DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FOI

Food and Drug Administration
Rockville MD 20857

JAN 24 1997

TRANSMITTED VIA FACSIMILE

Ronald J. Garutti, MD
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# 5077

Dear Dr. Garutti:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed promotional materials (e.g., VD0039 visual aid, press release) for Vanceril 84 mcg Double Strength (beclomethasone dipropionate) Inhalation Aerosol that contain promotional claims that are false and/or misleading and therefore violative of the Federal Food, Drug, and Cosmetic Act and regulations.

- **"A New Source of Strength--Twice the Strength Per Puff***
  "*As compared with regular strength beclomethasone dipropionate."

The above comparative "strength" claims are misleading because they imply that Vanceril 84 mcg Double Strength Inhalation Aerosol is more clinically efficacious than Vanceril Inhaler (42 mcg or regular strength). However, such superiority claims are not supported by the approved product labeling for Vanceril 84 mcg. Vanceril 84 mcg has been demonstrated to be comparable in efficacy to Vanceril Inhaler when administered at the same total daily dose, and thus only represents a more concentrated strength and perhaps more convenient dosage form that delivers comparably effective therapy with half as many puffs, rather than a dosage form that provides a superior clinical effect.

- **bar graph with headline:**
  "An additional 7% improvement in pulmonary function at endpoint (P</=0.01)"

The headline as well as the NDA data presentation in the bar graph are misleading because they imply that only Vanceril 84 mcg provides this clinical effect, whereas Vanceril Inhaler also

provided a comparable effect on FEV1. Therefore, to avoid being misleading by implying that Vanceril 84 mcg is superior to Vanceril Inhaler or any other oral inhaled steroid, the bar graph should be revised to reflect the comparable efficacy between Vanceril 84 mcg and Vanceril Inhaler.

- **"Important new indication"**

The claim, "Important new indication" is misleading because it omits the qualifier "class" ("important new class indication") to clarify that this indication is not unique to Vanceril 84 mcg Inhalation Aerosol.

- **"A New Source of Strength--With The Proven Safety of Beclomethasone Dipropionate"**

- **Headline: "Same Trusted Safety Profile*"**
  "* as compared with regular strength beclomethasone dipropionate"

The above global safety claims are misleading because they imply that the safety record of Vanceril 84 mcg is as well documented as that for Vanceril Inhaler, and that all of the supplemental headlines/bullets adequately support the above claim. However, the following supplemental claims are false and/or misleading and therefore not providing adequate support for the global claim:

"No evidence of HPA axis suppression even with doses up to 1,008 mcg in clinical trials"

The above claim is misleading without disclosing the drug tested (Vanceril Inhaler), the study duration (28 days) and the HPA axis suppression measurement utilized (basal plasma cortisol concentrations and plasma cortisol responses to tetracosactrin (ACTH 1:24) stimulation).

"No HPA axis suppression with Vanceril 84 mcg Double Strength dosed 840 mcg/day (5 inhalations BID) for at least 1 month"

The above claim is misleading without disclosing the measurement utilized (plasma cortisol concentration responses to 6 hour cosyntropin stimulation).

"No adrenal suppression with regular strength BDP, USP confirmed in clinical trials of up to 2 years in duration"--1/Francis, 1976

The above claim is misleading without disclosing the dosage (300 mcg), the difference in

formulation between that used in United Kingdom versus the United States, the measurement utilized (tetracosactrin stimulation), and that this was a study of 15 children. Furthermore, in the context of this safety claim presentation, use of "regular strength" to describe the BDP agent is misleading and should be deleted, because it implies that the agent studied was Vanceril brand beclomethasone dipropionate Inhaler, dosed above that actually studied in the referenced article.

> **"No growth suppression cited in children treated with regular strength BDP, USP for as long as 13 years"--2/Balfour-Lynn/1986**

The above claim is misleading because it does not disclose the dosage studied (i.e., up to 400 mcg/day) and in the context of this safety claim presentation, use of "regular strength" to describe the BDP agent is misleading and should be deleted, because it implies that the agent studied was Vanceril brand beclomethasone dipropionate Inhaler, dosed above that actually studied in the referenced article.

- **Headline: "Vanceril 84 mcg Double Strength and Placebo--Stimulated Plasma Cortisol Results" and accompanying bar graph**

The above presentation is misleading without disclosing the dosage (840 mcg), study duration (35 days) and that the headers clarify "stimulated mean plasma cortisol results."

- **fair balance paragraph of risk information following HPA axis presentation**

The paragraph of risk information displayed below the HPA axis headline and comparative table lacks fair balance because the presentation is not reasonably prominent and minimizes the risk information.

- **"In 20 years of U.S. clinical experience, beclomethasone dipropionate (BDP), the active ingredient in Vanceril and Vanceril 84 mcg Double Strength, has demonstrated a very favorable systemic safety profile with regard to HPA axis suppression, bone metabolism, long-term growth in children and adverse events."**

Reference: Wolthers, O.D. Long, intermediate and short-term growth studies in asthmatic children treated with inhaled corticosteroids. European Respiratory Journal, 1995; 9, 821-827

The above global safety claim is false and/or misleading because the cited reference does not substantiate the claim. The Wolthers article did not examine all of the safety parameters for which the article is cited and did not report on a prospectively designed study. Rather, Wolthers is a retrospective literature review of growth studies of varying dosages of beclomethasone and

other inhaled corticosteroids, and of studies of varying duration. In addition, the claim of favorable long-term growth in children is contradicted by a primary conclusion of the Wolthers literature review article: "Treatment growth with inhaled beclomethasone dipropionate, 400 and 800 mcg, from the Diskhaler suppresses short-term lower leg growth rates, but no firm conclusions can be drawn with respect to intermediate or long-term growth effects." Therefore, for these reasons, this claim is not adequately substantiated and should be deleted.

Schering should immediately cease its use of promotional materials that contain these or similar claims.

DDMAC requests that Schering provide a written statement to DDMAC describing the following:

1. Schering's commitment to cease promotional use of these materials, including the materials and activities described in this letter and all similarly violative material and activity;

2. A description of all promotional activities conducted by Schering or its agents that utilized materials containing these claims; and

3. A description of Schering's plan to ensure that its agents, including its sales force, cease further unsubstantiated and/or misleading comparative 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. Schering's response should be received no later than February 7, 1997. DDMAC reminds Schering that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 5077 in addition to the NDA number.

Sincerely,

Joan Hankin

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

File Name: vancrlds\visaid.nov

Drafted:	HANKIN	Date: 1/23/97
Comment:	HONIG	Date: 1/24/97
Revised:	HANKIN	Date: 1/24/97
Concur	ABRAMS	Date: 1/24/97

CC:
HFD-40/NDA # 20-486
HFD-40/Chron/HANKIN(2)/ABRAMS
HFD-570/NICKLAS/HONIG/JENKINS
HFD-570/NDA # 20-486

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MACMIS Action Code: VIOL

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2253 ID#: 47890 Material ID#: Sysgen ID9732 1/1/97 press release

Due Date: February 7, 1997

Close Out: N

FOI STATUS: RELEASABLE