European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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Withdrawal Public Assessment Report

Of the Marketing Authorisation Application for

Surfaxin
(Sinapultide, Dipalmitoylphosphatidylcholine, Palmitoyl-oleoyl phosphatidylglycerol, Palmitic acid)

This Withdrawal Public Assessment Report is based on the Day 120 assessment report, which is the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. This Withdrawal Public Assessment Report does not include all available information on the product as the CHMP assessment of the applicant's responses to Outstanding Issues raised by CHMP was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.

EMEA/H/C/625

Applicant: PRA International

Start of the procedure:	18.10.2004
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LIST OF ABBREVIATIONS

Abbreviation	Description
a/A O_2	Ratio of the partial pressure of oxygen in arterial blood compared to the alveoli
ABG	Arterial blood gas(es)
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ARDS	Adult Respiratory Distress Syndrome
ASM	Active Substance Manufacturers
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAL	Bronchoalveolar lavage
BPD	Bronchopulmonary dysplasia
BSA	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalopathy
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
COMP	Committee for Orphan Medicinal Products
CPK	Creatinine Phosphatekinase
CRF	Case Report Form
C-sectio	Sectio Caesarea
DPPC	Dipalmitoylphosphatidylcholine
DSMB	Data Safety Monitoring Board
EDMF	European Drug Master File
ETT	Endotracheal Tube
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GA	Gestational Age
GALT	Gastrointestinal associated lymphoid tissue
GCP	Good Clinical Practice
GLP	Good laboratory practice
γ-GT	γ-Glutamyltransferase
ID	Identity
i.v.	Intravenously
IVH	Intraventricular Haemorrhage
K	Lysine
KL_4	Sinapultide
L	Leucine
MAP	Mean Airway Pressure
MAS	Meconium Aspiration Syndrome
N/A	Not Applicable
ND	No Data
NE	Not Established
NEC	Necrotising Enterocolitis
NTEL	No Toxic Effect Level
OI	Oxygenation index
PaO_2	Partial Pressure of Oxygen in the Arterial Blood
PCA	Post Conceptional age
PEC	Predicted environmental concentration
PMA	post menstrual age
PDA	Patent Ductus Arteriosus

PIE	pulmonary interstitial emphysema
PEC	Predicted Environmental Concentration
PG	Phosphatidylglycerol
POPG,Na	Palmitoyl-oleoyl phosphatidylglycerol, sodium salt
PA	Palmitic acid
PVL	Periventricular Leukomalacia
QOS	Quality Overview Summary
R	Arginine
RBC	Red blood cells
RDS	Respiratory Distress Syndrome
RL_4	Peptide sequence of Arginine, and Leucine
ROP	Retinopathy of prematurity
SAB	Scientific Advisory Board
SBA	Summary Basis of Approval (FDA)
s.c.	Subcutaneously
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	Standard of Care
SP	Surfactant protein
SP-A	Surfactant Protein A
SP-B	Surfactant Protein B
SP-C	Surfactant Protein C
SP-D	Surfactant Protein D
VLBW	Very Low Birth Weight
WBC	White blood cells

I. CHMP RECOMMENDATION PRIOR TO THE WITHDRAWAL

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Surfaxin, an orphan medicinal product in the prevention of respiratory distress syndrome in premature neonates of less than 32 weeks of gestational age and treatment of respiratory distress syndrome in premature neonates of less than 37 weeks of age, is not approvable since specific outstanding issues involving certain "major objections" have not been resolved satisfactorily by the applicant, thus precluding a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

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Quality:

- Stability studies indicate analytical and/or intra/inter batch variations to an unacceptable extent.

Clinical

- Failure to provide unmistakable proof of efficacy for both the RDS treatment and prevention indications from the pivotal study:

  - No controlled clinical Phase 3 study with acceptable design was submitted to establish efficacy in the indication "treatment of RDS in premature neonates of less than 37 weeks gestational age".
  - Reliable conclusions on efficacy in the RDS prevention indication cannot be drawn in comparison to authorised natural surfactants as a suboptimal comparator was chosen. The primary endpoints chosen were not considered to be optimal and were not in accordance with Scientific Advice. There are doubts regarding the clinical significance of the study with respect to the transferability of the results to the European setting and choice of inclusion criteria.

- Potential safety data as regards a higher incidence of peridosing events needs to be adressed.

II. EXECUTIVE SUMMARY

II.1 Problem statement

RDS is a disease that mainly occurs in premature infants due to immaturity of the lung with a lack of sufficient amounts of pulmonary surfactant. Its incidence is inversely proportional to gestational age.
60 - 80% of infants of less than 28 weeks gestation suffer from RDS, in contrast to only 15 - 30% of those between 32 and 36 weeks of gestation. Natural, animal-derived, protein-containing (e.g., Survanta®; Curosurf®; Infasurf®) preparations, also known as "natural surfactants", and synthetic, non-protein-containing surfactant preparations (e.g., Exosurf®) are available for treatment and prevention of RDS.

Concerns about potential risks associated with natural surfactants, such as a potential immune response due to foreign antigens, potential transmissions of infectious agents on the one side, and the lack of surfactant proteins in synthetic surfactants on the other side led to the development of Surfaxin.

II.2 About the product

Surfaxin is a peptide-engineered synthetic surfactant. It has no animal-derived components and thereby is the first non-animal-derived, protein-containing surfactant preparation.

