DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Valerie K. Cotler
Senior Manager, Global Labeling and Promotion
Global Regulatory Affairs
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Re: NDA #20-762
Nasonex® (mometasone furoate monohydrate) Nasal Spray, 50 mcg
MACMIS # 14548

Dear Ms. Cotler:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional detail aid (detail aid) (NU0359) for Nasonex® (mometasone furoate monohydrate) Nasal Spray, 50 mcg (Nasonex) submitted by Schering Corporation (Schering) under cover of Form FDA-2253. This detail aid is false or misleading because it claims that Nasonex is more effective than has been demonstrated by substantial evidence or substantial clinical experience and makes unsubstantiated superiority claims for Nasonex. The detail aid therefore misbrands the drug in violation of the Federal Food, Drug and Cosmetic Act (Act). 21 U.S.C. 352(a) and 321(n); *cf.* 21 CFR 202.1(e)(6)(ii).

Background

According to the FDA-approved product labeling (PI), Nasonex is indicated for the following:

- The treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older.
- The prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years and older. In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, initiation of prophylaxis with Nasonex is recommended 2 to 4 weeks prior to the anticipated start of pollen season.
- The treatment of nasal polyps in patients 18 years of age and older.

Safety and effectiveness of Nasonex have not been established in pediatric patients less than 2 years of age for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis, and in pediatric patients less than 18 years of age for the treatment of nasal polyps.

The Clinical Studies section of the Nasonex PI discusses trials performed in patients with allergic rhinitis (in pertinent part):

> **Allergic Rhinitis**
> The efficacy and safety of NASONEX Nasal Spray, 50 mcg in the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis have been evaluated in 18 controlled trials, and one uncontrolled clinical trial, in approximately 3000 adults (ages 17 to 85 years) and adolescents (ages 12 to 16 years)….These trials evaluated the total nasal symptom scores that included stuffiness, rhinorrhea, itching, and sneezing. Patients treated with NASONEX Nasal Spray, 50 mcg, 200 mcg/day had a significant decrease in total nasal symptom scores compared to placebo-treated patients….
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> The efficacy and safety of NASONEX Nasal Spray, 50 mcg in the treatment of seasonal allergic and perennial allergic rhinitis in pediatric patients (ages 3 to 11 years) have been evaluated in four controlled trials….Pediatric patients treated with NASONEX Nasal Spray, 50 mcg (100 mcg total daily dose, 347 patients) had a significant decrease in total nasal symptom (congestion, rhinorrhea, itching, and sneezing) scores, compared to placebo-treated patients….
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> ….
>
> Prophylaxis of seasonal allergic rhinitis for patients 12 years of age and older with NASONEX Nasal Spray, 50 mcg given at a dose of 200 mcg/day, was evaluated in two clinical studies in 284 patients….Patients receiving 2 to 4 weeks of prophylaxis with NASONEX Nasal Spray, 50 mcg demonstrated a statistically significantly smaller mean increase in total nasal symptom scores with onset of the pollen season as compared to placebo patients.

Overstatement of Efficacy

As demonstrated by multiple prominent references to the term "congestion" (highlighted by large type, colored text, and bolding) and the presentation of data related to congestion alone, the detail aid repeatedly states or suggests that Nasonex is effective in the treatment of the specific symptom of nasal congestion, when this has not been demonstrated by substantial evidence or substantial clinical experience. For example, page one of the Nasonex detail aid contains the headline claim, "**Nasal allergy sufferers report Congestion at night can be a BIG problem**" (original emphasis). To the right of the detail aid is a tab that asks, "How BIG?" When the tab is pulled, the following claims appear:

- **In a nasal allergy survey** [1]
  48% of respondents reported difficulty falling asleep due to congestion
  51% said that congestion woke them up
- **Congestion during the day can also be a BIG problem for sufferers**
  In the same survey
  59% of adults reported that they were affected at work. (original emphasis)

[1] Roper Public Affairs and Media. Impact of nasal congestion among allergic rhinitis sufferers. 2004.

Pages two and three of the Nasonex detail aid contain the headline, "**NASONEX® for BIG CONGESTION RELIEF night and day**…" (original emphasis) along with the claim, "**TREATS…BIG reduction in congestion sustained throughout a 90-day study**[2]" with a presentation of mean percentage decrease in AM/PM diary symptom scores for total nasal symptom scores and congestion scores at days 0, 1-15, 16-30, 31-45, 46-60, 61-75, and 76-90 in patients with moderate-to-severe perennial allergic rhinitis treated with Nasonex, Flonase (fluticasone propionate), or placebo. Accompanying this presentation and throughout the Nasonex detail aid is the tagline "**BIG congestion relief**" (original emphasis). The back cover of the Nasonex detail aid includes the claim "…the only nasal-inhaled steroid that's also FDA approved to help PREVENT congestion" (original emphasis).

