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RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 5, 2012
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 21-746
Supplement#	
Applicant	Discovery Laboratories, Inc.
Date of Submission	September 6, 2011
PDUFA Goal Date	March 6, 2012
Proprietary Name / Established (USAN) names	Surfaxin/lucinactant
Dosage forms / Strength	Intratracheal Suspension Dosing Regimen: 5.8 mL/kg body weight q 6 hr, up to 4 doses in the first 48 hours of life
Proposed Indication(s)	Prevention of respiratory distress syndrome (RDS) in premature infants at risk for RDS
Recommended Action:	<i>Approval</i>

1. Introduction

This is the fifth review cycle for Surfaxin (lucinactant) Intratracheal Suspension (NDA 21-746), which was originally submitted by Discovery Laboratories on April 13, 2004. The original application included the results of a single pivotal study (study KL4-IRDS-06) which established the efficacy and safety of lucinactant for the proposed indication, “the prevention of RDS in premature infants at risk for RDS”. The clinical recommendation for the original submission was Approval; however, there were major CMC deficiencies that led to Approvable/Complete Response actions on February 11, 2005, March 31, 2006, May 1, 2008, and April 17, 2009. These have included drug substance related impurities for (b) (4), (b) (4) that exceed the qualification threshold of 0.15% recommended by the ICH guidance Q3A and major deficiencies related to inadequate specifications for release and stability, inadequate information on the manufacturing process, inadequate stability data, inadequate acceptance criteria for impurities, and inadequate validation of the lucinactant bioassay to be used for lot release testing. Over the course of the previous four review cycles, most of the CMC deficiencies have been resolved. The last outstanding CMC issue that Discovery addresses in this submission is the lack of a validated bioassay to demonstrate biological activity of the drug. This is a critical element in the development of locally active surfactant products as it is used to establish the release specifications and guarantee the consistency and quality of new batches of a life-saving drug for use in critically ill premature infants. Specifically, the company has been unable to demonstrate the ability of their bioassay using fetal rabbits to differentiate Surfaxin activity between the inactive (expired) and active (unexpired) batches or lots of drug product. This review will briefly describe the Surfaxin development program with a focus on the ongoing attempt on validating the company’s fetal

rabbit bioassay. For additional more specific information refer to previous Primary discipline and CDTL reviews and Division, and Office summary reviews.

2. Background

Respiratory Distress Syndrome (RDS) is a clinical condition found almost exclusively in premature infants characterized by inadequate production of endogenous pulmonary surfactant that is required to reduce surface tension at the pulmonary alveolar air/liquid interphase. Lack of endogenous surfactant results in greatly increased work of breathing, hypoxemia, and eventual alveolar collapse with resultant respiratory failure and the need for mechanical ventilation. Surfactant replacement therapies, in which non-native surface active agents are instilled into the lungs of premature infants to prevent and/or treat RDS have been developed and were approved by the FDA in the 1990s (Exosurf/colfosceril palmitate 1990, Survanta/beractant 1991, Infasurf/calfactant 1998, and Curosurf/poractant alpha 1999). The use of these agents has resulted in greatly reduced morbidity and mortality from RDS. The initial product marketed, Exosurf, was completely synthetic and lacked a protein component while the other product are derived from animal (bovine or porcine) lung surfactant and standardized for surfactant protein and phospholipid content. Initial concerns over potential immunogenicity and transmission of infectious diseases for the animal-derived products have not been realized in the approximately 22 year history of use of their use.

Because these drugs are locally active at the alveolar air/liquid interphase (b) (4)

[REDACTED] drug lots of surfactant products are subject to a bioassay (typically performed in rat or rabbit pup lungs) prior to lot release in order to demonstrate biological activity in reducing surface tension with a resultant increase in lung compliance. These bioassays should be developed at or before the time that pivotal clinical studies are performed in order that the assay procedure can be linked and thereby validated, to the performance of the clinical lots demonstrated to be effective in the clinical studies conducted to support approval of the surfactant product. One of the major problems with the rabbit model bioassay proposed by the Applicant for the determination of biological activity for Surfaxin has been that it was not developed until after the pivotal clinical trials were conducted and no original drug product remained and therefore has not been able to be linked to the biological activity and subsequent clinical efficacy demonstrated in the pivotal clinical trial. This lack of a validated bioassay that is able to be linked to the clinical efficacy of the drug lots used in the pivotal clinical study is exacerbated by the significant changes made in the manufacture of Surfaxin since the clinical trials were conducted for the RDS indication and has remained a major issue that would need to be resolved prior to approval.