In natural (i.e., human/animal) pulmonary surfactant, 4 proteins have been identified (surfactant proteins SP-A, SP-B, SP-C, and SP-D), of which SP-B, when combined with phospholipids, exhibits the strongest capacity to reduce surface tension and induce pulmonary expansion in experimental models (Curstedt 1987, Yu 1988 , Revak 1988, Sarin, 1990). Infants born with a genetic deficiency of SP-B, but with abundant SP-A and SP-C, develop respiratory distress, have pronounced respiratory failure, and die in the first months after birth (Nogee 1993) even if given regular exogenous surfactant replacement therapy. Synthetic peptides constructed using the sequence of SP-B, or resembling the pattern of SP-B, demonstrate surfactant function when combined with aqueous dispersions of phospholipids (Revak 1991).

The amino acid sequence of SP-B responsible for its function consists of stretches of hydrophobic amino acids with intermittent, generally basic, hydrophilic amino acids (Revak 1991, Cochrane 1991). The role of SP-B is thought to provide lateral stability to the phospholipid monolayer lining alveolar walls and to prevent atelectatic collapse through hydrophobic and electrostatic interactions with the phospholipids (Cochrane 1991, 1994).

The peptide sequences derived from the C-terminal region of SP-B and ranging in length from 11 to 45 amino acids were tested for their ability to lower surface tension. Of the peptide sequences studied, RL_4 (peptide sequence of arginine and leucine) and KL_4 (peptide sequence of lysine and leucine) possessed good surface tension lowering characteristics. Ultimately, the KL_4 peptide (sinapultide) was chosen for subsequent development based on its greater ease of bulk synthesis as compared to RL_4 (Cochrane 1991).

Following the identification of the peptide, the drug product phospholipid and neutral lipid components were selected based on the initial consideration of simulating the human physiological phospholipid system. The key phospholipids in human surfactant are dipalmitoylphosphatidylcholine (DPPC) and phosphatidylglycerol (PG), and the neutral lipid system, containing mainly palmitic acid.

The drug product (Surfaxin) that resulted from this pharmaceutical development program consisted of the synthetic peptide sinapultide, a 21-residue peptide made up of lysine (K) and leucine (L) residues with the sequence KLLLLKLLLLKLLLLKLLLLK (KL_4), in aqueous dispersion with the phospholipids DPPC (dipalmitoylphosphatidylcholine), POPG (1-palmitoyl-2-oleoyl-3-[phospho-rac-(1-glycerol)), and palmitic acid.

This application was filed for the 30 mg/ml (phospholipids) concentration. It consists of dipalmitoylphospatidylcholine (22.5 mg/ml), palmitoyl-oleoylphospatidylglycerol (7.5 mg/ml), palmitic acid (4.05 mg/ml), and sinapultide (KL4 peptide) (0.801 mg/ml).

The following indications are proposed:

"The proposed clinical use of Surfaxin is the prevention and treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants:

- Prevention of Respiratory Distress Syndrome in premature neonates of less than 32 weeks of gestational age.
- Treatment of Respiratory Distress Syndrome in premature neonates of less than 37 weeks of gestational age."

The proposed dose is 175mg/kg birth weight (5.8ml/kg) administered by endotracheopulmonary instillation.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The areas covered in the non-clinical application include primary pharmacodynamics, safety pharmacology, distribution, excretion, genotoxicity, and single-dose and repeated-dose toxicity. The toxicity studies were mainly performed on premature animals, which is suitable in view of the proposed indication. The non-clinical development program is in reasonable agreement with EU/ICH guidelines.

CPMP-advice was sought on the 29th of June 2000. At that time, the intended indications were treatment of RDS, Meconium Aspiration Syndrome (MAS) in full-term infants and Acute Respiratory Distress syndrome (ARDS) in adults. It was concluded by the CPMP that the sinapultide (synthetic peptide), the phospholipids and palmitic acid components of Surfaxin all should be considered as active substances. With respect to non-clinical aspects, the applicant was advised to include two-week repeated-dose toxicity studies and consequently three two-week studies performed in different species are included in the application. Furthermore, the applicant was advised to include the standard battery of tests for genotoxicity and reproduction toxicity studies and to consider the addition of safety pharmacology studies. It was recommended by the CPMP that the metabolism of sinapultide be studied in more detail.

Based on the evidence established in preclinical studies, a Phase 2 study in 47 preterm neonates for the treatment of RDS initially employed a Surfaxin dose of 133 mg/kg phospholipid delivered in a volume of 5 ml/kg within the first 4 hours of life (study KL4-IRDS-01). Subsequently, the Surfaxin dose was increased to 200 mg/kg delivered in a volume of 5.7 ml/kg following evidence from additional preclinical toxicology studies that the higher dose was safe and more effective.

The remaining clinical studies for the indication of RDS were conducted using a lower dose of 175 mg/kg administered in a total volume of 5.8 ml/kg with up to 3 additional retreatments permitted at 6-hour intervals under protocol-specified criteria. A prophylactic strategy in very low birth weight (VLBW) neonates was used based on data that suggests that surfactant therapy given earlier to neonates with RDS or expected RDS is associated with a more successful clinical outcome (Yost 2004, Soll 1999). This prophylaxis approach was subsequently employed in a second Phase 2 study in 11 preterm neonates at risk for the development of RDS (KL4-IRDS-05).

