DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Munir Abdullah, Ph.D.
Director, U.S. Regulatory Affairs
GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Re: NDA # 20-121
Flonase® (fluticasone propionate) Nasal Spray, 50 mcg
MACMIS # 13807

Dear Dr. Abdullah:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional detail aid (detail aid) (MH2026R0) for Flonase® (fluticasone propionate) Nasal Spray, 50 mcg (Flonase) submitted by GlaxoSmithKline (GSK) under cover of Form FDA-2253. This detail aid is misleading because it makes unsubstantiated superiority claims for Flonase, omits material facts about Flonase, and claims that Flonase is more effective than has been demonstrated by substantial evidence or substantial clinical experience. 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), Flonase "is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older. Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established."

As set forth in the Clinical Trials section of the PI,

> A total of 13 randomized, double-blind, parallel-group, multicenter, vehicle placebo-controlled clinical trials were conducted in the United States in adults and pediatric patients (4 years of age and older) to investigate regular use of FLONASE Nasal Spray in patients with seasonal or perennial allergic rhinitis …. These trials evaluated the total nasal symptom scores (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks.

According to the PI, subjects treated with Flonase exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients.

Unsubstantiated Superiority Claims

The first page of the detail aid presents the following misleading claims regarding the superiority of Flonase over Nasonex® (mometasone furoate – Schering Corporation) (Nasonex):

- "Choose greater EFFICACY for your patients with SEASONAL ALLERGIC RHINITIS…" (original emphasis) above a chart titled, "SUPERIOR REDUCTION in Patient-Rated TOTAL NASAL SYMPTOM SCORES (TNSS) vs NASONEX[1]" (original emphasis) which in turn presents data that Flonase patients experienced a superior reduction of 25% (*P*=0.03) in TNSS versus Nasonex patients.

- "Patients given **FLONASE** experienced **GREATER RELIEF** of **NASAL SYMPTOMS** in a head-to-head clinical study of seasonal allergic rhinitis (SAR) sponsored by Schering Corporation, the maker of Nasonex®" (original emphasis).

These claims and presentations are misleading because they suggest that Flonase is superior to Nasonex for the treatment of seasonal allergic rhinitis symptoms, when this has not been demonstrated by substantial evidence or substantial clinical experience. The reference cited[1] to support this claim does not provide substantial evidence for the following reasons. First, the study design raises multiplicity issues. It was designed as a placebo-controlled trial comparing Nasonex to placebo; the active comparison was not clearly planned. It is therefore difficult to determine exactly what significance level should be attached to that comparison. Second, the study was not replicated. In general, a claim of superiority, like other claims under the Act, should be based on comparisons of the two drug products in two adequate, well-designed, head-to-head clinical trials. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Flonase is superior to Nasonex. If you have additional data to support such claims, please submit them to FDA for review.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The detail aid fails to present the full approved indication for Flonase (see Background section), including material limitations to the indication. Specifically, although the detail aid presents claims about Flonase's use in treating seasonal allergic rhinitis and nasal allergies, it fails to reveal that Flonase is only indicated in "adults and pediatric patients 4 years of age and older. Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established." Your failure to disclose the complete indication, including the material limitation that safety and effectiveness of Flonase in children below 4 years of age have not been adequately established, renders your detail aid misleading. This is especially concerning in light of the Precautions-Pediatric Use section of the Flonase PI which states that "Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients."

[1] Drouin MA. Trial I94-001. Efficacy and safety of mometasone furoate aqueous nasal spray vs placebo and vs fluticasone propionate (Flonase) in seasonal allergic rhinitis (SAR) patients. FDA Web site. Summary Basis of Approval section of the New Drug Application for Nasonex, NDA #20-762. Available at http://www.fda.gov/cder/foi/nda/97/020762ap_Nasonex_medrP2.pdf. Accessed June 7, 2005.

Overstatement of Efficacy

The detail aid highlights "congestion" as a specific symptom for which Flonase should be prescribed, and includes the claim, "WHEN NASAL **CONGESTION** IS CERTAIN, BUT THE TRIGGERS ARE NOT *PRESCRIBE FLONASE FIR$_x$ST*" (original emphasis). This presentation is misleading because it implies that Flonase is specifically indicated to treat nasal congestion. In fact, Flonase is not specifically approved for treatment of nasal congestion. Rather, according to the PI, "FLONASE Nasal Spray is indicated for the management of the nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older. Safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been adequately established." The Clinical Trials section of the Flonase PI indicates that Flonase was evaluated in clinical trials that measured total nasal symptom scores (TNSS). That section variously indicates that TNSS is a composite measure of symptoms including "rhinorrhea, nasal obstruction, sneezing, and nasal itching" in patients with known seasonal and perennial allergic rhinitis and that patient-rated TNSS is a composite measure of symptoms including "nasal obstruction, postnasal drip [and] rhinorrhea" in patients with perennial nonallergic rhinitis. However, demonstrating an effect on composite multiple symptom measures of the TNSS and patient-rated TNSS do not represent a clear effect on any individual component of the TNSS or patient-rated TNSS, and in the absence of substantial evidence or substantial clinical experience demonstrating Flonase's effect on the particular component symptom, making a claim related only to the component symptom of the TNSS or patient-rated TNSS overstates Flonase's efficacy. FDA is not aware of any substantial evidence or substantial clinical experience demonstrating that Flonase specifically treats nasal congestion. If you have additional data to support such claims, please submit them to us for review.

Conclusion and Requested Action

The detail aid is misleading because it contains unsubstantiated superiority claims, omits material facts, and overstates the effectiveness of Flonase. 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).

DDMAC requests that GSK immediately cease the dissemination of promotional materials for Flonase that are 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 Flonase 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 # 13807 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 Flonase 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
5/7/2007 07:36:05 AM