DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Lorraine J. Lucas, PhD
Senior Director, Regulatory Affairs
Discovery Laboratories, Inc.
2600 Kelly Road, Suite 100
Warrington, PA 18976

RE: NDA 021746
SURFAXIN® (lucinactant) Intratracheal Suspension
MA #29

Dear Dr. Lucas:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the homepage of a website[1] (webpage) for SURFAXIN® (lucinactant) Intratracheal Suspension (Surfaxin) submitted by Discovery Laboratories, Inc. (Discovery) under cover of Form FDA 2253. The webpage is false or misleading because it makes unsubstantiated superiority claims. Thus, the webpage misbrands Surfaxin within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and make its distribution violative. 21 U.S.C. 352(a) & (n); 331(a). *See* 21 CFR 202.1(e)(6)(ii), (x); (e)(7)(i). The webpage also provides evidence that Surfaxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Surfaxin misbranded or otherwise makes its distribution violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Surfaxin.[2] According to its FDA-approved product labeling (PI):

> SURFAXIN® (lucinactant) Intratracheal Suspension is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS. SURFAXIN reduces the incidence of RDS at 24 hours and mortality due to RDS.

The PI for Surfaxin contains warnings and precautions regarding acute changes in lung compliance, administration-related adverse reactions, and increased serious adverse reactions in adults with Acute Respiratory Distress Syndrome (ARDS). The PI also indicates

[1] Surfaxin homepage at www.Surfaxin.com (last accessed March 3, 2015).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

that the most common adverse reactions associated with the use of Surfaxin are endotracheal tube (ETT) reflux, pallor, ETT obstruction, and the need for dose interruption.

Unsubstantiated Superiority

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The webpage includes the following claims and presentations (emphasis in original):

- "**SURFAXIN®, THE ONLY AVAILABLE SYNTHETIC ALTERNATIVE TO ANIMAL-DERIVED SURFACTANTS APPROVED BY THE FDA"** and "*Join the Therapeutic Evolution…"* in conjunction with graphics of a pig, a cow, and a human-like robot
- "Direct clinical comparisons to Exosurf®, Survanta® and Curosurf®[3,4]„

These claims and presentations are misleading because they imply that Surfaxin, a synthetic surfactant depicted by the image of the human-like robot, is superior because it has "evolved" from more primitive, animal-derived surfactants, such as Curosurf (poractant alfa), an extract of natural porcine lung surfactant, and Survanta (beractant), an extract of natural bovine lung surfactant. We are not aware of substantial evidence that supports the implication that Surfaxin is superior to Curosurf or Survanta. No references are cited to support the claims and presentations in the first bullet point above. To support the claim in the second bullet point, the webpage cites two publications[3,4] which describe the two clinical studies used for approval of Surfaxin. While these studies are included in the PI, and Curosurf and Survanta were used as active comparators, the studies do not constitute substantial evidence to support a direct clinical comparison between Surfaxin and these other surfactants. As indicated in the CLINICAL STUDIES section of the PI, the efficacy of Surfaxin was demonstrated in a single phase 3 study that compared Surfaxin to colfosceril palmitate (Exosurf Neonatal®, a synthetic surfactant that is no longer marketed). In this study, Surfaxin demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through day 14 compared to Exosurf. Survanta was also used as an additional active comparator in this study; however the study was not powered to make any meaningful efficacy comparison between Surfaxin and Survanta. The CLINICAL STUDIES section of the PI also describes a second clinical study, which included a Curosurf treatment arm; however, this study was used only to support the safety, not the effectiveness of Surfaxin. Therefore, based on these studies which have been cited as references for these claims and presentations, "direct clinical comparisons" cannot be made regarding the efficacy of Surfaxin compared to that of Curosurf, Survanta, or any other animal-derived product.

[3] Moya, F.R., Gadzinowski, J., Bancalari, E., et al. A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. *Pediatrics.* 2005; 115: 1018-1029.
[4] Sinha, S.K., Lacaze-Masmonteil, T., Valls i Soler, A., et al. A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. *Pediatrics.* 2005; 115: 1030-1038.

Furthermore, these claims and presentations are misleading because they imply that Surfaxin is the result of a "therapeutic evolution" in this class of drugs, and therefore may be safer than animal-derived surfactants. The ADVERSE REACTIONS section of the PI states:

> Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia.

Therefore, the phrase "therapeutic evolution" is misleading because the ADVERSE REACTIONS section of the PI indicates that Surfaxin is not safer than animal-derived surfactants.

