.**



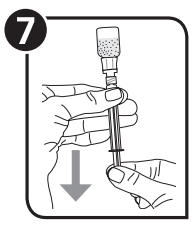
Draw up the suspension overhead into the syringe and reinject again into the vial.

Repeat this procedure until a homogeneous suspension is obtained.



Wait about one minute.
Afterwards a separation of foam and suspension has taken place.

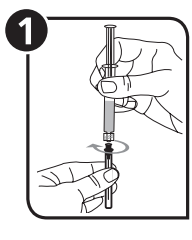
Recommendation:
Use the stand assistant in the pack!



Draw the suspension overhead into the syringe for use.

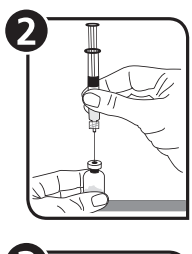
A residual amount of foam remains thereby in the vial.

<u>Option 2 – with cannula</u>
Remark: The syringe with vial adapter remains inserted in the vial throughout the reconstitution procedure and is also used for withdrawing the reconstituted suspension.

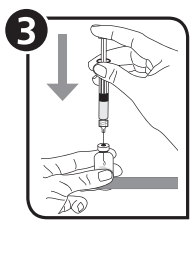


Open the packaging of the cannula at the top. Twist the plastic cap off the syringe.

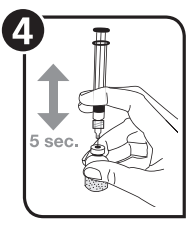
Then place the Luer lock adapter of the syringe on the cannula and fix it in place with a twisting motion.



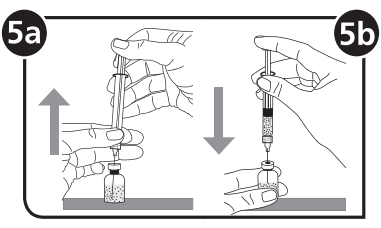
Remove the cap from the vial and insert the cannula through the rubber stopper into the vial.



Inject the solvent into the vial.

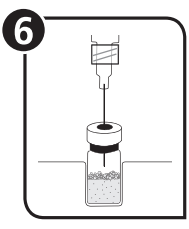


Then swirl it for **5 seconds and shake it gently.**

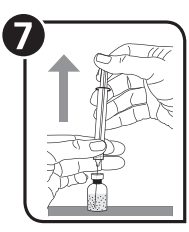


Draw up the suspension into the syringe at an angle and inject it back into the vial. **Repeat this procedure until a homogeneous suspension is obtained.**

Then withdraw the cannula from the suspension (but not from the vial) to prevent the suspension from rising into the syringe.



Wait until the foam and the suspension have separated (about 1 minute).
Recommendation:
Use the holder in the package!



Remove the suspension by slowly drawing it into the syringe.

A residual amount of foam may remain in the vial.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Special instruction for use :
- Check that the application catheter is positioned correctly in the tracheal tube prior to administration of Alveofact®.
- The pCO_2 values can change rapidly within the first hour of administration of Alveofact®. It is therefore advisable, by means of continual transcutaneous pCO_2 and pO_2 measurements or by means of repeat capillary blood gas analysis, to ensure that pronounced changes in the CO_2 partial pressure through the adjustment of the respiratory parameters (peak inspiratory pressure, respiratory frequency) are avoided.
- Care must also be taken that through the adjustment of the inspiratory oxygen concentration, arterial pO_2 does not exceed the desired limits so as to ensure that the risk of retinopathy of prematurity is not increased.
- When using high-frequency mechanical ventilation (respiratory frequency above 60 per minute, expiratory time less than 0.6 seconds) it is essential to ensure that the expiratory period following Alveofact® administration is sufficiently long.
  If the ventilation is not adapted in such a way following Alveofact® therapy, there is a risk of slowly increasing hyperdistension of the lung from "inadvertent or auto-PEEP":
  If passive expiration is incomplete, the intrapulmonary end-expiratory pressure will be higher than the setting on the respirator. A pathologically high functional residual capacity can thus develop. The peak inspiratory pressures required for ventilation must then be inappropriately increased, thereby increasing the risk of barotraumatic pulmonary injury.
- Until Alveofact® has been fully distributed in the lungs, coarse inspiratory rhonchi can be auscultated from the thorax in the first few minutes after administration. They are not an indication for tracheal aspiration, which otherwise may be done at any time.
- If the need for oxygen with normoventilation exceeds a level of 40 %, up to three followup applications of 1.2 ml Alveofact® per kg body weight (corresponding to 54 mg total phospholipids per kg body weight) may be given at intervals of 12 to 24 hours. If the response to the initial dose is inadequate, a prompt second dose (30 to 60 minutes after initial administration) of 1.2 ml Alveofact® per kg body weight (corresponding to 54 mg total phospholipids per kg body weight) is recommended.
- Through tracheal aspiration is required prior to each application in order to prevent impaired proliferation and foaming of Alveofact®, caused by the mucosa.
- If the oxygenation is acutely deteriorated (rise in pCO_2 and drop in pO_2) it is recommended to check the correct positioning and patency of the ventilation tube.
- Metabolic or respiratory acidosis should be corrected prior to administration of Alveofact®, since preclinical findings suggest that the efficacy of the preparation can thereby be impaired.
- When using a double-lumen-tube or "side port connector" to administer Alveofact® without interrupting ventilation, the respiratory parameters must be adjusted with particular care.

