Alveofact 45 mg/ml
Powder and solvent for preparation of a suspension

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alveofact 45 mg/ml powder and solvent for suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Phospholipid fraction from bovine lung (surfactant).

One vial of 54 mg contains 50.76 – 60.00 mg phospholipid fraction from bovine lung (dried mass), equivalent to a content of 66 µmol or 54 mg total phospholipids as lyophilised powder.

One vial of 108 mg contains 101.52 – 120.00 mg phospholipid fraction from bovine lung (dried mass), equivalent to a content of 66 µmol or 108 mg total phospholipids as lyophilised powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension.

Off-white powder and clear, colourless solvent (pH 7.2 – 8.3).
The reconstituted suspension has a pH of 6.0 – 7.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alveofact is used in preterm infants:
- as prophylactic treatment if they are at high risk of developing respiratory distress syndrome (RDS).
- as early treatment or interventional treatment in the presence of clinical and/or radiological signs of RDS.

4.2 Posology and method of administration

Posology
An initial dose of 2.4 ml Alveofact per kg body weight (BW), corresponding to 108 mg total phospholipids/kg BW, is recommended.

As prophylaxis for respiratory distress syndrome, the dose should be given within one hour after birth.

Treatment for respiratory distress syndrome should be initiated as soon as possible once RDS is diagnosed.

If the oxygen requirement under normoventilation exceeds 40%, follow-up doses of Alveofact can be given at intervals of 12 to 24 hours. If the response to the initial dose is inadequate, rapid administration of a second dose (30 to 60 minutes after the first dose) is recommended.

Depending on the need for ventilation, one follow-up dose of 108 mg/kg BW or two follow-up doses of 54 mg/kg BW may be given.

The total dose should not exceed 216 mg total phospholipids/kg body weight over the child's first five days of life.

Method of administration
For endotracheopulmonary instillation.

Alveofact is administered as a bolus injection via an endotracheal catheter.

Precautions before/during handling and before/during use of the medicinal product
For instructions on how to reconstitute the medicinal product and precautions, see section 6.6.

Pass an appropriately prepared catheter (e.g. umbilical catheter or gastric tube) through the in situ tracheal tube and position the opening of the catheter level with the tip of the tube. Using a syringe, inject the single dose as a bolus through this catheter. Then inject some air to ensure that instillation is complete. Reconnect the patient to the ventilation system after removing the catheter.

To ensure that Alveofact is distributed evenly, the baby can be gently rolled to the left and right, in each case for a few seconds.

Special precautions for use
- Aspirate the trachea thoroughly before each dose to avoid obstruction from mucus and to prevent Alveofact from foaming.
- Before administering Alveofact, check that the delivery catheter is positioned correctly in the tracheal tube.
- Until Alveofact has spread completely across the lungs, coarse inspiratory crackles may be heard over the thorax during the first few minutes after instillation. These are not an indication for tracheal aspiration, which may otherwise be performed at any time.
- The pCO_2 levels may change rapidly during the first few hours after instillation of Alveofact. Hence, it is important to avoid – preferably by continuously measuring transcutaneous pCO_2 and pO_2 or repeatedly analysing the capillary blood – pronounced changes in the partial pressure of CO_2 by adjusting the ventilation parameters (peak inspiratory pressure, ventilation frequency).
- Likewise, to avoid any increased risk of retinopathy of prematurity, the inspiratory oxygen concentration should be adjusted to ensure that the arterial pO_2 levels do not exceed the target limits.
- In case of mechanical ventilation with higher frequencies (ventilation frequency above 60 per minute, expiration time under 0.6 seconds) it is essential to ensure a sufficiently long expiration time after application of Alveofact.
  If the ventilation is not adjusted in such a way after Alveofact treatment, pulmonary hyperinflation could slowly increase due to "inadvertent or auto-PEEP":
  In case of incomplete passive expiration, the intrapulmonary end-expiratory pressure remains higher than the setting on the respirator. A pathologically high functional residual capacity can therefore develop. The peak inspiratory pressures required for ventilation must then be inappropriately increased, thereby increasing the risk of pulmonary barotrauma.
- If there is an acute deterioration in oxygenation (pCO_2 increase and pO_2 decrease), it is advisable to check that the ventilation tube is positioned correctly and not obstructed.
- If using a double-lumen tube or side-port connector to administer Alveofact without interrupting ventilation, the ventilation parameters must be adjusted with particular care.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

So far there are no known substance-specific contraindications.