This issue has been conveyed to and discussed with the Applicant on multiple occasions during the clinical development of Surfaxin. Discovery subsequently acknowledged that no batches used in the clinical trials were available to be used as an internal standard to validate the proposed bioassay however, an it was discovered that an animal study was conducted with the original clinical trial material in a fetal lamb model of RDS which demonstrated some degree of biological activity (approximately a 150% increase in lung compliance; Pediatrics 2006, vol 117:295-303). The Division at a meeting on December 21, 2006, agreed to allow the

lamb model to be used as a bridge to the efficacy demonstrated in the clinical lots of Surfaxin provided that currently manufactured lots of Surfaxin were found to demonstrate a similar degree of biologic activity when administered to fetal lambs in a manner comparable to the methods used in the published study. The Division then stated that since the lamb model demonstrated the bioactivity of the batches used in pivotal clinical trials, to be validated, the rabbit model should show comparable bioactivity to the lamb model. In subsequent submissions, Discovery has demonstrated that the currently manufactured drug product has comparable bioactivity to the drug product used in the pivotal clinical trial in the lamb model but has been unable to demonstrate that the proposed rabbit bioassay shows comparable activity to the lamb model. In short, the rabbit bioassay lacked sensitivity and, unlike the lamb assay, was not able to capture the loss of drug activity over time due to degradation and loss of the synthetic (b) (4) structure in drug product that had reached gone beyond its expiration date. This problem is apparent in Table 1 below from Dr. Pei’s review from the last review cycle which clearly demonstrates that the rabbit assay is not as sensitive as the lamb assay in predicting decreases in lucinactant activity.

Table 1: Results of the Lamb and Rabbit Assays

Lot	Expiry status	Mean Increase in Compliance (%) ^a				
		Rabbit ^b				Lamb ^c
		Lucinactant		Beractant		Lucinactant
		5.8 ml/kg	8.0 ml/kg	4.0 ml/kg	5.6 ml/kg	5.8 ml/kg
T7002, T7003	Yes	403	238	1079	1205	63
T8004, T8005, T8006	No	416	377	1062	1198	127
Mean	-	411	341	1068	1201	-

- Changes in lung compliance 30 minutes after intratracheal instillation of 5.8 ml/kg of lucinactant. These numbers were obtained by subtracting 100 from the reported % of control.
- Increases over negative (air) control in specific dynamic lung compliance C_{RS}/kg . The data was normalized by subtracting 100% from the reported data.
- Increases (%) over base line in lung compliance in lambs. The compliance was measured by ml/cm H_2O/kg .

3. CMC/Device

The drug product is an aqueous suspension of sinapultide, a synthetic peptide of 21 lysine residues and a mixture of synthetic phospholipids [(dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol (POPG), and palmitic acid (PA)]. While phospholipids are common to all surfactant products, the sinapultide peptide is designed to simulate the function of natural surfactant proteins which are present in the currently marketed surfactant products made from animal lung extracts. The drug product is sterile-filled to 10 mL sterile glass vials and contains 0.86 mg/mL of sinapultide, 22.5 mg/mL of DPPC, 7.5 mg/mL of POPG, and 4.05 mg/mL of PA, in 8.5 mL per vial. This corresponds to a concentration of 30 mg of total phospholipids per each mL of drug product suspension. The commercial drug product will be manufactured by Discovery at their Totowa, NJ site.

The requested expiry period for the drug product is 12 months and it is supported by the submitted data. This is a rather short expiry period but is the result of limited stability of the drug product due to a chemical reaction occurring between the active ingredients, notably, the

(b) (4)
This seems to alter the peptide conformation and decreases the biological activity of the drug product as evidenced by about a 25% decline in the biological activity over 12 months. Due to the observed instability of the formulation and recent changes to the manufacturing process, the expiry period may be extended only via a prior approval NDA supplemental application containing adequate supporting stability data.

The proposed acceptance criteria for (b) (4) impurities, biological activity, surface tension, viscosity, particle size distribution, foreign particulate matter and volume in container were revised to reflect results for drug product batches representative of the to-be-marketed product and were accepted by the Applicant.

All current DMFs have been judged as adequate.

