CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021746Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	March 6, 2012
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 21-746
Applicant Name	Discovery laboratories, Inc.
Proprietary / Established (USAN) Names	Surfaxin lucinactant
Dosage Forms / Strength	Intratracheal Suspension (30 mg phospholipids/ml) 5.8 mL/kg per Kg birth weight every 6 hours, 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
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding Surfaxin and the reader should refer to the reviews in the action package for a more detailed discussion. Surfaxin is an aqueous suspension of sinapultide, a synthetic peptide of 21 lysine residues and a mixture of synthetic phospholipids to be used as a prevention of Respiratory Distress Syndrome (RDS). Surfaxin has a long, tortured history exemplified by this being the fifth review cycle for this product. Drs. Durmowicz and Chowdhury have summarized the review history and I will not repeat it here. Also as noted in Dr. Durmowicz's and Chowdhury's reviews, the safety and efficacy of the product tested in the original NDA submission in 2004 has been established during previous review cycles and I will not review previous decisions made in that regard. Rather, I will focus on the last major outstanding issue which is the validation of the bioassay to evaluate the level of biological activity of the drug product. A trustworthy bioassay is imperative for this type of product, and the bioassay is used to determine the potency and release specifications of new batches of drug.

Respiratory Distress Syndrome (RDS) in premature infants is due to failure of the full development of the pulmonary surfactant system. Surfactant prevents the collapse and atelectasis of lung at the end of the expiratory cycle. Use of surfactant type agents have revolutionized the treatment of these patients and has greatly reduced the morbidity and mortality associated with RDS. The currently available agents are derived from animal products and have a good track record, while this product is composed of four synthetic compounds; a 21-amino acid peptide (sinapultide), dipalmitoylphosphatidylcholine (DPPC), sodium salt of palmitoylphosphatidylglycerol (POPG), and palmitic acid (PA). It is important to note that these are synthetic components as this product seems to have less stability than the naturally derived lung surfactants. Early breakdown of these synthetic components affects the tertiary structure of the peptide, and the tertiary structure of the peptide is critical to the

biological activity of this type of product in RDS. Therefore, it is imperative that acceptable biological activity of this product is documented prior to release. Measurement of biological activity is also crucial for expiry dating, assuring the shelf-life of the product. During the development of this product, the sponsor failed to develop a validated bioassay with the original clinical trial, despite our explicit advice, as recorded in pre-NDA meeting minutes dated June 13, 2003. This in and of itself may not have been a problem, but the applicant did not save any of the original batch, or it expired during development as the drug has very limited shelf life. The drug product potency/biological activity came to play during the NDA review (multiple cycles) as the sponsor has had major CMC deficiencies that have led to major manufacturing changes, such that there has been a major problem linking the current product to that tested in the efficacy trials. Not anticipating the need for access to any of the original batches has been a major oversight on the sponsor's part and has limited options that can be used to link the product used in the clinical trial to the present product. The Division and the sponsor have struggled as to how to overcome this hurdle short of conducting another trial. It was discovered that a published study (*Pediatrics*, February 2006; vol. 117:2 p.295-303) used the original batches in a lamb animal study. It was decided that the only viable path forward, short of repeating a clinical trial or trials, was for the applicant to use the information in this published study as a means to bridge the results from the lamb study to some other bioassay model (usually rabbit), or to further develop the lamb model (which would be very unwieldy).

For the previous review cycle, the sponsor was able to repeat the original fetal lamb studies using comparable methodology and demonstrated similar results between the batches used in the clinical trials to the new batches. However, they were not able to link the results from the lamb studies to the proposed rabbit bioassay. The previous fetal rabbit model bioassay that the sponsor had proposed was unable to differentiate surfactant activity between inactive (expired) and active (unexpired) batches of drug product.

With this submission, the sponsor has introduced a revised analytical program. This program and the results were reviewed by a multi-disciplinary team as discussed in Dr. Durmowicz's review (pages 4-7). The review team determined that this new program does have acceptable specificity, precision, range, linearity, and accuracy. Comparison with the lamb assay demonstrated the results below (Dr. Durmowicz review page 6).

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

		% C_{RS} (mean ± SD)	
Lot	**Age (mo.)**	**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.

Based on this information, the review team has concluded that the rabbit bioassay has met the criteria for acceptability for product assessment.

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DPARP has determined that there is now an appropriate fetal rabbit model bioassay based on the results of the above testing. However, inspection of the testing sites has identified concerns. Bioassay evaluation is performed at two separate sites; (b) (4) (raw data generation) and Warrington, PA (raw data interpretation). An inspection of the (b) (4) where raw data is generated identified some concerns, but it was deemed that the method validation is appropriate and that the data generated at this site are acceptable. The concerns focused mainly on deficiencies in quality systems that could be remediated and compliance has entered an acceptable recommendation. The raw data generated at (b) (4) is then transferred and interpreted at the Discovery site in Warrington, PA. This site was re-inspected to evaluate how this data was handled. The office of compliance has rendered an acceptable recommendation for this site as well.

Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The application did not raise significant safety or efficacy issues in the intended population. Additionally, outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

Conclusions and Recommendations

This drug is being used in Respiratory Distress Syndrome (RDS), a life-threatening condition found in premature infants, for which surfactant type products have been proven to be life saving. It is critical that the activity and potency of such products are established before they are released. With this submission, the sponsor has adequately addressed the deficiencies identified during the last review cycle. Efficacy and safety have been determined during earlier cycles to be appropriate. As such, I recommend that this drug should be approved with appropriate labeling and PMC agreements.

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/s/

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03/06/2012