Note:
The benefits and risks of Alveofact treatment for congenital infections in preterm infants have not yet been fully examined. The efficacy of the surfactant may be reduced in the presence of congenital pneumonia. The pulmonary function may also deteriorate in the presence of concomitant pulmonary hypoplasia (prolonged oligohydramnios from amniorrhexis or congenital renal dysfunction).

4.4 Special warnings and precautions for use

Alveofact may only be used if appropriate equipment is available with which to ventilate and monitor preterm infants with RDS.

Any metabolic or respiratory acidosis must be corrected prior to using Alveofact, as preclinical findings suggest that the efficacy of the product may otherwise be compromised.

Preclinical studies have shown that granulocytes in the immune system (macrophages, leukocytes) cause phagocytosis of lipid emulsions. Alveofact can impair this system in the presence of pneumonia and/or sepsis.

There have been isolated reports of tracheal tube obstruction from viscous material. The origin and composition of this material are not known. Although there is no concrete evidence of a causal relationship between the use of Alveofact and this life-threatening event, it is important to heed the instructions for use and storage (see sections 4.2 and 6.4). Aspiration or replacement of the ventilation tube is recommended if there is any suspected obstruction.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Alveofact contains less than 1 mmol (23 mg) sodium per pre-filled syringe of solvent (single dose), i.e. it is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

So far there are no known substance-specific contraindications.

No negative effects have been observed with Alveofact treatment following successful **prenatal** prophylaxis for respiratory distress syndrome with ambroxol concentrate for solution for infusion or glucocorticoids in the mother.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

So far there are no known substance-specific undesirable effects.

Due to the fluid volume, short-term tracheal or bronchial obstruction may develop immediately after administering Alveofact. This can be resolved by increasing the inspiratory pressure for 30 to 60 seconds.

Note:
There have been isolated reports of tracheal tube obstruction from viscous material. No evidence has been found of a causal relationship with the use of Alveofact.

There have been reports of cerebral and pulmonary haemorrhage, the incidence of which is roughly consistent with reports in the literature for this patient population.

Pre-existing sensitisation (hypersensitivity) to bovine lung protein is unlikely in preterm infants but could in principle lead to anaphylactoid reactions, necessitating standard emergency therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the

Germany
Federal Institute for Drugs and Medical Devices, Department of Pharmacovigilance, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany, website: http://www.bfarm.de

and

Austria
Federal Office for Safety in Health Care
Traisengasse 5, 1200 VIENNA, Austria
Fax: + 43 (0) 50 555 36207
Website: http://www.basg.gv.at/

4.9 Overdose

There are no known cases of overdose to date. In the unlikely event of inadvertent overdose, it is recommended to aspirate as much of the applied fluid as possible if the patient's clinical condition deteriorates. Symptomatic treatment should be initiated, if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural phospholipids from bovine lung, ATC code: R07AA05

Depending on the dose, Alveofact improves pulmonary mechanics and gas exchange in immature rabbit and lamb foetuses.
In animals with mature lungs, the endotracheal instillation of Alveofact causes a reversible impairment to the respiratory function, which returns to normal within one week.
In low-birth-weight preterm infants with respiratory disorders, opening and stabilising the alveoli can be expected to positively influence pulmonary compliance and gas exchange.

5.2 Pharmacokinetic properties

Maximum levels of radioactivity were found in the blood (2.5% – 5% of the total dose) of adult rabbits 7 – 24 h after endotracheal instillation of radiolabelled Alveofact (14^C-labelled lecithin) and distribution across the surface of the alveoli.

Radioactivity was detectable throughout the body both in adult rats and in rabbits, with accumulation in the liver, kidneys and adrenal glands. The half-life in the blood was calculated as 70 h. Most of the radioactivity was detectable 7 h after instillation in the lungs (rat) and could still be found 7 days later, though traces were also found in the liver, kidneys and adrenal glands.