The Phase 3 clinical development program consists of 2 clinical studies. The pivotal study, KL4-IRDS-06, conducted in Central Europe and Latin America, was designed utilising a superiority approach to test Surfaxin versus Exosurf, the prototype non-protein-containing synthetic surfactant. Survanta was also included as an active reference arm.

For the supportive trial, KL4-IRDS-02, conducted in Europe and North America, Curosurf was chosen as the protein-containing, animal-derived comparator. A non-inferiority approach was chosen to establish efficacy of Surfaxin with the leading surfactant prescribed in Europe.

No clinical pharmacokinetic and pharmacodynamic studies have been conducted.

Especially the pivotal study deviated from the Scientific Advice given by the CPMP in October 2000 concerning comparator and primary endpoints. This is detailed in the clinical assessment.

II.4 General comments on compliance with GMP, GLP, GCP

The genotoxicity studies and the large majority of single- and repeated-dose toxicity studies were performed in accordance with GLP regulations. A few pivotal studies were not performed in compliance with GLP but the quality of these studies seems adequate.

The applicant states that study KL4-IRDS-01 was conducted in accordance with the ethical principles defined in the Declaration of Helsinki, and that studies KL4-IRDS-05, KL4-IRDS-06 and KL4-IRDS-02 were conducted according to GCP.

II.5 Type of application and other comments on the submitted dossier

This is a full application applied via the centralised procedure.

The quality part of the dossier is generally considered acceptable.

The clinical overview lacks criticism. An electronic version of the dossier has been provided. References to published literature are among others made with regard to in vitro studies for identification of the synthetic protein, surface lowering ability of the product as well as composition of the product.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

To summarise, the quality of this product is not considered acceptable at this time. Although information has been provided regarding the manufacture, control, and stability, *major objections* will have to be clarified to support the adequacy of the whole process for both the drug substances and the drug product. In addition, *other concerns* that affect both the drug substances and the drug product need to be resolved before an approval can be considered.

Drug substance

The drug product Surfaxin, Endotracheopulmonalinstillation, suspension, consists of a liposomal formulation containing a target of 30 mg/ml phospholipids (DPPC, and POPG), palmitic acid, and a synthetic 21-amino acid peptide (sinapultide) in an aquous medium. The four drug substances (sinapultide, dipalmitoylphosphatidylcholine (DPPC), palmitoyl-oleoyl phosphatidylglycerol (POPG), and palmitic acid) are supplied by contract manufacturers (ASM).

Sinapultide:

Sinapultide is a synthetic 21 amino acid peptide consisting the amino acids leucine and lysine in a repeating sequence. Sinapultide mimics the function of human surfactant protein B (SP-B), the protein in natural pulmonary surfactant that increases inter- and intra-molecular ordering of the phospholipid layer and is required to form a functional surfactant.

Sinapultide is manufactured under GMP conditions.

The control of the manufacture of the sinapultide relies on the documentation provided in relation to the control of materials, control of critical steps and intermediates, process validation and manufacturing process development.

Sinapultide has been adequately characterized.

Analytical testing methods are documented and validated. They are considered to be acceptable.

Batch analysis data and results of stability testing at –20°C, 2-8°C, and 25°C/60% RH have been provided.

Palmitic acid

Palmitic acid is described in a Ph. Eur. monograph. An ASMF is provided by the applicant. The manufacturing process and in-process testing are adequately described. Palmitic acid has been characterised. Palmitic acid is a stable compound and therefore degradation is unlikely. The specification for the control of the drug substance sufficiently describes the quality of the drug substance. However, the specification should be amended to comply with the Ph. Eur. monograph and the suitability of the monograph should be discussed. The analytical methods are described, and the results of stability testing are acceptable.

1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)

The manufacturing process and in-process testing are adequately described. A specification for the drug substance is documented. The analytical methods are described.

1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol, sodium salt (POPG)

The manufacturing process and in-process testing are adequately described. A specification for the drug substance is documented.

Drug Product

The drug product Surfaxin, a suspension for endotracheopulmonary instillation, consists of a liposomal formulation containing a target of 30 mg/ml phospholipids (DPPC, and POPG), palmitic acid, and a synthetic 21-amino acid peptide (sinapultide) in an aqueous medium. The drug product is a white to off-white suspension consisting of a liposomal formulation of an aqueous core surrounded by phospholipid moieties. The product is packaged in a 8 ml nominal fill in a 10 ml type I glass vial with rubber stopper and flip-off seal. Prior to administration the applicant recommends that the product be warmed at 44ºC and then shaken to ensure smooth flowability. The administered dose will thus reach a temperature of about 37ºC when administered.

The drug product replaces surfactants lacking in the human pulmonary system simulating the action of the human lung surfactant system in lowering the lung surface tension. There is no other established biological activity for this product. The combination of drug substance has been selected to optimally mimic the behaviour of the in vivo system responsible for lowering surface tension in the human lung. The principle lipid component of the monolayer is DPPC, with sinapultide holding the DPPC layer together via electrostatic interaction between the positively charged lysine residues on the sinapultide and the negatively charged polar head group of the lipid, and POPG/palmitic acid serves to destabilise DPPC lipid bilayer formation.

Intensive developmental work was performed to select the peptide component using a huge number of independently synthesised peptides that simulate all or part of the structure of SP-B. Finally, sinapultide was found to be suitable for the intended use. The combination of the drug substances and the development of the formulation is justified.