The webpage also includes the claim, "Sinapultide (KL_4 peptide) mimics critical surfactant protein B function." However, no reference is cited to support this claim, and the FDA is not aware of any substantial evidence to support the implication that the ingredient, KL_4, actually functions as a "mimic" for endogenous human SP-B. Upon clicking this text on the webpage, a pop-up window appears, which shows a bar graph titled, "Comparison of SP-B or SP-B mimic (KL_4) as a Percent of Phospholipid Across Commercially Available Surfactants." The graph depicts SP-B or KL_4 (sinapultide or "SP-B Mimic") content as a percentage of total phospholipid content per milliliter in various lung surfactant products and in human surfactant. This presentation is misleading because it suggests that Surfaxin is superior to Curosurf, Infasurf (calfactant), and Survanta based on Surfaxin's higher concentration of SP-B, when this has not been demonstrated by substantial evidence. In support of this presentation, the graph cites the PIs for Curosurf, Infasurf, Survanta, and Surfaxin, a study by Notter, et al.[5], and a textbook by Polin, et al[6]. However, a cross-comparison of certain ingredients as discussed in these references is not sufficient to support the implication that higher SP-B levels correlate to better clinical outcomes, that KL_4 functions as a "mimic" for SP-B, or any implications of superiority based on differences in the levels of this protein in each surfactant formulation. In fact, the lung surfactant products included in this presentation are composed of complex mixtures of ingredients, and clinical efficacy *in vivo* cannot be attributed to any one ingredient alone.

Finally, the webpage includes the claim: "Neonatologists and parents share concerns regarding animal-derived medications." Upon clicking this text, a pop-up window appears containing a presentation titled: "Concerns About Animal-Derived Products" which includes the claims, "92% of neonatologists expressed concerns over exposure of newborn infants to animal-derived medicines," and "67% of parents want to be informed if an animal-derived medicine is to be administered to their newborn," along with pie charts representing the summary of survey results of opinions of neonatologists and parents of infants in the NICU, respectively.[7] These claims and presentations are misleading because they imply that, due to its synthetic formulation, Surfaxin is superior to animal-derived surfactants, when this has not been demonstrated by substantial evidence. In support of these claims, the webpage

[5] Notter, R. H., Wang, Z., Egan, E. A., et al., Component-specific surface and physiological activity in bovine-derived lung surfactants. *Chemistry & Physics of Lipids*. 2002;114:21-34.
[6] Polin, R.A., Fox, W.W., Abmam, S. H. Fetal and Neonatal Physiology. 3rd ed. New York, NY: Saunders; 2004.
[7] Sarkar, S. and Donn, S.M. Do neonatologists and parents share the same concerns about animal-derived pharmaceutical agents? *J of Neonatal Perinatal Medicine.* 2011;4(3):235-239.

references a study by Sarkar and Donn, which describes the results of a survey comprised of general, hypothetical questions that do not specifically address Surfaxin. For example, the survey asks "How concerned are you about exposure of your patients to animal proteins?," "Do you advise parents of a product's animal derivation when there is an obvious cultural, religious, or social objection to its use?," "What percentage of parents do you think would want to know if a medication was animal derived?," and "Would you be concerned if a medication that is given to your baby comes from an animal source?" The survey did not include any measures that specifically evaluate Surfaxin against its comparators; therefore, the results from the survey cannot support **any** suggestion or claim that Surfaxin is superior to animal-derived surfactants.

The overall impression created by the various unsubstantiated superiority claims regarding the efficacy and safety of Surfaxin throughout the webpage are particularly concerning given that Surfaxin is intended to be used for a vulnerable patient population.

Lack of Adequate Directions for Use

The webpage also contains the following claims (emphasis in original):

- "**SURFAXIN®, THE ONLY AVAILABLE SYNTHETIC ALTERNATIVE TO ANIMAL-DERIVED SURFACTANTS APPROVED BY THE FDA**"
- "First U.S. FDA approved alternative to surfactants made with animal extract in more than 20 years"

These claims are misleading because they suggest that Surfaxin is safe and effective for the treatment of RDS by implying that it is an "alternative" to all available animal-derived surfactants (i.e., Curosurf, Survanta, and Infasurf) for all uses, when this is not the case. Surfaxin is only approved for the **prevention** of RDS in premature infants at high risk for RDS, while Curosurf, for example, is indicated for the **treatment** of RDS in premature infants. Therefore, Surfaxin is **not** an "alternative" to Curosurf because the two drugs do not have the same indication. The PI for Surfaxin does not provide instructions for, or otherwise indicate that, Surfaxin will be safe and effective if used for the treatment of RDS. Information sufficient to demonstrate that Surfaxin is safe and effective for this new intended use has not been submitted to FDA in an application. Therefore, these claims provide evidence that Surfaxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use. We acknowledge that Surfaxin's full indication is included on the webpage. However, the mere inclusion of the full indication on this webpage does not mitigate the misleading impression that Surfaxin is an alternative to **all** animal-derived surfactants for all uses in RDS.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Surfaxin within the meaning of the FD&C Act, and make its distribution violative. 21 U.S.C. 352(a) & (n); 331(a). *See* 21 CFR 202.1(e)(6)(ii), (x); (e)(7)(i). The webpage also provides evidence that Surfaxin is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Surfaxin misbranded or otherwise makes its distribution

violative. *See* 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115; 201.128.

OPDP requests that Discovery immediately cease the dissemination of violative promotional materials for Surfaxin such as those described above. Please submit a written response to this letter on or before March 17, 2015, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Surfaxin that contain presentations such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP. Please refer to MA #29 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Surfaxin comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, RPh, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Kathleen Klemm, PharmD, RAC
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERTA T SZYDLO
03/03/2015

KATHLEEN KLEMM
03/03/2015