In preterm infants treated with Alveofact, the half-life of phosphatidylglycerol was estimated at 43 +/- 11 h.

5.3 Preclinical safety data

In animals with mature lungs, repeat endotracheal instillation of Alveofact results in proliferation and enlargement of alveolar macrophages which in some cases leads to focal accumulation. Localised areas of atelectasis thus result. After 14 days, these findings are not fully reversed.

The potential risk of localised pulmonary atelectasis depends on the total lipid load of the lungs. In light of the therapeutic benefit, the clinically recommended total dose of 4 x 54 mg total phospholipids per kg body weight within the first five days of life is justifiable.

Specific antibodies against Alveofact were found in 12 of 641 investigated patients (2%) four weeks after administration. In four of these patients, however, antibodies had already been detected prior to the administration of Alveofact. The mean birth weight of the patients testing positive for antibodies was somewhat higher than in the entire study population. The clinical significance of these findings is not known at present.

A sensitive preclinical study design demonstrated that the development of specific antibodies can be induced by Alveofact. The antigenic potential from endotracheopulmonary instillation is low, however.

No pre-existing antibodies were detected in the sera of healthy adult subjects.

It is essential to avoid a booster regimen unless the absence of a humoral or local immune response can be demonstrated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-filled syringe of solvent
Sodium chloride
Sodium hydrogen carbonate
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Conditions for storage of the reconstituted medicinal product
The reconstituted suspension can be stored for up to 6 hours at temperatures of up to 25°C or 24 hours at 2°C – 8°C (refrigerated). In this case, gently swirl the vial or pre-filled syringe once prior to use.

6.4 Special precautions for storage

Do not store the powder or solvent above 30°C.
Do not freeze the powder, solvent, or reconstituted suspension.

For storage conditions following reconstitution, see section 6.3.

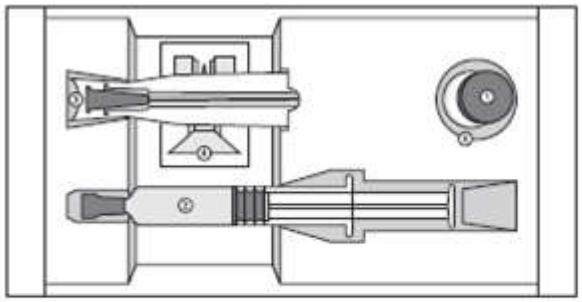
6.5 Nature and contents of container

Powder in a type I white glass vial with grey rubber stopper and aluminium cuff with a purple (54 mg) or blue (108 mg) tear-off seal. Solvent in a pre-filled white glass syringe with rubber plunger containing 1.2 ml or 2.4 ml. The pack also contains a cannula and vial adapter.

Alveofact is available in packs of:
- 1 vial of 54 mg or 108 mg powder, 1 pre-filled syringe of 1.2 ml or 2.4 ml solvent, 1 cannula, 1 vial adapter
- 2 vials of 54 mg or 108 mg powder, 2 pre-filled syringes of 1.2 ml or 2.4 ml solvent, 2 cannulas, 2 vial adapters
- 4 vials of 54 mg or 108 mg powder, 4 pre-filled syringes of 1.2 ml or 2.4 ml solvent, 4 cannulas, 4 vial adapters

Not all pack sizes may be marketed.

Alveofact blister pack



① Durchstechflasche mit Pulver
② Fertigspritze mit Lösungsmittel
③ Kanüle (steril verpackt)
④ Vial-Adapter (steril verpackt)
⑤ Standhalterung für Durchstechflasche

(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 0482.

6.6 Special precautions for disposal and other handling

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

Option 1 – with vial adapter

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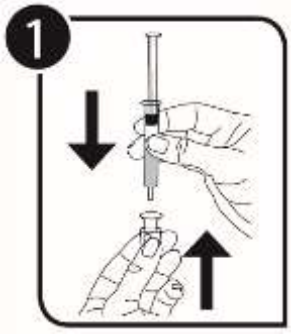
Remark: The syringe and vial adapter remain connected to the vial throughout the reconstitution procedure and are also used for withdrawing the ready-to-use suspension.