A recent GMP inspection evaluating the 2011-implemented changes to the sterile fill process has been judged as adequate. In addition, GLP and GMP inspections at the sites where the testing for biological activity of the drug product using the rabbit bioassay is performed (b) (4) and raw data analyzed, reported, and interpreted (Discovery site, Warrington, PA) have been judged as acceptable with one caveat. While the data generated and analyses of the raw data were accurate, the inspectors noted a general lack of quality assurance oversight for the bioassay. One specific issue was that while the raw data are generated at (b) (4) in (b) (4) the quality oversight is performed at Discovery in Warrington, PA. In order to assure better quality oversight, after discussion with Discovery, they have agreed to transfer quality assurance monitoring to the (b) (4) lab performing the assay. When accomplished, the company will submit a prior approval CMC supplement to the NDA which will likely generate a GMP inspection to assure adequate quality measures have been incorporated. This process will be documented as a post-marketing commitment by the company.

The importance of the analytical method evaluating the biological activity of the drug product (assessing drug potency in premature rabbits) is key for this application as it serves as a regulatory release and stability method for the drug product. In addition, by demonstrating comparable surface tension reducing activity to that of a lamb model of RDS, the rabbit bioassay is the bridge to link the bioactivity of the currently manufactured drug product to the drug product used in the pivotal clinical trial. Summary results of the validation process are outlined below.

As discussed above, the critical issue addressed in this submission was validating the proposed rabbit bioassay by demonstrating that the bioassay is consistent and reproducible and, like the fetal lamb model, is able to distinguish the differences in biological activity of Surfaxin lots that are current from those that have expired (with a known diminution in surface tension lowering activity that is noted from stability testing). The revised analytical method for testing of the drug product biological activity in fetal rabbits submitted this review cycle contained data from 12 lots of drug product. The primary analysis method involved measurements of changes in lung compliance (respiratory system compliance, $C_{RS} = \Delta V/\Delta P$) after instillation of drug product to the lungs of premature rabbits. In order to determine the validity of the method, the results were then evaluated by a multi-disciplinary review team consisting of Dr.

Luqi Pei (Pharmacology and Toxicology reviewer, DPARP), Dr. Jinglin Zhong (Mathematical statistician, Office of Biometrics), and Dr. Eugenia Nashed (Office of New Drug Quality Assessment) for specificity, precision, range, linearity, and accuracy. The definitions and acceptance criteria for each of the parameters are outlined Table 2 below duplicated from the joint review of the review team members. The results are then briefly discussed.

Table 2: Definition and Acceptance Criteria for Rabbit Bioassay Validation

Parameter	Definition	Acceptance criteria
Specificity	Specificity is demonstrated by: 1) meeting a specified increase in %CRS for 3 lots of unexpired and active KL4 surfactant drug product, and 2) failure to meet a minimum increase in %CRS for: <ul style="list-style-type: none"> • expired and inactive KL4 surfactant drug product lot, • inactive Tris buffer 	1) %CRS \geq 200% increase from the negative control 2) %CRS < 200% increase from the negative control
Precision	Repeatability: This will be demonstrated by measuring precision for test sample results for: <ul style="list-style-type: none"> • Three lots of unexpired and biologically active KL4 Surfactant drug product within the 1st 3 months after manufacture, • One lot unexpired and active KL4 surfactant drug product at 6, 9, or 12 months following manufacture, • One lot of expired and active KL4 surfactant drug product • Inactive Tris buffer Intermediate precision: Intermediate precision is demonstrated by varying the analyst used to run FRBAT for 3 lots of unexpired and biologically active KL4 surfactant drug product at 3 different time points (high: < 3 mo; medium: 6 mo; low: 12 mo)	Repeatability: %CV for the samples must be \leq 24% for the runs in each test
Range	Range of the method was determined by assessing accuracy and precision for degraded samples stored at 15°C through 8 weeks and stored at 25°C through 3 weeks	No more than $\pm (\sqrt{2}) \times 30\%$ of average %CRS
Linearity	Linearity of the method was determined by assessing the %CRS at differing active KL4 surfactant product concentration levels	%CRS values which are proportional to the concentration, via linear or quadratic regression
Accuracy	Accuracy of the method is determined by establishing a reference range for %CRS using newly manufactured active KL4 surfactant drug product at 3 months of age against this reference range	%CRS of all samples must be within 24% of a defined value

Abbreviations: C_{RS} = respiratory system compliance; KL4 = sinapultide peptide; CV = coefficient of variance

Specificity: All lots with shelf ages of 12 months or shorter showed efficacy (increase in C_{RS} of 333% or greater). Lot 7002 which had expired (shelf age of 44 months) demonstrated much lower activity with an efficacy of 41-72%. As a result of these findings, the proposed acceptable limit for demonstration of efficacy of >200% was revised to >300%.

Precision:

Repeatability: Repeatability was measured by percent coefficient variation (%CV) with the CV% required to be \leq 24% for the runs in each test. For the three drug lots used for the repeatability test, the %CV ranged from 3.2% to 20.9%, all below the 24% limit. Intermediate

precision was also evaluated by assessing the variance between 2 analysts (technicians performing the bioassay). The %CV ranged from 3.6% to 13.6% which was also acceptable.

Range: The range of the assay method was determined by assessing the accuracy and precision for drug lots under accelerated conditions (15 and 25°C) at different stability ages. Results showed that the bioassay detected a decrease in Surfaxin activities as age and temperature increased. The reduction in activity was more rapid and pronounced at 25°C than 15°C.

Linearity: Linearity of the method was determined by assessing the %C_{RS} at different Surfaxin product concentrations as determined by total phospholipid levels which ranged from 0.5 – 30 mg/mL in Tris buffer. It was determined that the C_{RS} values obtained when the bioassay was run with different concentrations of drug product was linear.

Accuracy: The accuracy of the rabbit bioassay was demonstrated by establishing an expected value (EV) of %C_{RS} and EV limits. The EV was a point estimate and an alternative to the internal standard, which normally would have been the drug product used in the pivotal clinical trial but the assay was not developed at that time. Criteria are that the point estimate should reliably represent the EV and the justifiable EV limits could define the range of the biological activity standards. Thirty three reportable values from 9 freshly manufactured Surfaxin lots were used to establish an acceptable EV. The expected EV was calculated as 467% with an 8.2% CV. Subsequently, 2 tests were carried to ensure that no paired Surfaxin lots were substantially different from each other. The first analysis was the Tukey's multiple comparison test that would demonstrate that no samples of paired Surfaxin lots were statistically significantly different from each other at the 0.05 level, with all simultaneous 95% confidence limits including the value 0. The second test determined the overall % CV for the paired lots. Results showed that the largest % CV for any pair of lots was 17%, a value well below the 24% set limit.

A comparison of the optimized rabbit bioassay and the preterm lamb model of RDS serving as a link to the efficacy of the drug product used in the pivotal clinical trial was performed in order to demonstrate that both bioassay methods were comparable. The method was to assess and compare the potency of Surfaxin at different stability ages (0 – 44 months) in the preterm lamb and rabbit models. The potency assessment was consistent with the measurement used to assess potency/efficacy in other validation studies, increase in respiratory system compliance over baseline. Results showed that for both assays, there were slight decreases in activity which occurred during months 6 to 12 with little or no activity detected in samples 38-44 months of age (Table 3). Despite a data gap for the period 12-44 months, overall concordance between the rabbit and lamb assays was felt to be established as both assays showed that the biological activities of Surfaxin decline for approximately 25% over of a course of 12 months and had negligible activity at 38-44 months.

Table 3: Comparison of Rabbit and Lamb Assay Results at Stability Ages of 6-44 Months

Lot	Age (mo.)	% C _{RS} (mean ± SD)	
		FRBAT	Lamb
T0002	6	430.7 ± 48.0	174.0 ± 118.8
T9003	9	417.0 ± 61.5	130.4 ± 35.7
T9002	12	356.7 ± 17.4	125.4 ± 46.0
T7002	38 – 44 ^a	56.9 ± 15.6	58.8 ± 49.5

a. Tested at 38 and 44 months of age in FRBAT and lamb assays, respectively.

