DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Elizabeth M. Zola, Pharm.D.
Associate Director, Regulatory Affairs
Ross Products Division
Abbott Laboratories
625 Cleveland Avenue
Columbus, OH 43215-1724

Re: NDA # 20-032
Survanta® (beractant) intratracheal suspension
MACMIS # 13536

Dear Dr. Zola:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional direct mailer (C1362C/4040) for Survanta® (beractant) intratracheal suspension (Survanta) submitted by Ross Products Division, a division of Abbott Laboratories (Abbott) under cover of Form FDA 2253. This direct mailer is false or misleading because it makes unsubstantiated effectiveness claims for Survanta and minimizes the risks associated with the drug, and, therefore, misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. §§ 352(a), 321(n).

Background

Survanta is a pulmonary surfactant made from natural bovine lung extract. According to its PI,

> SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.
>
> *Prevention*
> In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.
>
> *Rescue*
> To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

Survanta has no known contraindications, but has a number of important risks. For example, the WARNINGS section of the PI states,

> SURVANTA is intended for intratracheal use only.
>
> SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.
>
> DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

Furthermore, the PRECAUTIONS section states,

> Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials.

Unsubstantiated Effectiveness Claims

Your direct mailer contains several prominent efficacy claims, including the following:

- *Although Survanta infants weighed significantly less at entry, survival was better in the <600 g infants.*
- *17 of 23 Survanta-treated infants survived, compared to 11 of 30 Infasurf-treated infants (P=0.007).*
- *"Survanta infants required more days of intermittent mechanical ventilation and oxygen supplementation, primarily because of the survival of those <600 g at birth."*
- *"No significant differences in the incidence of adverse events, survival to 36 weeks' postmenstrual age without the need for oxygen supplementation or dosing complications."*
- Graph comparing survival to discharge between Infasurf and Survanta in infants <600 g birth weight

The direct mailer presents the above claims in conjunction with the header, "Compare survival to discharge in infants <600 g birth weight" and "Prevention arm of head-to-head study, with 374 infants ≤29 weeks' gestation and <1250 g birth weight." This presentation implies that Survanta has been shown to be effective in improving survival to discharge in infants weighing less than 600 g birth weight without RDS at the time of treatment allocation compared with Infasurf® (calfactant) Intratracheal Suspension. These claims are misleading because they are not adequately supported and are inconsistent with the Survanta PI. The PRECAUTIONS section of the PI specifically states, "Use of SURVANTA in infants less than 600 g birth weight…has not been evaluated in controlled trials" (see Background section).

Furthermore, we are not aware of any substantial evidence or substantial clinical experience demonstrating this effect of Survanta in this patient population. The prevention arm of the study, which is what is cited to support the above claims in the piece, enrolled infants of mothers who presented in labor or were expected to deliver before 30 weeks gestation and excluded infants greater than 1250 g birth weight, more than 15 minutes old before resuscitation was successful, or outborn infants.[1] For the prevention arm, the primary endpoint of the study was a 25% reduction in need for a second dose of surfactant. This study does not provide substantial evidence for the above claims for the following reasons. First, and most importantly, survival to discharge of infants less than 600 g birth weight, or any other analysis in this patient subset, was not a predefined endpoint of the study. In fact, survival to discharge does not appear to be a predefined endpoint of the study regardless of birth weight, and no effect on overall survival to discharge of infants was detected. An unplanned subset analysis of infants of less than 600 g birth weight does not provide substantial evidence of the drug's efficacy in this population. Furthermore, we note that the high survival rate for infants less than 600 g birth weight allocated to Survanta (17/23 (74%)) is at odds with other evidence relating to survival rate. Although none of the Survanta NDA controlled trials included patients less than 600 g, the open-label Survanta Treatment IND protocol, which included 261 neonates less than 600 g, only demonstrated a 44% survival rate.[2] Because of such conflicting evidence, the result from the Bloom et al study would need to be replicated by prospective, randomized, controlled clinical studies designed to measure survival rate to be credible. Finally, infants who were allocated to the Infasurf arm of the study were dosed based upon Survanta dosing recommendations, further undercutting the validity of any comparison.

The direct mailer also includes the following claim:

- *As you can see, her development is **right on track** and includes something that can't come fast enough for most teenagers: driving.*

This claim is presented in conjunction with a picture of a premature infant labeled "Mollie, then" and a picture of a teenage girl on a racetrack labeled "Mollie, now." The totality of this presentation is misleading because it implies that Survanta is effective in minimizing risks of long-term developmental disability in infants who receive Survanta, when this has not been supported by substantial evidence or substantial clinical experience. The Survanta PI includes data from multiple-dose studies, which indicated that at 24 months adjusted age evaluation, there were significantly fewer Survanta patients with rhonchi, wheezing, and tachypnea at the time of examination versus controls. No other differences, however, were found. There is no substantial evidence or substantial clinical experience to support a correlation between 24-month data and long-term outcomes such as developmental disability through the teenage years in this patient population. In fact, given that Survanta was only approved 14 years ago, there is limited evidence to evaluate its impact on any long-term outcome through the teenage years.

[1] Bloom BT, Kattwinkel J, Hall RT, et al. Comparison of Infasurf (Calf Lung Surfactant Extract) to Survanta (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome. Pediatrics 1997;100(1):31-38.
[2] Zola EM, Overbach AM, Gunkel JH, et al. Treatment Investigational New Drug Experience With Survanta (Beractant). Pediatrics 1993;91(3):546-551.

Minimization of Risk

Throughout the direct mailer, you present effectiveness claims using large, colorful, bolded headers as well as colorful charts, bullet points, and a significant amount of white space. In contrast, all of the risk information appearing in the direct mailer, including the important Warning information that Survanta can rapidly affect oxygenation and lung compliance and Warning information regarding transient bradycardia and decreased oxygen saturation, is relegated to page three of the four page piece and is presented in small font in two lines at the very bottom of the page, below both the references and footnotes. This presentation misleadingly minimizes the risks associated with the use of Survanta.

Conclusion and Requested Action

Your direct mailer is misleading because it contains unsubstantiated effectiveness claims and minimizes important risk information. Accordingly, the direct mailer misbrands Survanta under section 502(a) and 201(n) of the Act, 21 U.S.C. §§352(a), 321(n).

DDMAC requests that Abbott immediately cease the dissemination of promotional materials for Survanta that contain claims that are the same as or similar to those described above. Please submit a written response to this letter on or before July 29, 2005 describing your intent to comply with this request, listing all promotional materials for Survanta that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of these materials. Please direct your response to Michelle Safarik, MSPAS, PA-C at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 13536 in addition to the NDA number. We remind 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 Survanta comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Jialynn Wang, Pharm.D.
LT, USPHS
Regulatory Review Officers
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Michelle Safarik
7/15/05 09:13:48 AM

Jialynn Wang
7/15/05 09:53:56 AM