According to applicant, the formulation and manufacturing process used in phase 3 clinical studies are consistent with those for the proposed commercial product.

Based upon structural considerations and the drug product formal stability data, the drug substances have been shown to have a certain compatibility with the formulation excipients and each other when stored at 2 to 8ºC, and according to the applicant, the formulation pH has been optimised to minimise degradation although it is not possible at this time to assign a reliable product shelflife..

The test methods for the control of the drug product are described. All methods have been validated. Most of the methods are suitable for their intended use.

The drug product impurity/degradation profiles have been characterised with respect to each drug substance, and the finished product specifications are generally consistent with relevant guidelines and Ph. Eur. standards for parenteral formulations.

Stability studies have been performed in accordance to the ICH guideline at 2 –8°C and at 25°C/60% RH in the upright and inverted orientations. Additionally the stability testing studies have been performed at 13/15°C. The applicant claims a shelf life of 18 months for the drug product, but only limited stability data have been provided. Therefore, the stability of the drug product at the moment cannot be fully assessed,

since only limited data are available and there are signs of an unacceptably high intra/inter batch variability in the analytical results.

III.2 Non clinical aspects

Pharmacology

Primary pharmacodynamics showed that amino acid residues 59 to 80 were responsible for the surface tension lowering effect of SP-B. Intermittent charged hydrophilic residues were found to be requisite for surfactant activity. The synthetic peptide sinapultide resembles $SP\text{-}B_{59\text{-}80}$ with respect to hydrophilic and hydrophobic domains and has surfactant activity equal to that of the $SP\text{-}B_{59\text{-}80.}$ The surface tension lowering effect of the synthetic peptide fragments was investigated in combination with phospholipids in the pulsating bubble assay and by administration into the lungs of premature rabbits. The proposed mode of action of SP-B (and sinapultide) involves an interaction of the hydrophilic, charged residues with polar head groups of the phospholipids, whereas the hydrophobic stretches of the peptide interact with the acyl side chains. Hereby a destabilization of the phospholipid layer is induced, providing greater capacity to resist surface tension or alveolar collapse. Moreover, suppression of inflammatory activity and resistance to reactive species following respiratory burst have been shown *in vitro.* Treatment of RDS in premature monkeys with sinapultide in combination with DPPC, POPG and palmitic acid led to an improvement in oxygenation and the reversal of atelectasis was confirmed by necropsy and with microscopic examinations of the lungs. The literature provides proof of concept both *in vitro* and *in vivo* (in a highly relevant animal model).

Secondary pharmacodynamics were not investigated. The receptor binding profile of sinapultide should be investigated.

Specific safety pharmacology studies of Surfaxin have not been carried out.

No pharmacodynamic drug interaction studies have been carried out. This is acceptable since Surfaxin is administered directly to the lungs, absorption is likely to be limited and administration of other drugs to the lungs is limited to oxygen.

Pharmacokinetics

Pharmacokinetic studies were limited to distribution and excretion studies.

Absorption studies were not conducted. The applicant should quantify the extent of systemic absorption of sinapultide after treatment of neonatal or premature animals.

According to ICH S6 it is acceptable that no metabolism studies have been performed with respect to sinapultide. The phospholipid components of Surfaxin occur in natural surfactant and enter the lipid metabolism pathways. Pharmacokinetic drug interaction studies were not conducted.

Toxicology

Single-dose toxicity studies were performed by intratracheally administering Surfaxin to adult rats, newborn rabbits and in juvenile dogs. Moreover, two non-GLP studies were conducted in premature monkeys, where the monkeys were treated at the time of RDS onset. The toxicology studies in general have identified volume and viscosity of the test compound as a critical parameters for the clinical use of surfactants.

Repeat-dose toxicity studies comprised studies with treatment periods varying from 1 to 14 days. The experiments were performed in adult rats, newborn and baby rabbits, juvenile cats, premature monkeys with RDS, puppies and juvenile dogs. Findings were probably related to the volume of the test-product rather than to the quantity of active ingredient.

The maximal human exposure of Surfaxin will be about 600 mg/kg/day. NTEL values were not established in any of these studies, and as such, safety factors cannot be calculated. One of the main purposes of animal safety studies is to achieve exposures that are high enough to reveal toxic effects that are too subtle to be discovered in clinical trials. In the present application, animal toxicity studies were performed without dosages high enough (when based on body weight) to elucidate the toxic potential of Surfaxin. As a consequence, the applicant is requested to express the relative exposure of patients and experimental animals in relation to other parameters than body weight, e.g. relative lung weight, lung volume or alveolar surface area. When adequate systemic exposure cannot be achieved by intratracheal administration, the applicant should consider the possibility of conducting repeat-dose toxicity studies using i.v. administration at dose levels corresponding to a reasonable exposure multiple compared to the systemic exposure in humans.

Surfaxin was negative in two Ames tests and did not induce chromosomal aberrations in CHO cells and mouse bone marrow.

Carcinogenicity studies were not performed. This is reasonable due to the lack of genotoxicity. The phopholipid components of Surfaxin occur in natural surfactant and are unlikely to pose a carcinogenic risk. At all events, carcinogenicity studies are not performed with medicines for short-term treatment.

No reproductive and developmental toxicity studies were performed. This is acceptable based on the proposed indication and the population intended to be treated.

Local tolerance was investigated in the course of the single and repeat-dose toxicity studies, since the intended route of administration was used (endotracheapulmonary use).

Surfaxin did not induce immediate hypersensitivity in a conventional guinea pig model.

The $PEC_{Surfacewater}$ of DPPC, the active ingredient occurring in the highest concentration, was calculated at 0.00026 µg/L. This value is well within the established action limit. Therefore, Surfaxin is unlikely to represent any perceivable risk to the environment.

III.3 Clinical aspects

Pharmacokinetics

No human pharmacological studies have been performed to characterise the absorption, bio-transformation or excretion of Surfaxin. This has been justified by the direct administration of Surfaxin to the target organ, the lung.

The non-clinical pharmacological program for Surfaxin evaluated the disposition of phospholipids and peptide (Sinapultide) present in Surfaxin. These data suggest that absorption, metabolism and excretion takes place.

Considering that Surfaxin contains a new fully synthetic protein, never given to humans previously and despite that the applicant has performed two phase II clinical and two phase III trials the complete lack of studies on human PK and PD should be justified. It is however acknowledged that a full investigation of all aspects of both PK and PD for Surfaxin is not a prerequisite for a marketing authorization. This is both

due to the route of administration and in particular the nature of the patient population for which the product is intended.

Pharmacodynamics

Because of the nature of Surfaxin, no clinical pharmacodynamic studies have been conducted in healthy volunteers.

The non-clinical pharmacological program considered current scientific knowledge that demonstrates the surface activity, inhibition, and molecular biophysics of Surfaxin, and how endogenous surfactant can be replaced or supplemented with active exogenous substitutes in animals and humans with RDS and other conditions such as meconium aspiration syndrome (MAS), and adult respiratory distress syndrome (ARDS). These studies incorporated a spectrum of biophysical, biochemical, and physiological research, and pharmacology.

Surfaxin research examined the surface active interactions of a range of natural and synthetic lung surfactant materials, including biologic phospholipids, synthetic phospholipid analogues, synthetic hydrophobic peptides, purified surfactant proteins, phospholipid sub-fractions of native surfactant, and clinical exogenous surfactant drugs.

Experimental techniques were used to study absorption and dynamic surface tension lowering behaviour, as well as mechanisms of Surfaxin inactivation by plasma proteins, membrane lipids, lytic enzymes, and other compounds in RDS, MAS, and ARDS. Molecular interactions of different surfactant components were studied further at the molecular level using Fourier transform infrared spectroscopy, differential scanning calorimetry, Brewster-angle microscopy (Cochrane 1991), and related methods. Physiological studies focused on mechanisms of lung surfactant dysfunction and deficiency in animal models of RDS, MAS, and ARDS and their treatment with exogenous surfactants.

Clinical efficacy

Dose-response studies and main clinical studies

Dose finding studies were not conducted. The first dose in man was based on animal experiments (studies in monkeys given doses between 126 and 200mg/kg). With respect to the phospholipids contained in Surfaxin long-term experience has been gained with other surfactants containing the same substances. Other surfactants are administered at doses of 67.5mg to 200mg/kg of phospholipids, i.e. the proposed Surfaxin dose of 175 mg/kg is roughly said, within this range. However, Surfaxin is the first surfactant to contain a synthetic peptide, called sinapultide, which is claimed to mimic the essential characteristics of human surfactant protein B. Of the 4 proteins identified in natural surfactant (SP-A, SP-B, SP-C and SP-D), SP-B, when combined with phospholipids, exhibits the strongest capacity to reduce surface tension and induce pulmonary expansion in experimental models (Curstedt 1987, Yu 1988, Revak 1988, Sarin 1990).

This application for a marketing authorisation was filed for two indications:

- treatment of RDS in premature neonates of less than 37 weeks of GA;
- prevention of RDS in premature neonates of less than 32 weeks of GA .

The applicant conducted 4 clinical studies.

Treatment of RDS

Only one open, uncontrolled, Phase 1b study, **KL4-IRDS-01**, the first study in humans, was designed to investigate the effects of Surfaxin in this indication. Forty-seven (47) preterm neonates with established

RDS were enrolled. No prospective efficacy variables were defined. The enrolled patient collective does not cover the one applied for. The dose of 133 mg/kg at a volume of 5.0 ml/kg was, after inclusion of 8 patients, changed to 200 mg/kg at a volume of 5.7 ml/kg. Oxygenation and ventilation parameters, as well as the incidences of deaths, RDS and BPD were collected.

The concentration, mode of preparation and dose of the study drug are not identical with those of the proposed agent.

The additional analysis of results obtained from participants in the studies KL4-IRDS-02/06 and 05, is not sufficient either to establish efficacy in the indication "treatment of RDS in premature neonates of less than 37 weeks of GA", because the enrolled patient collective does not cover the proposed range of new-borns < 37 weeks GA and because all patients in these studies received the first dose of Surfaxin for preventive purposes. Only patients with insufficient preventive treatment, who developed RDS, received therapeutic re-treatment.

In summary, the provided data are unsuitable to support the proposed treatment indication.

Prevention of RDS

3 clinical studies were conducted in support of this indication. For these studies, a dose of 175 mg/kg at a volume of 5.8 ml/kg was chosen without providing a rationale. This dose and volume are proposed in the SPC.

Study **KL4-IRDS-05** was the first of the studies being conducted in the prophylaxis of RDS, by its size (11 premature neonates) and uncontrolled design rather a pilot study. None of the patients enrolled would have qualified for preventive treatment of RDS in Europe. There is a high percentage of patients with major protocol deviations and an unacceptable high mortality rate.