In summary, after careful review and frequent interaction with the Applicant, the review team concluded that the rabbit bioassay had met the criteria for acceptable specificity, precision, range, linearity, and accuracy and was also comparable to the preterm lamb model in demonstrating loss of drug biological activity over time.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding clinical pharmacology issues with this application other than the Pharmacology/toxicology consultative review to the CMC discipline by Dr. Luqi Pei noted in the Section 3, CMC/Device, above. Overall, the animal pharmacology and toxicology studies conducted for Surfaxin were somewhat limited because of the nature of the drug product and the fact that the drug is to be administered acutely over a period of at most, 48 hours. Animal pharmacology studies demonstrated that Surfaxin reduced surface tension in ex vivo systems; and increased lung compliance and expansion, improved gas exchange, and reduced ventilatory pressures in animal models of RDS. Animal toxicology studies were conducted in neonatal rabbits, neonatal dogs, and neonatal cats. The studies were characterized by respiratory distress in animals dosed, and early deaths in rabbits from pulmonary causes. Histopathology in repeat dose studies showed evidence of lung inflammation with lung histiocytosis and inflammatory cell infiltrates at all doses and NOAELs could not be established as a result. Clinical studies were allowed to proceed because of the intended clinical benefit, a decrease in RDS-related mortality. Reproductive and carcinogenicity studies were not performed for Surfaxin. Animal immunotoxicity studies in guinea pigs were performed and showed no evidence of a hypersensitivity response.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology studies were not required to be conducted for Surfaxin because it is both administered and active locally and does not gain significant entry into the systemic circulation.

6. Clinical Microbiology

Clinical microbiology is not applicable to this application. Microbiological testing deficiencies detected during the manufacturing process are captured in the CMC section.

7. Clinical/Statistical- Efficacy

The initial NDA submission submitted by Discovery Laboratories on April 13, 2004, for Surfaxin® (lucinactant) Intratracheal Suspension for the proposed indication of “prevention of

RDS in premature infants” demonstrated sufficient efficacy for approval. In that submission there was a single pivotal study upon which clinical support for the indication rested, study KL4-IRDS-06, a randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants which was conducted in Eastern Europe and Latin America that compared Surfaxin to Exosurf (colfosceril palmitate, a synthetic surfactant no longer marketed due to lack of efficacy compared to animal surfactant extract preparations) in a superiority design. A second active comparator, Survanta (beractant, a marketed lung surfactant prepared from bovine lungs), was included as a reference drug arm. The study included 646 males and 648 females who weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Seventy-eight percent of the infants were white, 1% black, and 21% classified as other. Within the first 30 minutes after birth, infants were randomized to receive 1 of 3 surfactants, Surfaxin (N = 527), Exosurf (N = 509), or Survanta (N = 258). Surfaxin was administered at a dose of 5.8 mL per kg, Exosurf at a dose of 5.0 mL per kg, and Survanta at a dose of 4.0 mL per kg. Infants in the Surfaxin and Survanta groups could be given up to 3 additional doses between 6 and 24 hours of birth, as often as every 6 hours, if they subsequently developed RDS and required mechanical ventilation with an FiO₂ ≥ 0.30 and a mean airway pressure (MAP) ≥ 6 cm H₂O. Infants in the Exosurf group could receive up to 2 additional doses at least 12 hours apart if they met the retreatment criteria. Some infants received sham air to maintain blinding of the study. All doses were calculated based on birth weight. Infants were followed through 12-months corrected age. In this study, Surfaxin was demonstrated to be superior to the active comparator, Exosurf, on both co-primary endpoints, the incidence of RDS at 24 hours and RDS mortality at 14 days (Table 4). Specifically, the incidence of RDS was about 17% less in patients treated with Surfaxin than with the active comparator Exosurf, and RDS-related mortality was approximately half the rate in Surfaxin patients [(4.7 vs. 9.6%)]. Results were consistent across population subgroups based on birth weight, gender, and race. Results for Survanta were similar to those for Surfaxin.

Table 4. Results from a Controlled Prophylaxis Study in Preterm Infants (Study KL4-IRDS-06)

	Surfaxin (N = 527) n (%)	Exosurf (N = 509) n (%)	P-value Surfaxin vs. Exosurf
RDS at 24 hours	206 (39)	240 (47)	<0.01
RDS-related mortality through Day 14	25 (5)	48 (9)	<0.01
Non-RDS-related mortality through Day 14	59 (11)	37 (7)	0.04
Sepsis-related mortality through Day 14	21 (4)	17 (3)	0.70
All-cause mortality			
Through Day 28	100 (19)	108 (21)	0.23
Through 36-weeks PCA	111 (21)	121 (24)	0.18
Pulmonary air leak through Day 7, all types	82 (16)	93 (18)	0.15
Oxygen requirement			
At Day 28	304 (58)	316 (62)	0.06
At 36-weeks PCA	210 (40)	227 (45)	0.05

Additional follow-up data (review of the long-term follow-up for 394 patients who received Surfaxin in study KL4-IRDS-06) included in a complete response received October 6, 2005

failed to show any significant changes in mortality or neurologic complications between treatment groups.

A second study, KL4-IRDS-02, was positioned by the Applicant as being supportive, but the Division considered its support to be limited because of design weaknesses and because it was not completed. The study was a double-blind, active-controlled study involving 252 premature infants and included 126 males and 126 females who weighed between 600 g and 1250 g at birth with a gestational age ≥ 24 weeks but < 29 weeks. Eighty-three percent of the infants were white and 5% black. Study participants were from North America and Europe. Within the first 30 minutes after birth, infants were randomized to receive 1 of 2 surfactants, Surfaxin (N = 124) or Curosurf (poractant alpha) (N = 128). Surfaxin was administered at a dose of 5.8 mL per kg and Curosurf was dosed at 2.2 mL per kg for the first dose and 1.25 mL per kg for subsequent doses. Infants in each group could be given up to 2 additional doses during the first 48 hours of life if they continued to require mechanical ventilation with an $\text{FiO}_2 \geq 0.30$ to maintain arterial $\text{PaO}_2 \geq 50$ mmHg or an oxygen saturation $\geq 90\%$ and a chest radiograph consistent with RDS. The primary endpoint was the incidence of being alive without bronchopulmonary dysplasia at Day 28 of life. Bronchopulmonary dysplasia was defined as a requirement for mechanical ventilation or use of supplemental oxygen in order to maintain oxygen saturation $\geq 90\%$. The study was designed with the intent of demonstrating non-inferiority between Surfaxin and Curosurf with a planned sample size of 248 infants per treatment group. However, the basis of the non-inferiority margin could not be justified; the study was also terminated prematurely. As such, Study KL4-IRDS-02 can only be used to support the safety of SURFAXIN relevant to another surfactant product.

For a more in depth discussion of the clinical program see the initial clinical review of NDA# 21-746 by J. Harry Gunkel, MD, dated January 14, 2005, the subsequent joint complete response review by J. Harry Gunkel, MD and Anthony G. Durmowicz, MD, dated March 10, 2006, and subsequent reviews by Anthony G. Durmowicz, MD, dated March 19, 2008, and April 14, 2009.

8. Safety

In reviewing the safety of Surfaxin compared to other active comparator surfactants (Survanta and Curosurf) used in the pivotal clinical trials in this critically ill population, it is clear that patients who received Surfaxin had a higher incidence of prospectively defined negative reactions to dosing (dose interruption, endotracheal tube obstruction, ETT reflux, pallor, etc.) than those who received other surfactant products. While this issue was not addressed by the Applicant, the most obvious likelihood is that the larger dose volume of Surfaxin per kg of patient weight compared to other marketed surfactant products is responsible. This information has been added to the proposed product label.

Subsequent previous clinical submissions have consisted of safety updates for ongoing studies involving Surfaxin; however, none were conducted in the same study population for which this NDA applies (premature infants at risk for RDS). The study that was conducted in a population closest to the indicated population was Study KL4-BPD-01. This was a randomized, double-blind, placebo controlled, Phase 2 trial designed to evaluate the safety and efficacy of up to 5 doses of lucinactant in 136 very low birth weight premature infants between

3 and 10 days of life still requiring mechanical ventilation and at risk for developing bronchopulmonary dysplasia. For this study there was no new safety signals noted; the most common adverse reactions continued to be those related to surfactant administration and included hypoxia and bradycardia.

A previous safety update also noted the finding of increased serious adverse reactions, including an increase in deaths and other serious adverse reactions in adults with ARDS who received high doses of Surfaxin via segmental bronchial lavage in study KL4-ARDS-04. Information about the increase in serious adverse reactions, including death, in adults with ARDS who received Surfaxin via segmental bronchial lavage has been included in the proposed product label.

For this NDA cycle, the safety update contained unblinded safety data for the recently completed study, KL4-ARHF-01, a randomized, placebo-controlled study to assess the safety and efficacy of lucinactant (Surfaxin) in children up to 2 years of age with acute hypoxic respiratory failure. One hundred sixty five patients with hypoxemic respiratory failure were enrolled (Surfaxin = 84, sham air placebo = 81) to receive up to two 5.8 mL/kg doses of Surfaxin separated by at least 12 hours. Fifty five patients were enrolled from the US and 110 from Chile. Clinical endpoints included duration of mechanical ventilation, duration of ICU stay, duration of supplemental oxygen use, and duration of hospitalization. There were no differences in efficacy between Surfaxin and placebo for any of the efficacy endpoints. Analysis of the safety data revealed, similarly to other lucinactant/Surfaxin studies, that peri-dosing adverse reactions including hypoxemia and bradycardia were higher in the Surfaxin-treated group than those who received sham air placebo. A notable finding was that for the 7 deaths noted for the study, 6 were in Surfaxin-treated patients. Of the 6 patients treated with Surfaxin who died, 4 died from infectious disease (3 from pertussis, 1 from RSV) and the other 2 were from hepatitis with gram negative sepsis and a child with Down syndrome and pre-existing pneumonia. So, while a death imbalance was noted, the types of deaths which occurred were not consistent with an adverse Surfaxin treatment effect.

