

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-051

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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m1.3.5.1 Patent Information

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 22-051	
		NAME OF APPLICANT / NDA HOLDER Glaxo Group Limited d/b/a GlaxoSmithKline	
The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.			
TRADE NAME (OR PROPOSED TRADE NAME) _____			
ACTIVE INGREDIENT(S) Fluticasone furoate		STRENGTH(S) _____mcg	
DOSAGE FORM Nasal spray			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,858,596		b. Issue Date of Patent 2/22/2005	c. Expiration Date of Patent 3/8/2021
d. Name of Patent Owner Glaxo Group Limited		Address (of Patent Owner) Glaxo Group Limited Glaxo Wellcome House Berkeley Avenue	
		City/State Greenford, Middlesex EB6 0NN ENGLAND	
		ZIP Code	FAX Number (if available)
		Telephone Number 919-483-2370	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) <input checked="" type="checkbox"/> Charles E. Dadswell Vice President- US Patents RTP		Address (of agent or representative named in 1.e.) GlaxoSmithKline Five Moore Drive	
		City/State Research Triangle Park, North Carolina	
		ZIP Code 27709	FAX Number (if available) 919-483-5730
		Telephone Number 919-483-6983	E-Mail Address (if available) charles.e.dadswell@gsk.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

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m1.3.5.1 Patent Information

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

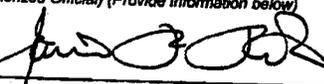
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m1.3.5.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes <input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
<i>Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:</i>	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
24	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Treatment of seasonal and perennial allergic rhinitis in adults and children ≥ 2 years.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
<input type="checkbox"/> Yes	

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6. Declaration Certification	
<p>6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)</p> 	<p>Date Signed</p> <p align="center">30 MAY 2006</p>
<p>NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>James P. Riek</p>	
<p>Address</p> <p>Five Moore Drive, P.O. Box 13398</p>	<p>City/State</p> <p>Research Triangle Park, NC</p>
<p>ZIP Code</p> <p>27709-3398</p>	<p>Telephone Number</p> <p>(919) 483-8022</p>
<p>FAX Number (if available)</p> <p>(919) 483-7988</p>	<p>E-Mail Address (if available)</p> <p>jim.p.riek@gsk.com</p>
<p>The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <p align="center">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p align="center"><i>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/foahm/foahm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Section 4 Annex for FDA Form 3542a- for NDA No. 22-051

Nasal Spray

4. Method of Use (continued)- Claim No. 25	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 25	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of seasonal and perennial allergic rhinitis in adults and children ≥2 years.
4. Method of Use (continued)- Claim No. 36	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 36	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of seasonal and perennial allergic rhinitis in adults and children ≥2 years.
4. Method of Use (continued)- Claim No. 37	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 37	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of seasonal and perennial allergic rhinitis in adults and children ≥2 years.

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4. Method of Use (continued)- Claim No. 38	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 38	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> Treatment of seasonal and perennial allergic rhinitis in adults and children ≥ 2 years.



GlaxoSmithKline
Legal Operations
2301 Renaissance Blvd.
King of Prussia, PA
19406-2772

Timothy M. Cramer
Direct Tel: 610-787-3287
timothy.m.cramer@gsk.com

September 19, 2006

VIA DHL EXPRESS

Sheldon T. Bradshaw, Esq.
Chief Counsel
U.S. Food and Drug Administration
5600 Fishers Lane
Room 6-57
Rockville, MD 20857

Re: Statement of Claimed Exclusivity for Fluticasone Furoate Nasal Spray

Dear Mr. Bradshaw:

We are writing with regard to a New Drug Application for Fluticasone Furoate Nasal Spray (NDA 22-051) that GlaxoSmithKline (GSK) submitted to FDA on June 28, 2006, and that FDA accepted for filing on August 28, 2006, after determining that it was sufficiently complete to permit a substantive review. Included with this letter as Attachment A is a copy of the introductory statement to NDA 22-051, which provides some background information regarding this pending new drug.