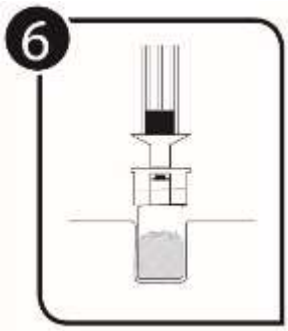
Open the packaging of the vial adapter at the top.
Attach the cone of the syringe to the vial adapter.

Push the vial adapter with syringe firmly onto the rubber stopper of the vial until it clicks into place.

Inject the solvent into the vial.

Then immediately **swirl and shake gently for five seconds.**

With the vial inverted, draw the suspension into the syringe then inject it back into the vial.
Repeat this step a total of five times!

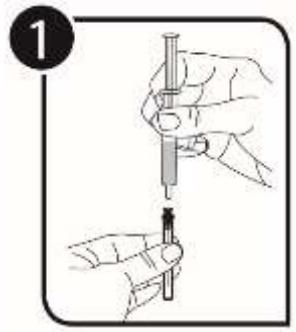


Wait approx. one minute.
The foam and suspension will then have separated.

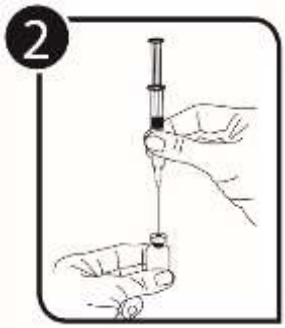
Recommendation:
Use the stand included in the pack.

With the vial inverted, draw the suspension into the syringe and remove the syringe ready for administration.
Residual foam will remain in the vial.

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



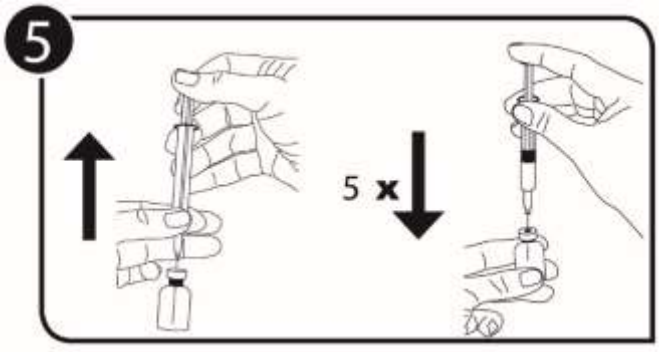
Open the packaging of the cannula at the top.
Attach the cone of the syringe to the cannula.



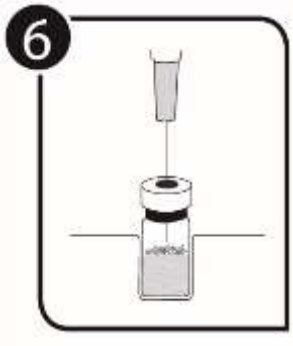
Insert the cannula into the vial through the rubber stopper.

Inject the solvent into the vial.

Then immediately **swirl and shake gently for five seconds.**



With the vial at an angle, draw the suspension into the syringe then inject it back into the vial.
Repeat this step a total of five times.
Then withdraw the cannula from the suspension (but not from the vial) to prevent the suspension from rising into the syringe.



Wait approx. one minute.
The foam and suspension will then have separated.

Recommendation:
Use the stand included in the pack.

Slowly withdraw the suspension.
Residual foam will remain in the vial.

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

7. MARKETING AUTHORISATION HOLDER

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Fax: +49 89 45080878-50
E-mail: info@lyomark.com

MARKETED BY:

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Address: 17th Floor, Hoechst House,
Nariman Point, Mumbai -400021, INDIA
Tel.: +91-22-6656 0900/6656 0980
Fax: +91-22-6656 0980/6656 0903

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8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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9. DATE OF REVISION OF THE TEXT

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10. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

PRESCRIPTION/PHARMACY REQUIREMENT

Subject to prescription and pharmacy dispensing