DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Ms. Ashlie Adams, M.S., RAC
Manager, Regulatory Affairs
Cornerstone Therapeutics Inc.
1255 Crescent Green Drive, Suite 250
Cary, NC 27518

RE: NDA 020744
CUROSURF® (poractant alfa) Intratracheal Suspension
MA #195

Dear Ms. Adams:

The Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion (DPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional pitch letter which includes an attached press release (C-Q311-17) for CUROSURF® (poractant alfa) Intratracheal Suspension (Curosurf) submitted by Cornerstone Therapeutics Inc. (Cornerstone) under cover of Form FDA 2253. The pitch letter is false or misleading because it omits important risk information associated with the use of the drug and the pitch letter and the press release are false or misleading because they present unsubstantiated superiority claims. Thus, the pitch letter and press release misbrand Curosurf in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n) and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(ii) & (e)(7)(i). Cornerstone also did not comply with 21 CFR 201.10(g)(1).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Curosurf.[1] According to its FDA-approved product labeling (PI):

> CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

Curosurf is associated with serious risks. The PI contains Warnings regarding intratracheal use, rapid effects on oxygenation and lung compliance which necessitate frequent clinical and laboratory assessments, as well as transient adverse effects including bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation which require stopping Curosurf administration and taking appropriate measures to alleviate the condition. The

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

Precautions section of the PI indicates that correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia is recommended prior to Curosurf administration. The Adverse Reactions section of the PI indicates that common complications of prematurity observed in the Curosurf single dose clinical trials include acquired pneumonia, acquired septicemia, bronchopulmonary dysplasia, intracranial hemorrhage, patent ductus arteriosis, pneumothorax, and pulmonary interstitial emphysema.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The pitch letter contains several efficacy claims for Curosurf, but fails to communicate **any** risk information associated with the use of the drug. By omitting the serious risks associated with Curosurf, the pitch letter misleadingly suggests that Curosurf is safer than has been demonstrated. We acknowledge that the press release which accompanies the pitch letter contains an Important Safety Information section for Curosurf. However, this does not mitigate the complete omission of important risk information from the pitch letter itself.

Unsubstantiated Superiority Claims

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 pitch letter contains the following claim:

- "The study[2] demonstrates that the use of Curosurf® (poractant alfa) Intratracheal Suspension results in lower mortality rates compared to other animal derived surfactants."

Similarly, the press release which accompanies the pitch letter contains claims such as the following (bolded emphasis in original):

- "**New Research Indicates Treating Neonatal Respiratory Distress Syndrome with CUROSURF® Results in Lower Rate of Mortality Compared to Competitive Surfactants**" (page one; headline claim)
- "Overall, CUROSURF treatment for RDS was associated with a significantly reduced likelihood of death compared to Infasurf, and a trend toward reduced mortality when compared with Survanta." (page one)
- "Key study findings are as follows:
    - When compared to infants treated with CUROSURF, the likelihood of mortality was 49.6 percent greater for Infasurf patients (p=0.043), and 37.0 percent greater for Survanta patients (p=0.053).

  . . .

[2] Ramanathan R, Bhatia JJ, Sekar K, et al. Mortality in preterm infants with respiratory distress syndrome treated with poractant alfa, calfactant or beractant: A retrospective study. *Journal of Perinatology* advance online publication, 2011 Sep 1; doi: 10.1038/jp.2011.125.

  - The unadjusted mortality rates were lowest for the infants treated with CUROSURF (3.61 percent), followed by Survanta (4.58 percent) and Infasurf (5.95 percent)." (page two)
- "When stratified by birth weight, the greatest benefits were recognized by the smallest infants (500-749g), the population with the highest mortality in the study. In this group, the unadjusted mortality rate was significantly lower for CUROSURF treated infants (11.72 percent) versus those treated with Survanta (17.39 percent) or Infasurf (20.67 percent)." (page two)

The totality of these claims misleadingly implies that Curosurf is superior to the two other animal derived surfactants for reducing the rate of mortality associated with RDS, when this has not been demonstrated by substantial evidence or substantial clinical experience. The claims above refer to a study by Ramanathan, et al. This study was a retrospective, observational, cohort study comparing all-cause, in-hospital mortality in preterm infants with RDS treated with one of three surfactants marketed in the United States between 2005 and 2009. This study design is insufficient to support these claims because it did not include a pre-specified efficacy analysis for comparison of the three surfactant products. Generally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug to comparator drugs. In addition, the information relied upon from the Premier Database used for this analysis is inadequate because details are not available regarding precise causes of death, the number of surfactant doses administered, nor data regarding concomitant treatment with antenatal steroids. We note that the accompanying press release discloses the Ramanathan, et al. study design and some of its limitations. However, this does not mitigate the misleading implication conveyed by the overall presentation that Curosurf provides a superior mortality benefit compared to all other available animal derived surfactants.

The presentation of misleading unsubstantiated superiority claims regarding mortality for Curosurf in an array of professionally-directed promotional materials, including pieces not discussed within this letter, is extremely concerning given the vulnerable patient population.

Inadequate Presentation of Established Name

The press release fails to present the established name (poractant alfa) in direct conjunction with the proprietary name (Curosurf) where the proprietary name is featured in the headline at the beginning of the press release, as required by 21 CFR 201.10(g)(1).

Conclusion and Requested Action

For the reasons discussed above, the pitch letter and press release misbrand Curosurf in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n) and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(ii) & (e)(7)(i). Furthermore, Cornerstone did not comply with 21 CFR 201.10(g)(1).

OPDP requests that Cornerstone immediately cease the dissemination of violative promotional materials for Curosurf such as those described above. Please submit a written response to this letter on or before November, 15, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for

Curosurf that contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). 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. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA # 195 in addition to the NDA number in all future correspondence relating to this particular matter. 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 Curosurf comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, R.Ph.
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
Group Leader
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

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/s/

ROBERTA T SZYDLO
10/31/2012

LISA M HUBBARD
10/31/2012