DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 10 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# 7262

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., VDN0008/2134503 and VD0197/201967807 visual aids) for Vanceril 84 mcg Double Strength (beclomethasone dipropionate) Inhalation Aerosol. DDMAC has concluded that these materials lack fair balance and contain false or misleading claims, including mischaracterizations about a competitor's safety profile, and are therefore violative of the Federal Food, Drug, and Cosmetic Act and implementing regulations.

<u>False or Misleading Accolate Risk Information Mischaracterizes the Accolate Safety Risk Profile</u>

These Schering/Key visual aids mischaracterize various aspects of the safety risk profile for another long-term control asthma therapy, the leukotriene receptor antagonist, Accolate (zafirkulast) Tablets. Such misleading representations by Schering/Key about Accolate, based on the Accolate approved product labeling (i.e., package insert), misbrands Vanceril 84 mcg.

One Schering/Key visual aid (entitled "It's In Black And White..." "Accolate 'Precautions' and 'Adverse Events' Labeling Revised", dated June 1998) is a partial reproduction of a July 1997 letter sent by Accolate's sponsor, Zeneca Pharmaceuticals, to health care professionals regarding important changes to the Accolate package insert pursuant to 21 CFR 200.5 ("Important Prescribing Information). However, the Schering/Key visual aid counterdetails Accolate in a misleading manner by omitting material facts from the revised Accolate package insert that the visual aid represents to be paraphrasing from. Such selective omissions and misleading interpretations of risk information from the Accolate package insert mischaracterize the safety

profile of Accolate.

For instance, under the heading "Adverse eosinophilic reactions (Churg-Strauss syndrome)", the Schering/Key visual aid paraphrases the selections from the Accolate Adverse Reactions section of the package insert. However, it misleadingly omits that the occurrence of these events is *rare*, and also fails to include the precautionary statement "caution is required when oral steroid reduction is being considered."

Similarly, under the heading "Adverse hepatic reactions", all three bulleted statements from the Accolate package insert are misleadingly paraphrased, as illustrated by the first bullet: "Revised labeling states elevations of one or more liver enzymes may occur with Accolate on rare occasions; most cases occurred at four times the recommended dose." This statement misleadingly omits from the package insert that these rare events were found in *controlled clinical trials*, mostly in *asymptomatic patients*, at doses four times higher than recommended, or that these elevations in liver enzymes *returned to normal range after a variable period of time upon discontinuation of* Accolate therapy. This misrepresentation of risk information results in a lack of fair balance.

Finally, it appears that this promotional labeling was not submitted upon first dissemination as required by 21 CFR 314.81(b)(3)(i).

Another Schering/Key Vanceril 84 mcg visual aid (an explicitly comparative piece, entitled "Asthmatic inflammation: a multi-mediator event", April 1997) made false or misleading safety claims about Accolate drug interactions. Under the subheading "Safety Considerations", the first bulleted claim "Potential for significant drug interactions (including terfenadine, erythromycin, theophylline, aspirin)" is false or misleading because it mischaracterizes the Drug Interactions Section of the Accolate package insert. According to the package insert, no dosage adjustments for either Accolate or the other listed product are necessary when these products are co-administered, nor any monitoring, warnings, or other precautionary measures are stipulated.

In addition, the second "Safety Considerations" bullet states "Prothrombin monitoring required in warfarin patients." However, this statement also mischaracterizes and omits pertinent information from the Accolate package insert (i.e., that patients on oral warfarin anticoagulant therapy and Accolate *should* have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly; and that the doses of Accolate used in these interaction trials were generally higher than that of the recommended daily dose). Thus, these presentations in the visual aid misleadingly portray the drug interaction profile of Accolate.

Vanceril 84 mcg Visual Aid Lacks Fair Balance About Its Own Safety Risk Information

Moreover, the visual aid lacks fair balance because the risk information for Vanceril 84 mcg is incomplete (i.e., it does not substantiate the claim that the incidence of adverse events for (Vanceril 42 mcg and) Vanceril 84 mcg was similar to that reported for placebo and the remaining safety risk information, presented in footnote format, is not presented with a prominence and readability that is reasonably comparable to the benefit claims).

Vanceril 84 mcg Visual Aid Makes Unsubstantiated Implied Superior Efficacy Claims

In addition, to safety claims, under the headline "From inflammatory cascade to clinical effect...", the visual aid includes two bullets presenting clinical efficacy data. The first is an implied superior efficacy claim against Accolate that is juxtaposed to an explicit superiority claim against Zyflo (zileuton) Tablets, based on one unreplicated study. In contrast to the presentation of the Zyflo versus beclomethasone dipropionate data, the claim about Accolate's efficacy "Improved FEV1 5% to 11% in clinical trials", lacks adequate context to identify the patient population, trial size, number of trials, length of trial and/or statistical significance of these FEV1 changes as compared to placebo. The juxtaposition of the Accolate claim to the data presentation favoring Vanceril 84 mcg over Zyflo implies that Vanceril 84 mcg provides greater improvements in FEV1 over Accolate without comparative data from head-to-head clinical trials.

Schering should immediately cease its use of promotional materials that contain these or similarly violative claims. Schering should respond in writing no later than December 24, 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 # 7262 in addition to the NDA number.

Sincerely,

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