4.3 Contraindications

Hypersensitivity to the phospholipid fraction from bovine lung or any of the other ingredient. No substance-related contraindications are known so far.
Caution: The benefits and risks of Alveofact® therapy for congenital infections in premature neonates have not yet been adequately elucidated. The acute effect may be reduced if connatal pneumonia is suspected. Pulmonary function may also deteriorate in the event of concomitant under development of the lung (prolonged deficiency of amniotic fluid due to ruptured membranes or congenital renal function impairment).

4.4 Special Warnings and Precautions for use

Preclinical studies demonstrate that the granulocytic defence cells (macrophages, leukocytes) phagocyte lipid emulsions. This process may be impaired by Alveofact® in the presence of pneumonia and/or sepsis.
Alveofact® may only be used if adequate facilities for ventilation and monitoring of premature neonates with respiratory distress syndromes are available. There have been singular case reports of obstruction of the tracheal tube by viscous material. The origin and composition of this material is unknown. Although a certain causal connection between the use of Alveofact® and such a life-threatening event has not been proven, it is important to heed the given instructions for use and storage (refer to 4.2 "Special Instruction for Use and 6.4 Special Instruction for Storage).
If obstruction of the tracheal tube is suspected, it is advised to aspirate the ventilation tubing and change the ventilation tube, respectively.
Following Alveofact® administration, monitoring of the arterial blood gases, the fraction of inspired oxygen and ventilatory change is required to ensure appropriate adjustments.
If during the dosing procedure, episodes of bradycardia and decreased oxygen saturation occur, stop the dosing procedure and initiated appropriate measure to alleviate the condition.
After stabilization, the dosing procedure should be resumed.

The pre-filled syringe with 1.2 ml solvent contains 0.078 mmol (=1.8 mg) sodium, thus less than 1 mmol (23 mg) sodium per pre-filled syringe (= single dose), i.e. almost free from sodium.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

No substance-related interactions are known so far.

4.6 Pregnancy and Lactation

Not applicable.

4.7 Effects on Ability to Drive and Use Machines

Not applicable

4.8 Undesirable Effects

The following frequencies are used as the basis for assessment of the undesirable effects :

Very commons	(≥1/10)
Common	(≥1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to 1/1,000)
Very Rare	(≥ 1/10,000 or unknown)
Not Known	(frequency cannot be estimated from the available data)

(refer also to sections 4.2, 4.4, 4.9)

No substance-related side effects are to be expected when using as directed.
Due to the quantity of fluid, brief obstruction of the upper airways may occur immediately after

application of Alveofact®, which can be remedied by increasing the respiratory pressure for 30 to 60 seconds.

Caution:
There have been single reports of obstruction of the tracheal by viscous material. A causal connection to the use of Alveofact has not been proven. Cerebral and pulmonary haemorrhage has been described. Their frequency correlates roughly to declarations in the literature for this patient population.

4.9 Overdose
It is unlikely that premature neonates are already sensitive (hypersensitivity) to protein from bovine lung, but such a condition may cause anaphylactoid reactions which require the usual emergency treatment.
Overdose has not yet been reported. In the unlikely event of inadvertent overdose, it is recommended to aspirate the applied quantity of liquid applied as much as possible if there is a clinical deterioration. Symptomatic therapy should be given where necessary.
If an excessively large dose of Alveofact® is given, observe the infant for signs of acute airway obstruction.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: bounding surface active phospholipids (natural surfactant).
ATC Code : R07AA02
Alveofact® effects a dose-dependent improvement in the pulmonary mechanisms and gas exchange in immature rabbit and lamb foetuses. Endotracheal instillation of Alveofact® in animals with mature lungs causes reversible impairment of respiratory function. Which will return to normal within a period of one week.
A favorable effect on pulmonary compliance and gas exchange can be expected from opening and stabilising the alveoli in immature, premature neonates with respiratory disorders.