Page four of the Nasonex detail aid includes the claim, "**Allergists and ENTs prescribe for tough-to-treat congestion – NASONEX® continues to be their #1 new Rx…."**

Nasonex, however, is not specifically indicated for congestion. As discussed above, it is indicated, in part, for the prophylaxis and treatment of seasonal allergic rhinitis (SAR). The SAR indication is based upon the results of clinical trials in which the primary efficacy endpoint was measured by the total nasal symptoms score (TNSS) which included four symptoms: congestion, rhinorrhea, itching, and sneezing, as opposed to results with respect to individual nasal symptoms such as nasal congestion. These studies did not specifically evaluate efficacy for the stand-alone symptom of nasal congestion. Consequently, they are not considered substantial evidence to support a claim of efficacy for nasal congestion.

There are two references cited to support the claims above. One of the references cited[1] is an online survey sponsored by Schering regarding nasal congestion in allergic rhinitis patients. This survey, however, does not provide substantial evidence to support claims that Nasonex treats the specific symptom of nasal congestion in allergic rhinitis patients because, as a general matter, surveys alone cannot support claims of efficacy. The other reference cited[2] also does not provide substantial evidence to support claims that Nasonex treats the specific symptom of nasal congestion in allergic rhinitis patients. The primary efficacy variable in the referenced study was the TNSS, not nasal congestion. TNSS is a composite measure of symptoms. Demonstrating an effect on a composite multiple symptom measure of the TNSS does not represent a clear effect on any individual component of the TNSS. Absent substantial evidence or substantial clinical experience demonstrating Nasonex's effect on the particular component symptom, making a claim related only to the component symptom of the TNSS overstates Nasonex's efficacy. FDA is not aware of any substantial evidence or substantial clinical experience demonstrating that Nasonex specifically treats nasal congestion. If you have additional data to support such claims, please submit them to us for review.

Unsubstantiated Superiority Claims

Pages four and five of the Nasonex detail aid contain the headline claim, "**NASONEX® – BIG with physicians, preferred by patients**" (original emphasis) along with the claim, "**Patients preferred NASONEX® overall** –Primary endpoint: NASONEX® 53%, Flonase® 34% ($P<.05$)" (original

[2] Based on a mometasone furoate aqueous nasal spray controlled study. Protocol no. I94-079.

emphasis). Page five also includes the following claim: "Based on scent and taste attributes in a head-to-head preference study[3] Patient-preferred 2 to 1 versus Flonase®" along with a graph entitled, "Patients Preferred NASONEX® versus Flonase®," which shows the percentage of subjects who preferred Nasonex to Flonase with respect to the following sensory attributes: (1) scent/odor; (2) immediate taste; and (3) aftertaste. These claims and presentations are misleading because they imply that patients prefer Nasonex to Flonase based on all of the attributes assessed in the "preference study" and that patients prefer Nasonex to Flonase overall, when this has not been demonstrated.

The support for the claims of patient preference for Nasonex to Flonase with respect to sensory attributes and overall patient preference is subject responses to an "overall product preference" questionnaire.[3] The claim of "overall patient preference" for Nasonex is misleading because it is based on patient responses to a single question in the "overall preference questionnaire" that assessed eight product sensory attributes ("Based on these attributes which product do you prefer overall?"). The use of responses to this single question is not sufficient to support the broad concept of overall patient preference because patient preference cannot be adequately measured by a single item in an instrument. Patient preference encompasses multiple aspects of patient experiences such as convenience, ease of use, dosing, dosage form, all aspects of efficacy, and adverse events. Additionally, patient preference is influenced by more than just sensory attributes of a drug. Further, it is unknown whether the eight sensory drug attributes cited in the reference[3] are the most concerning and relevant to patients taking nasal steroids. Patient preference claims should be well-designed and controlled head-to-head studies using well-developed instruments that can evaluate patient preference. Thus, the reference cited to in the detail aid is not sufficient to support these claims.

Moreover, your presentation is misleading because the prominent graph on page five of the detail aid selectively presents from the questionnaire only results favorable to Nasonex. In fact, the questionnaire contained eight questions about specific sensory attributes of Nasonex and Flonase, and Nasonex received significantly better scores than Flonase for only half of these questions. While the graph prominently presents the data for three of the attributes where Nasonex scored better than Flonase and is headlined by a claim indicating that patients prefer Nasonex "2 to 1" to Flonase, it misleadingly omits the results from the other sensory attribute questions where Nasonex did not score significantly better than Flonase. While we note that a footnote to the graph lists the eight sensory attributes measured in the questionnaire, this disclosure is not sufficient to mitigate the selective and misleading presentation in the graph.

Conclusion and Requested Action

For the reasons stated above, the detail aid is misleading and therefore, it misbrands your drug in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf.* 21 CFR. 202.1(e)(6)(ii).

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[3] Meltzer EO, Bardelas J, Goldsobel A, Kaiser H. A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis. *Treat Respir Med*. 2005;(4):289-296.

DDMAC requests that Schering immediately cease the dissemination of promotional materials for Nasonex the same as or similar to those described above. Please submit a written response to this letter on or before May 18, 2007, describing whether you intend to comply with this request, listing all promotional materials for Nasonex that contain claims that are the same as or similar to those described above, and explaining your plan for discontinuing use of these materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or by facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 14548 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Nasonex comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Michelle Safarik
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