9. Advisory Committee Meeting

An Advisory Committee meeting was not assembled for this NDA submission because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease, and there were no controversial issues that would have benefited from advisory committee discussion.

10. Pediatrics

Premature infants with RDS are considered an orphan drug population and, as such, PREA is not applicable. In any event, indication (prevention of RDS) is in a narrow niche of the general pediatric population, premature infants at risk for RDS. Because this disease entity does not exist outside the premature infant population, no additional studies in other pediatric populations would be relevant to the indication.

11. Other Relevant Regulatory Issues

There are no outstanding issues with consult reviews received from groups within the Agency. There are no outstanding audits or financial disclosure issues.

12. Labeling

During a previous (third) review cycle the Division performed a thorough review of the product label and made many changes to the original labeling proposed by the Applicant including the addition of (b) (4) the increased risk of death observed when lucinactant was administered to the lungs of adults with ARDS via flexible bronchoscopy. For the current submission, Discovery was required to submit the product label in the PLR format. The Division extensively revised the Warnings and Precautions, Adverse Reactions, and Clinical Studies sections of the PI submitted by the company to better comply with the required PLR format and add context to many of the statements made in the previous version of the label which, at the time it was written, was modeled after the labels of other approved surfactant product labels which remain in the older format. At the time of this review, final labeling has been agreed to with the company.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is for Approval. The efficacy and safety of Surfaxin has previously been demonstrated in one large randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants. The development of a validated bioassay helps assure the biological activity of the drug product and supports the approval of Surfaxin for the prevention of respiratory distress syndrome in premature infants.

- Risk Benefit Assessment

Administration of exogenous surfactant products are potentially life-saving treatments for the prevention and treatment of RDS in premature infants.

For previous review cycles, while the efficacy and relative safety of Surfaxin had been demonstrated, the lack a validated rabbit bioassay able to assure consistent drug quality placed critically ill premature infants at undue risk that any Surfaxin drug product administered may not possess adequate biologic activity to prevent RDS. This is especially true in light of the availability for over 20 years of surfactant products available in the United States which have been used successfully to prevent and/or treat RDS. In the current submission the company has adequately addressed this deficiency by validating the surfactant bioassay which should ensure a consistent biologically active drug product.

- Recommendation for Postmarketing Risk Management Activities
- Recommendation for other Postmarketing Study Commitments

Office of Compliance inspectors noted a lack of quality assurance oversight for the bioassay. While the raw data are generated at (b) (4), the quality oversight is performed at Discovery in Warrington, PA. In order to assure better quality oversight, Discovery has agreed to transfer quality assurance monitoring to the (b) (4) lab performing the assay. When accomplished, the company will submit a prior approval CMC supplement to the NDA which will likely generate a GMP inspection to assure adequate quality measures have been incorporated. This process will be documented as a post-marketing commitment by the company. The recommended PMC language follows:

- You commit to transfer responsibility from Discovery to (b) (4) (b) (4) for quality assurance and data analysis of the analytical method for testing biological activity of the drug product (Method DP-032). Your final study report to support transfer of responsibility should be submitted as a Prior Approval Supplement and address the following: personnel training, installation of additional equipment, implementation of appropriate standard operating procedure for data analysis, documentation practices, deviation and investigation, corrective and preventive action. Your PAS should include a statement that that the analytical facility at (b) (4) is ready for inspection and is qualified to assume full responsibility for all functions related to Method DP-032, including data QA and analysis. The transfer of responsibilities from Discovery to (b) (4) will occur upon the approval of PA supplemental application by the Agency.

Final Report Submission: January 30, 2014

- Recommended Comments to Applicant

None other than the PMC language.

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/s/

ANTHONY G DURMOWICZ
03/05/2012