5.2 Pharmacokinetic Properties.
After endotracheal instillation of radio active marked Alveofact® (14-C lecithin) and distribution over the surface of the alveols maximum values of radioactivity has been found in the blood (2.5 – 5% of the total dose) of adult rabbits after 7–24 hours.
With adult rats as well as with rabbits radioactivity could be proven over the whole body with accumulation in the liver, the kidneys and adrenal glands. The half time in the blood was calculated to be 70 hours. The most part of radioactivity could be detected 7 hours after application in the lung (rat), but also traces in the liver, the kidneys and the adrenal glands.
Radioactivity could also be found in the lung after 7 days. The half time of phosphatide glycerol could be estimated with 43 ± 11 hours in premature infants treated with Alveofact®.

5.3 Preclinical Safety Data
In animals with mature lungs, repeat endotracheal installation of Alveofact® leads to an increase and enlargement of the alveolar macrophages which are to some extent accumulated focally. Rounded atelectasis thereby forms, Such findings are not fully reversed within 14 days.
The potential risk of development of rounded atelectasis depends on the total lipid load of the lungs. With a view to the therapeutic benefit, the clinically recommended total dose of 4 x 54 mg total phospholipids per kg body weight with the first 2 days of life is justifiable.
Specific antibodies against Alveofact® were found in 12 of 641 tested patients (2%) four weeks after administration. In four of those patients antibody detection was positive prior to Alveofact® administration. The patients in whom the antibodies were found had a mean birth weight which was somewhat higher than in the entire population studied.
The clinical significance of these findings is not currently clear.
A sensitive preclinical test design demonstrated that Alveofact® may trigger the development of specific antibodies. The antigenic potential from endotracheal administration is low, however.
Pre-existing antibodies could not be detected in the sera of healthy adult probands. It is essential to avoid a booster regimen, unless the absence of a humoral or local immune response can be proven.

6. Pharmaceutical particulars

6.1 List of excipients
1 pre-filled syringe of solvent of 1.2 ml contains: sodium chloride, sodium hydrogen carbonate, water for injections.

6.2 Incompatibilities
No incompatibilities are known so far.

6.3 Shelf life
36 months.
Storage conditions for the reconstituted medicinal product.
The reconstituted suspension can be kept for up to six hours at temperatures up to 25 °C or 24 hours at 2–8 °C (refrigerated). In such a case the vial and pre-filled syringe, respectively, need to be lightly agitated once prior to use.

6.4 Special Precautions for storage
Do not store the powder and the solvent at temperatures above 30 °C
Do not freeze the powder, the solvent or the reconstituted suspension
Storage conditions for the reconstituted medicinal product see section 6.3

6.5 Nature and Contents of Container
One pack of Alveofact® containing:
1 vial of 54 mg powder
1 pre-filled syringe containing 1.2 ml solvent
1 cannula
1 vial adapter

6.6 Special Precautions for disposal
No special requirements

HARUS DENGAN RESEP DOKTER
NO. REG: DKI1423600244A1

Manufactured by :
Lyomark Pharma GmbH
Keltenring 17
82041 Oberhaching
Germany
Tel. : +49 (0) 89 45 0808 78 - 0
Fax: +49 (0) 89 45 0808 78 - 50

Imported by :
PT. Dexa Medica
Palembang – Indonesia

Alveofact pack

① Vial of powder
② Pre-filled syringe of solvent
③ Cannula (in sterile packaging)
④ Vial adapter (in sterile packaging)
⑤ Vial stand

The supplied vial adapter is a medical device and therefore carries CE mark 0344.

10130273

Objektinformationen	
Bezeichnung	Alveofact 45 mg/ml Gebrauchsinformation
Sprache – Land	englisch – Indonesien
Farben	Schwarz
Schrift	Myriad Pro, FF Dingbats Arrows Two, Zapf Dingbats Schriftgröße Copy + Sublines: 7,0 pt Schriftgröße Headlines: 8,0 pt
Größe	124 mm x 620 mm
PZN	ohne
Artikelnummer	10130273

Freigabe	
MKT	
RA	
SCM	