DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE NOV 12 1999

George R. Hemsworth, Ph.D.
Director, Regulatory Affairs
Carter-Wallace, Inc.
Half Acre Road
P.O. Box 1001
Cranbury, NJ 08512-0181

Re: NDA# 20-114
Astelin (azelastine HCl) Nasal Spray
MACMIS ID# 7538

Dear Dr. Hemsworth:

This letter concerns promotional materials for the marketing of Astelin (azelastine HCl) Nasal Spray) by Carter-Wallace, Inc. (Wallace). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed various health care professional promotional materials[1] and concluded that they lack fair balance, and contain false or misleading claims. Therefore, these materials violate the Federal Food, Drug, and Cosmetic Act and implementing regulations.

Unsubstantiated and Misleading Equivalence Claim

- "One therapy as effective as two"
- "As effective as the combination of oral loratadine ***plus*** intranasal beclomethasone"
- "The results of the studies clearly demonstrated that azelastine nasal spray monotherapy was effective as combination therapy [loratadine plus beclomethasone] in improving moderate-to-severe symptoms of seasonal allergic rhinitis." (quoting Berger, et al.) [2]

The above claims promote Astelin monotherapy to be as effective as (i.e., clinically equivalent to) a combination therapy of an oral antihistamine (loratadine) with a nasal corticosteroid (beclomethasone dipropionate or BDP) in the treatment of moderate to severe seasonal allergic

1 These materials include, but are not limited to, visual aid AST 2000 and slim jim AST3000.
2 Berger, et al., "Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis." Ann Allergy Asthma Immunol. 1999;82:535-541.

rhinitis (SAR). The above claims of clinical equivalence are misleading because they have not been demonstrated by substantial evidence (i.e., generally two adequate and well-controlled studies). The trial methodology is not adequate to demonstrate equivalency and the premise of comparing Astelin to combination (loratadine plus BDP) therapy is misleading because the patients were selected for study if their SAR symptoms were inadequately controlled (i.e., non-responders) using either the oral antihistamine monotherapy or the nasal corticosteroid monotherapy. Therefore, the finding that Astelin monotherapy is as effective as the "loratadine plus BDP combination" therapy in improving SAR symptoms is misleading because the patients who supposedly received this combination allergy therapy were actually only getting the benefit of SAR symptom relief from either loratadine or BDP, and not from any additive effect of the combination drug therapy.

Other study design deficiencies included: the lack of a placebo control arm, thus overstating any drug treatment effect; rather than evaluating allergy symptoms using validated categorical scales, the trials relied upon subjective and insensitive efficacy endpoints ("physician assessment of need for additional therapy", and "patient global assessment"); and a study period of only seven days, an inadequate period of time to fairly assess the maximum effect of intranasal BDP. Thus, for numerous reasons, these equivalence claims are based on unfair comparisons, not substantiated by the cited data, and are consequently, false or misleading.

Unsubstantiated and Misleading "no effect on motor performance" Claims

Headline: "No effect on motor performance" and accompanying claims: (no citation)
"In well-controlled studies with oral azelastine—(no citations)
--4 mg BID and 8 mg QD over 10 days did not adversely affect:
visual orientation, concentration, speed of reaction, and eye-hand coordination";
--"1 mg BID over 2 days did not interfere with the performance of complicated tasks"

Because of various study design deficiencies, these "no effect on motor performance" efficacy claims are not supported by substantial evidence and are therefore false or misleading. All four studies relied on an inappropriate patient population of healthy volunteers rather than patients suffering from SAR and under treatment. Motor performance may be different in allergy sufferers than in healthy individuals where there is no disease-based potential for motor performance impairment. Other inadequacies included: inadequate demonstration of the psychometric properties of the instruments used to measure motor performance; an inadequate statistical plan to identify primary endpoints and address multiple comparisons; and a trial design inadequate to demonstrate equivalence between subjects on Astelin versus placebo in order to support a claim of "no effect on motor performance." Moreover, the overall presentation promotes an implied safety claim (i.e., the lack of somnolence and consequent impairment while on Astelin). However, this implied safety claim is not balanced by the disclosure of

precautionary language from the approved labeling concerning activities that require mental alertness. Therefore, the "no effect on motor performance" claims are both unsubstantiated and unbalanced, and consequently false or misleading.

Relief of Nasal Congestion Claims

A variety of graphical and textual claims appear throughout these promotional materials which promote Astelin for the relief of nasal congestion. However, because of various study design deficiencies, these nasal congestion relief claims are not supported by substantial evidence based on the cited studies. For instance, the claim "First-dose relief of total symptom complex—Nasal symptoms...congestion") is cited to several two-day dose ranging studies (Meltzer, et al.[3]; and Weiler, et al.[4]). These two-day studies are not of adequate duration to demonstrate the efficacy of Astelin in the treatment of nasal congestion.

