DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 24 1998

TRANSMITTED VIA FACSIMILE

Mary Jane Nehring
Director, Marketed Products Support
Worldwide Regulatory Affairs
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

RE: NDA# 20-486
Vanceril 84 mcg Double Strength (beclomethasone dipropionate) Inhalation Aerosol
MACMIS ID# 6775

Dear Ms. Nehring:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed promotional materials (e.g., VDM0101A/21522600 visual aid) for Vanceril 84 mcg Double Strength (beclomethasone dipropionate) Inhalation Aerosol. DDMAC has concluded that these materials contain promotional claims that are false or misleading and therefore violative of the Federal Food, Drug, and Cosmetic Act and implementing regulations.

Pages 2 and 3:
"No Other Inhaled Corticosteroid Delivers Therapy Through --
Headline: An Extension of Anti-Inflammatory Activity"—"From the parent drug, a more active metabolite forms", "Both BDP and BMP Play Important Anti-Inflammatory Roles"

The above statements make implied claims superiority based on two active moieties (parent drug, beclomethasone dipropionate/BDP and active metabolite beclomethasone monopropionate/BMP). The claims imply that additional benefit is provided to the patient because the metabolite is "active." However, clinical relevance is based on the parent drug product administered as a single entity and not on the individual activities of the moieties. There are no clinical data supporting the relative contributions of each moiety. The footnoted disclaimer "The clinical relevance of these data has not been established." does not remedy this misleading impression.

Page 4:
1. Headline "No other drug class is recommended to prevent irreversible lung damage"

The irreversible lung damage prevention claim is inconsistent with the product's indication and is therefore false or misleading. Furthermore, the claim is misleadingly paraphrased and referenced to the Expert Panel Report 2 of the National Asthma Education and Prevention Program (NAEPP) (or 1997 NHLBI Guidelines) that mentions that there are "*preliminary* studies to suggest that (inhaled corticosteroids) *may* prevent irreversible lung injury." (emphasis added). Thus, there is not yet conclusive evidence demonstrating that inhaled corticosteroids prevent irreversible lung damage or airway remodeling of asthma.

2. Subheadline "Early intervention with inhaled corticosteroids is recommended—even in mild asthma—because the lung damage starts early"

This subheadline is false or misleading because it implies that Vanceril 84 mcg prevents irreversible lung damage. However, Vanceril 84 mcg is not indicated for prevention of irreversible lung damage and the theory that prevention of long-standing inflammation with inhaled corticosteroids results in the prevention of airway remodeling or irreversible lung damage has not yet been established in humans.

3. Photographs of pathologic findings under "irreversible lung damage" below headlines 1 and 2

The presentation of photographs of damaged airway linings juxtaposed under the two headlines discussing irreversible lung damage is misleading because inhaled corticosteroids have not been shown to prevent irreversible lung damage.

Page 5:
1. Headline: "Inhaled corticosteroids afford: Broad Mediator Coverage"
Table: Inflammatory Mediator Inhibited by: Inhaled Corticosteroids, Leukotriene Modifiers"

The comparative table shows a list of inflammatory mediators and biomarkers, all of which the chart reflects have been shown to be inhibited by inhaled corticosteroids, while only one group in the chart, leukotrienes B_4, C_4, D_4, and E_4, indicates is inhibited by leukotriene modifiers. The implication of inhaled corticosteroids inhibiting these inflammatory mediators is that there is clinical improvement in asthma, and therefore, clinical superiority of Vanceril 84 mcg over leukotriene modifiers. However, the clinical relevance of this mediator inhibition is not established. Therefore, this presentation of comparative clinical pharmacology data is misleading because it implies clinical superiority of inhaled corticosteroids over leukotriene modifiers in treating asthma when such clinical superiority has not been demonstrated by substantial evidence.

Furthermore, the cited reference (8) (Serafin, "Drugs used in the treatment of asthma" a chapter in the 9th edition of Goodman and Gilman's The Pharmacological Basis of Therapeutics") is inaccurate because it does not discuss information regarding inhaled corticosteroid effects on inflammatory mediators in asthma.

"...further clinical experience and study are needed to establish [the role of leukotriene modifiers] in asthma therapy." Referenced to "1997 NHLBI Guidelines"

This quotation is taken out of context from the Expert Panel Report 2 of the NAEPP and is therefore misleading, particularly when presented above a graph showing clinical data from a study comparing BDP and montelukast. The Expert Panel Report states that the initial clinical experience and tablet-form of leukotriene modifiers make these new medications a therapeutic option but that it is not yet clear what their role is in stepwise therapy.

Page 7:
Headline: "Lung Deposition Varies With Addition and Design of Holding Chamber, As Well as Technique"; Quotation from 1997 NHLBI Guidelines; and a Comparative Table: "Effects of Inhalation Device and Technique on Lung Deposition"

The entire page discussion of comparative lung deposition (based on inhalation device and technique) is misleading because it implies clinical benefit and superiority when such clinical pharmacology data have not been correlated with clinical effect. Furthermore, this clinical pharmacology claim of *in vivo* performance of inhaled drug delivery is misleading because it is intermingled with clinical efficacy and safety claims to suggest that the drug deposition data confers clinical significance in the treatment of asthma when no such significance has been demonstrated.

Page 11:
1. Headline: "BDP: The Only Inhaled Corticosteroid With No HPA Axis Suppression Within Recommended Doses" (cited to 16/Brannan)

This global safety superiority claim is misleading because it is not supported by substantial evidence. The cited reference, Brannan et al., did not study any inhaled corticosteroids other than beclomethasone dipropionate (42 mcg or 84 mcg) and therefore cannot be used to imply a comparison versus other inhaled corticosteroids. Furthermore, given the lack of sensitivity of the HPA axis testing performed in the study (based on the 250 mcg cosyntropin stimulation test over six hours, rather than based on the urinary free cortisol level), it is not clearly established that there is not HPA axis suppression with BDP.

"A majority of the studies of the use of inhaled corticosteroids by children have not demonstrated an effect on growth." Referenced to "1997 NHLBI Guidelines"

This quotation is misleading because it is taken out of context from the Expert Panel Report 2 and implies that the Expert Panel Report minimizes any concern regarding growth delay in association with inhaled corticosteroid use in children. However, the full quotation urges caution in monitoring growth and stepping down therapy when possible. Furthermore, it appears that it is no longer accurate to conclude that the majority of studies of the use of inhaled corticosteroids in children have not demonstrated an effect on growth. The July 30-31, 1998, combined FDA Pulmonary-Allergy Drug Advisory Committee/Metabolism-Endocrine Advisory Committee established a consensus on the class labeling of inhaled corticosteroids in which patients/physicians are advised that growth suppression has been identified in this class of drugs.

Schering should immediately cease its use of promotional materials that contain these or similarly violative claims. Schering should respond in writing no later than September 8, 1998, describing its commitment to cease use of these materials, include a list of materials containing similarly violative claims, and describe its plan to ensure that its agents, including its sales force, cease further false or misleading safety and efficacy claims.

Schering's response should be directed to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Schering that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 6775 in addition to the NDA number.

Sincerely,

Joan Hankin, JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications