DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 12 1997

TRANSMITTED VIA FACSIMILE

Mr. Dennis J. Bucceri
Vice President, Regulatory Affairs
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

RE: NDA# 20-441
Pulmicort Turbuhaler (budesonide inhalation powder)
MACMIS# 6026

Dear Mr. Bucceri:

It has come to the attention of the Division of Drug Marketing, Advertising, and Communications (DDMAC) that Astra USA, Inc. (Astra) has disseminated promotional materials for Pulmicort Turbuhaler (budesonide inhalation powder) directed to manage care organizations that contain unapproved product use claims and comparative promotional claims which are false or misleading and therefore violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Furthermore, it appears that these materials have not been submitted as required by 21 CFR 314.81(b)(3)(i) on FDA Form-2253.

Superiority Claims Unsupported by Lung Deposition Studies

- "The Turbuhaler, Patient Benefits: - better deposition and distribution allow for less drug to be used thus...decreasing the risk of systemic and oral side effects", slide 15

  "The Turbuhaler, What it does - produces higher proportions of respirable particles than an MDI, thus facilitates superior lung distribution", "Deposits 32-34% of the drug directly on the lung tissues (MDI products deposit 15-18%)", slide 14

  "Pulmicort Turbuhaler Benefits Summary: Superior lung deposition", slide 20

As DDMAC previously commented on June 24, 1997, and June 27, 1997, these comparative ("better", "superior") lung deposition claims are misleading because they suggest Pulmicort Turbuhaler has superior clinical efficacy to the Pulmicort propellant metered dose inhaler (MDI) (a foreign budesonide inhalation aerosol product that has not been approved for use in the United States) and to all other conventional aerosol inhalers containing various inhaled corticosteroids

because of Pulmicort Turbuhaler's asserted ability to deliver twice as much medication (per puff) as any MDI. Such clinical superiority claims implying or suggesting that Pulmicort Turbuhaler is more effective than inhaled corticosteroids administered by conventional aerosol inhalers/MDIs, including the Pulmicort MDI, are false and/or misleading because they have not been demonstrated by substantial evidence (i.e. adequate and well-controlled studies). Furthermore, it is false to suggest that all other MDI products deposit 15-18% of drug to the lung. For example, the Clinical Pharmacology Section of the approved product labeling for Flovent (fluticasone dipropionate) Inhalation Aerosol states that the oral bioavailability of Flovent is less than 1%, and the overall systemic bioavailability (which includes oral and lung bioavailability) is approximately 30%. Therefore, approximately 30% of Flovent is deposited to the lung, not 15-18% as is implied by slide 14.

- "Systemic half-life [of Pulmicort Turbuhaler] is 2-3 hours (significantly shorter than fluticasone)", slide 18/Pulmicort, Key Product Attributes

The comparative pharmacokinetic half-life claim is misleading because it implies a clinical advantage for Pulmicort by suggesting that Flovent accumulates in the body and therefore has a greater potential for systemic effects. However, half-life comparisons do not necessarily correlate with clinical effects. Half-life is only one determinant of systemic exposure (and therefore systemic safety), with other factors such as dose, relative bioavailability, and distribution also being important. The presentation of the half-life claim without additional disclosure of a complete profile of pharmacokinetic characteristics of Pulmicort and Flovent (e.g., from a head-to-head comparison) misleading implies a clinical safety benefit for Pulmicort.

Unapproved Dosing Regimen and Product Formulation

The discussions about
Pulmicort (nebulizing solution) are misleading because they promote unapproved uses for Pulmicort Turbuhaler.

Misleading Comparative Pricing Claims and Unsubstantiated Cost-Effectiveness Claim

- Inadequate context for comparative pricing information, slides 9 and 26

The various comparative pricing claims are misleading because they lack adequate context. On slide 9, the prices for Flovent include the price for only one dosage strength of Flovent, 220 mcg; slide 26 provides the price for all three Flovent dosage strengths but lacks adequate information to qualify the price comparisons, including a reference stating the source and date of the pricing information, a disclaimer that actual prices paid by health care facilities or individual payers may vary, and that price comparisons do not imply similar efficacy among the listed products.

- "Cost-Effective"

The cost-effectiveness claim is misleading because the claim is not supported by reference to average wholesale price (AWP). Although Pulmicort is effective in the treatment of asthma, this fact, in association with an alleged lower price would not be adequate to support a "cost-effectiveness" claim. A cost-effectiveness claim should reflect that a product has been compared to another product (or treatment) with data that demonstrate relative effectiveness and relative cost.

Astra should immediately cease its use of promotional materials that contain these or similar claims or presentations. Astra should respond in writing no later than December 31, 1997. Astra's response should include a list of all similarly violative materials and a description of its method for discontinuing their use.

Astra'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 Astra that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 6026 in addition to the NDA number.

Sincerely,

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