Furthermore, the nasal congestion relief claim was not substantiated by a cited two-week study (Storms, et al.). In this study and similarly designed trials (e.g., La Force, et al.), no placebo data were presented for comparison that would reflect the net treatment effect. Moreover, no data were generated demonstrating efficacy for nasal congestion based on mean improvement in nasal congestion. The symptom of nasal congestion was not included in the composite primary efficacy endpoints of "major symptom complex" and "total symptom complex", nor was it evaluated as an individual symptom primary endpoint. In addition, when evaluated as an individual symptom secondary efficacy endpoint, the mean improvement in nasal congestion was neither clinically nor statistically significantly different than placebo. Therefore, all presentations and claims for "relief of nasal congestion" referenced to these studies are unsubstantiated, and consequently false or misleading.

Misleading Implied Clinical Benefit Based on Clinical Pharmacology Activity

- Headline: "Azelastine demonstrates antihistamine and anti-inflammatory activity[+]"
- "In vitro studies, animal studies, and clinical studies...have shown that...azelastine also has anti-inflammatory properties, as demonstrated by its effects on inflammatory cells and inflammatory mediators...in both the early-and late-phase of the allergic reaction." (Berger)

Footnote: "[+] The clinical relevance beyond H1-receptor antagonist activity has not been established."

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3 Meltzer, et al., "Azelastine nasal spray in the management of seasonal allergic rhinitis." Ann Allergy. 1994;72:354-359.

4 Weiler, et al., "A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model." J Allergy Clin Immunol. 1994;94:972-980.

This presentation is misleading because it implies that Astelin antihistamine Nasal Spray provides a clinical benefit (i.e., relief of nasal congestion) similar to that provided by an intranasal corticosteroid, where the drug's mechanism of action is based on anti-inflammatory action. Notwithstanding any possible anti-inflammatory "activity" based on in vivo endpoints in the "clinical studies" referenced in the above quotation, no data are presented to substantiate an implied efficacy claim for nasal congestion based on anti-inflammatory activity. Furthermore, the presentation's footnoted disclaimer does not remedy the overall suggestion of clinical benefit derived from anti-inflammatory "activity", particularly given the other claims of clinical relief commingled with these clinical pharmacology claims.

Lack of Fair Balance

The overall presentation of risk information in these materials lacks fair balance. The table of selected adverse events compares data from "preapproval clinical studies" (a reference to that data in the approved product labeling reporting on 391 patients on Astelin and 353 patients on placebo) and to "recent comparative clinical studies" (a reference to Berger, reporting adverse events for 538 patients on Astelin and 532 patients on loratadine plus BDP combination therapy; Berger was the study citation for the misleading equivalence claim discussed above). This comparative adverse events table is misleading and minimizes important risk information.

The characterizations are false or misleading that "recent comparative" studies with Astelin demonstrates a more favorable safety profile due to lower percentages of adverse events reported in Berger--a methodologically flawed study--than the percentages reported in the approved product labeling, and that this "recent" data with larger study populations is more relevant than the "preapproval" adverse event data reported in the approved product labeling. In addition, use of the term "preapproval" is misleading because it suggests that there has been a change in the adverse event profile since Astelin was approved.

Moreover, the presentation of specific adverse events information (particularly for somnolence or drowsiness) also lacks fair balance and is inconsistent with the approved product labeling. The adverse events table in the promotional materials omits disclosing that somnolence occurred statistically significantly more often for patients treated with Astelin (11.5%) than with vehicle placebo (5.4%); this disclosure was also omitted for the adverse event of bitter taste (19.7%) versus vehicle placebo (0.6%). Furthermore, the three accompanying safety claims discussing somnolence reported from the "preapproval clinical studies" lacks fair balance. This discussion omits the precaution from the approved product labeling regarding activities requiring mental alertness due to the occurrence of somnolence in Astelin patients. In addition, the claim "in the majority of Astelin Nasal Spray patients reporting somnolence, this symptom resolved during treatment" was not prospectively studied and is therefore unsubstantiated, and consequently false or misleading.

Wallace should immediately cease its use of promotional materials and activities that contain these or similar violative claims. We should receive your written response no later than November 29, 1999, describing your commitment to cease use of these materials, include a list of materials containing similarly violative claims, and describe its plan to ensure that the dissemination and use of these materials has been discontinued.

Please direct your response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind Wallace that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 7538 in addition to the NDA number.

Sincerely,

/S/

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