Both controlled studies, KL4-IRDS-06 and KL4-IRDS-02 enrolled premature neonates with a birth weight of 600-1250g; in study KL4-IRDS-06 the limit in terms of gestational age was ≤32 weeks, in study KL4-IRDS-02 it was <29 weeks. A part of the enrolled neonates, namely those born at > 28~30 weeks GA would not have qualified for preventive treatment in Europe. Prerequisite for being enrolled was successful endotracheal intubation.

The **pivotal study, KL4-IRDS-06** was a large study in 1294 premature neonates. The study was conducted in 54 centres in Latin America (Mexico, Panama, Uruguay, Chile, Brazil), Hungary, Poland, Russia and the USA. Surfaxin was compared to the synthetic surfactant Exosurf, and the natural (bovine) surfactant Survanta was included as a reference arm at a randomisation ratio of 2:2:1. Statistical comparisons between Surfaxin and Survanta, however, were not provided. It should be noted that the design of the study deviated from what was proposed at the time of the Scientific Advice in 2 decisive factors: active comparator and choice of primary endpoint. For the Scientific Advice the CPMP endorsed the applicant‘s proposal to conduct a superiority study vs. Survanta and to use the primary endpoint "incidence of infants being alive without broncho-pulmonary dysplasia at 36 weeks post-conceptional age without the diagnosis of RDS at 24 hours of age", provided that mortality also was included as a major endpoint.
However, for the pivotal trial the applicant finally chose the co-primary endpoint "Incidence of RDS at 24 hours" and "RDS-related mortality through 14 days of age".

Certainly, the primary target of surfactant administration is the avoidance of RDS. However, the originally proposed endpoint (alive without BPD at 36 weeks PCA) is the clinically most accepted and common and most relevant endpoint after overall mortality.

Furthermore it is known that natural surfactants have a more rapid impact than synthetic surfactants, due to the protein component of the natural surfactants. Provided that this also applies for Surfaxin with its

synthetic protein, the choice of "incidence of RDS at 24 hours" does not appear to be the most suitable endpoint as it may be expected that the synthetic surfactant Exosurf would be inferior and Surfaxin be favoured in the study. On the other hand no studies have been conducted evaluating the onset of action of Surfaxin in comparison to other surfactants, i.e. the assumption of a more rapid onset of action of Surfaxin than the synthetic surfactant remains speculative.

Importantly, several trials have suggested an advantage of natural surfactants vs. synthetic surfactants as confirmed by a Cochrane review by Soll and Blanco, 2001. According to this review, greater early improvement in the requirement for ventilator support, fewer pneumothoraces, and fewer deaths were associated with natural surfactant treatment. Natural surfactants may be associated with an increase in intraventricular haemorrhages, though the grade 3 and 4 haemorrhages were not increased.
The synthetic surfactant Exosurf must therefore be regarded as suboptimal as active comparator.

The second controlled study conducted, **KL4-IRDS-02**, was a non-inferiority trial with Curosurf as comparator. For this study, however, it appears that for the sample size calculation the assumption of a 55% BPD free survival (derived from a published trial in treatment of RDS) at day 28, the primary endpoint, was set too low as published surfactant studies have shown a BPD free survival at 28 days in the range of 70%. Furthermore, it can be questioned whether the non-inferiority margin set at –14.5% is appropriate. Finally, as only half of planned patients were actually enrolled in the study, the study was seriously underpowered and thus of limited usefulness. The formal criteria for non-inferiority were fulfilled, with a BPD free survival at day 28 of 38% in the Surfaxin group and 33% in the Curosurf group. These percentages appear, however, to compare unfavourably with published surfactant studies.

Mortality was in both controlled studies lowest at time points 28 days/36 weeks PCA/predischarge in the Surfaxin treatment groups, the differences were however not statistically significant. In published studies mortality rates between 11 and 21% were reported (Hoekstra 1991, Kendig 1991, Walti 1995, Bevilacqua 1996, Egberts 1997, Hudak 1997). No differences in the occurrence of the typical complications that affect preterm neonates (IVH, PVL, NEC, PDA, ROP, pulmonary haemorrhage, sepsis) could be observed in either of the controlled studies between Surfaxin and the comparator groups.

For the incidences of some endpoints (e.g., RDS, RDS-mortality) considerable differences were observed between the controlled clinical studies, whereas incidences of other endpoints (e.g. air-leak, BPD) were consistent between the controlled studies. Furthermore considerable differences were observed within studies for some endpoints when imputed for death and not imputed for death (i.e., last known status for the variable in question was carried forward), respectively.

The table below provides an overview of the key endpoints from both controlled phase III studies.

Endpoint	**KL4-IRDS-02**		**KL4-IRDS-06**			**p-value**		
	Surfaxin N = 119	Curosurf N = 124	Surfaxin N = 527	Exosurf N = 509	Survanta N = 258	Surfaxin vs. Curosurf	Surfaxin vs. Exosurf	Survanta vs. Exosurf
RDS at 24hours	18.5%	15.3%	**39.1%**	**47.2%**	**33.3%**	0.508	**0.005**	**<0.001**
RDS related mortality at 14 days of age	0.8%	0.0%	**4.7%**	**9.6%**	**10.5%**	0.779	**0.001**	**0.843**
Alive and without BPD at 28 days	**37.82%**	**33.06%**	41.9%	37.3%	41.1%	**0.251***	0.044	0.197
All-cause mortality by 36 weeks PCA	16.0%	18.5%	21.1%	23.8%	26.4%	0.478	0.182	0.467

Please note that the results for the primary endpoints are written in bold letters
*Surfaxin was shown to be non-inferior to Curosurf, 95% confidence interval: -7.3 - 16.8

In all trials the majority of neonates (approximately 58%) received one prophylactic dose of surfactant only, whereas approximately 20% received a total of 2 doses, and approximately 10% received a total of 3 doses. Four or more doses were given only in few patients. The toxicological data provided, should, however, not qualify for repeated administration in the proposed doses.

In summary, Surfaxin is without doubt a new surfactant with some efficacy for the prevention of RDS in preterm neonates. However, due to the choice of a suboptimal comparator in the pivotal study and limited reliability of the supporting study KL4-IRDS-02, this new synthetic surfactant is difficult to position in the group of surfactants. With the data provided, no reliable conclusion can be drawn that Surfaxin is at least as effective as natural, protein-containing surfactants, which are the "gold-standard" in Europe.

Limited usefulness of the study comes also from the fact that in the pivotal study neonates born up to 32 weeks GA were enrolled in the study, whereas in Europe only neonates born at < 28~30 weeks GA would qualify for preventive treatment of RDS.

The transferability of the results to the European setting is also questioned as the study was conducted in middle-income countries with a potentially lower standard of care for preterm neonates. Mortality rates in study KL4-IRDS-06 are higher than in KL4-IRDS-02, though the proportion of more mature infants is lower in KL4-IRDS-02.

The results of the phase III studies' longer term outcome data have not yet been submitted.

Clinical safety

Patient exposure
Safety data from 11 clinical studies (4 neonate RDS studies, 3 infant MAS studies, and 4 adult ARDS studies) in 1,765 patients (1,604 RDS, 77 MAS, 84 ARDS) are presented. Of these, 813 patients (701 RDS neonates, 45 MAS infants, and 67 ARDS adults) were exposed to Surfaxin.

	Patients enrolled	**Patients exposed to Surfaxin**	**Patients exposed to the proposed dose range (175 mg/kg)**	**Patients with long term safety data**
RDS-studies	1604	701	693	No final data from controlled studies available
MAS-studies	77	45	BAL	14
ARDS-studies	84	67	BAL	Not assessed in study report, when applicable
Post marketing	none	None	none	none
Compassionate use	none	None	none	none

Adverse events
In the RDS studies over all 1585 neonates (99.7%) experienced a treatment-emergent AE: 698 (99.6%) in the Surfaxin group versus 887 (99.9%) in the control groups. The most commonly reported AEs are displayed in the following table.

Most commonly reported AEs in all RDS studies combined

AE	**Surfaxin (N=701)**	**Control group (N=888)**
Anaemia neonatal	71.5%	78.5%
Jaundice neonatal	59.8%	61.0%
Neonatal apnoeic attack	49.2%	52.4%
IVH	45.8%	50.8%

Neonatal RDS	43.5%	46.2%
BPD	37.1%	39.3%
Sepsis neonatal	36.7%	38.2%
PDA	40.5%	36.4%
Metabolic acidosis NOS	26.4%	31.9%
Oxygen saturation decreased	29.1%	24.7%
Retrolental fibro-dysplasia	28.1%	24.7%
Hyperglycaemia NOS	24.0%	25.9%
Pneumonia NOS	23.1%	25.5%

Serious adverse events and deaths
It is reported that in the RDS studies 69% of the Surfaxin treated neonates and 75% of the infants treated with a comparator experienced a SAE. The most commonly reported serious AEs were neonatal RDS, BPD, intraventricular haemorrhage neonatal, sepsis neonatal, PDA, necrotising enterocolitis, apnoe.
However, this information is of limited value as the classification of AEs as "serious" does not adhere to the definition of a "serious AE".

No overview of serious AEs in the MAS and ARDS studies has been provided by the applicant.

Deaths:
RDS controlled studies (KL4-IRDS-06 and –02): all cause mortality, Surfaxin vs. synthetic vs. animal derived surfactant

Time Point	**SURFAXIN (N=651)**	**Exosurf (N=509)**	**Animal-Derived Surfactant (N=386)**	**SURFAXIN vs. Exosurf P-Value**	**SURFAXIN vs. Animal-Derived Surfactant P-Value**
By Day 14	99 (15.2%)	86 (16.9%)	66 (17.1%)	0.488	0.245
By Day 28	116 (17.8%)	109 (21.4%)	83 (21.5%)	0.208	0.044
By 36 Weeks PCA	132 (20.3%)	121 (23.8%)	93 (24.1%)	0.191	0.045
Predischarge	131 (20.1%)	119 (23.4%)	91 (23.6%)	0.191	0.067

Note: Birth weight strata are Stratum 1 (600-1000g) and Stratum 2 (1001-1250g).
Note: Pooled study centres were defined as protocol centre, e.g., centre #1 in KL4-IRDS-02 defined as Centre #2001 and centre #1 in KL4-IRDS-06 as Centre #6001, etc.

Note: p-value assesses treatment group difference using logistic regression adjusting for centre and birth weight stratum.

Peridosing events
Consistently through both controlled studies, the peridosing events dose interruption, pallor, endotracheal tube (ET) reflux, ET obstruction were higher in the Surfaxin group than in the control groups. At some points of time these differences were statistically significant. In the view of the assessors the reason for this may very well be the higher volume administered with Surfaxin compared to other surfactants (Curosurf: 200mg/kg ≅ 2.5ml, Survanta 100mg/kg ≅ 4.0 ml; Exosurf 67.5mg/kg ≅ 5.0ml) or the rather complicated mode of preparation as well as the seemingly higher viscosity of the agent.

Laboratory findings
The study protocols did not foresee any laboratory tests, apart from arterial blood gas analyses, i.e. not even routine measures such as a blood count or electrolytes. Nevertheless, anemia, for instance, is registered as an AE in approximately 70% of patients. The lack of appropriate laboratory data including tests for liver function abnormalities is not acceptable.

Values of ABG analysis were statistically significantly different at several points of time, but the clinical significance of these findings seems to be low.

Safety in special populations
The incidence of treatment-emergent serious AEs was higher in male neonates compared to female neonates in both the Surfaxin and control groups.

The incidence of treatment-emergent serious AEs was higher in white neonates compared with non-white neonates in both the Surfaxin and control groups.

Overall, the incidence of treatment-emergent serious AEs was higher in neonates weighing 600 to 800 g compared with neonates weighing 801 to 1000 g, 600 to 1000 g, and 1001 to 1250 g in both the Surfaxin and control groups.

Immunological events
It may be supposed that the immunogenic response in the target population of preterm neonates is limited as the immune system has not yet fully developed. Furthermore, prenatal corticosteroids might contribute to reduce any potential immune response. However, Surfaxin contains a new synthetic protein and in view of that justification is needed why immunogenicity was not addressed in the clinical dossier.

Safety related to drug-drug interactions and other interactions
No specific interaction studies were carried out. Concomitant medication in this population with a high morbidity and mortality is common and drug interactions are not likely to be easily evaluable. There were no obvious differences between the treatment groups in the controlled RDS studies.
From Non-clinical data interactions with narcotics/sedatives are suggested.

Discontinuation due to AES
In the RDS studies 11 of the 1589 treated neonates were discontinued from study therapy. 9 patient discontinuations occurred in study KL4-IRDS-06 and 2 in study KL4-IRDS-01. 6 of the 9 cases of discontinuations in KL4-IRDS-06 were due to AEs.

Other safety questions
The manufacturing process employs ethanol and hence limits for ethanol should be addressed and the potential, if any for toxicity should be discussed.

So far no complete report of longer-term outcome data of the controlled studies has been presented.

Post marketing experience
Not applicable.

IV. ORPHAN MEDICINAL PRODUCTS

According to the conclusion of the COMP (Opinion dated 16 June 2004) the prevalence of the "condition" "Prevention of respiratory distress syndrome in premature neonates of less than 32 weeks of gestational age" is 1.1 per 10000 individuals in the EU and the prevalence of the condition "treatment of respiratory distress syndrome in premature neonates of less than 37 weeks of gestational age" is 1.5 in 10,000 individuals in the EU.
The decision of the European Commission on the designation of Surfaxin as and orphan medicinal product in respect of the before mentioned conditions was issued on 29 July 2004.

V. BENEFIT RISK ASSESSMENT

The benefit risk profile of Surfaxin is at present considered unfavourable as there are still major objections that need to be addressed by the applicant.
Though superiority with respect to RDS at 24 hours and RDS related mortality through 14 days of age – endpoints not being fully in concordance with the Scientific Advice given - over the synthetic surfactant Exosurf was demonstrated in the pivotal study KL4-IRDS-06, these results have some limitations.
As confirmed by a Cochrane review by Soll and Blanco (2000), natural surfactants have an advantage vs. synthetic surfactants. The synthetic surfactant Exosurf must therefore be regarded as suboptimal as active comparator.

For the supporting study KL4-IRDS-02, which could have supported the results of the pivotal study, some statistical shortcomings concerning the design were identified. Furthermore this study was unfortunately underpowered, which limits its usefulness.
As a result no reliable data have been provided that Surfaxin is at least as effective as natural protein-containing surfactants.

For the incidences of some endpoints (e.g. RDS, RDS-mortality) considerable differences were observed between the controlled clinical studies, whereas incidences of other endpoints (e.g. BPD) were consistent between the controlled studies. On the other hand, considerable differences were observed within studies for some endpoints when imputed for death and not imputed for death, respectively.

The dosefinding was more or less empirical.

The safety of Surfaxin is difficult to evaluate, as the premature neonates are a very vulnerable population with a very complex and high morbidity. However, the complexity of reporting adverse events/serious adverse events also contributes to the difficulties in the evaluation of safety data. The issue of immunogenicity is not addressed in the clinical setting. The issue of peridosing events has not been satisfactorily addressed.

This Withdrawal Public Assessment Report is based on the Day 120 assessment report, which is the latest assessment report adopted by the CHMP prior to the Applicant's withdrawal of the marketing authorisation application. This Withdrawal Public Assessment Report does not include all available information on the product as the CHMP assessment of the applicant's responses to Outstanding Issues raised by CHMP was still ongoing.
It should therefore be read in conjunction with the Questions and Answers Document on the withdrawal of the marketing application for this product, which provides an overview on all available information on the product at the time of the Applicant's withdrawal.