In the recently filed NDA, GSK raised a complex issue concerning eligibility of Fluticasone Furoate Nasal Spray for 5-year (NCE) marketing exclusivity. We are writing to draw your attention to the need for a careful exclusivity determination.

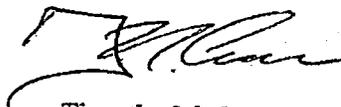
Module 1.3.5.3 of the NDA (a copy of which is included as Attachment B to this letter) explains GSK's position that Fluticasone Furoate Nasal Spray qualifies for NCE exclusivity, notwithstanding FDA's prior approval of products containing the different active ingredient, fluticasone propionate (e.g., Flonase® Nasal Spray, NDA 20-121). Fluticasone furoate, the new active ingredient now pending review, is a unique molecular entity that exhibits distinctive functional characteristics of clinical significance that are

directly attributable to the continuing presence of the furoate ester group at the local site of drug action. As is explained in the attached statement, the furoate ester group remains an integral part of this new chemical entity while exerting therapeutic activity at the site of action, and reviewers should appreciate that neither fluticasone furoate nor fluticasone propionate is ever metabolized to fluticasone.

As a result of the somewhat unusual circumstances presented by our exclusivity claim, we are providing this letter and have previously submitted (as part of the NDA) the attached statement of claimed exclusivity in order to assist the agency in making an appropriate exclusivity determination. GSK looks forward to FDA's consideration, and remains available to address any questions arising out of the agency's review of this issue.

If you or your staff should have any questions, please do not hesitate to call me at 610-787-3287.

Sincerely,



Timothy M. Cramer
Senior Counsel

Attachments

cc: Badrul A. Chowdhury, M.D.
Elizabeth H. Dickinson, Esq.
John K. Jenkins, M.D.
Robert J. Temple, M.D.

ATTACHMENT A

MODULE 2.2 INTRODUCTION TO SUMMARY

Fluticasone furoate (GW685698X) is a new corticosteroid developed by GlaxoSmithKline (GSK) presented as an aqueous suspension in a novel side-actuated nasal spray device for the once daily treatment for the symptoms of allergic rhinitis. Fluticasone furoate is the proposed International Nonproprietary Name (INN) and the United States Adopted Name (USAN).

GlaxoSmithKline is submitting this New Drug Application (NDA) in Common Technical Document (CTD) format to obtain marketing approval of fluticasone furoate nasal spray as a treatment for the symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children aged 2 years and older.

The Phase 2b/3 program for fluticasone furoate was designed taking into consideration the Food and Drug Administration (FDA) Guidance For Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products (Draft Guidance April 2000) and in consultation with the Division of Pulmonary and Allergy Drug Products (DPADP). The overall development program was discussed with the FDA in the course of several meetings and teleconferences, including a pre-IND meeting (held on August 8, 2003) and an end of Phase 2 meeting (held on July 19, 2004). A pre-NDA meeting to discuss and agree on the format and content of the NDA/CTD was held with DPADP on February 13, 2006. The attached table provides the Regulatory History of the fluticasone furoate development program.

Allergic rhinitis, a common inflammatory condition of the membranes lining the nose, is induced by an IgE-mediated inflammation of the upper airways following allergen exposure. It is characterized clinically by a combination of nasal and ocular symptoms that primarily include nasal congestion, itching, rhinorrhea and sneezing, as well as itching, redness and watering of the eyes. These symptoms are manifestations of the allergic response of the nasal mucosa and conjunctiva to the allergen, and involve the release of inflammatory mediators and activation and migration of the inflammatory cells. These responses occur both in the early and late phases of the disease. Overall, the symptoms may be extremely troublesome and have a profound negative impact on the allergy sufferer's quality of life.

Based on the triggers of the symptoms, allergic rhinitis may be classified as either seasonal or perennial. SAR is caused by exposure to seasonal allergens such as grass, trees and weeds, while PAR is caused typically by exposure to year-round allergens, such as pet dander, molds and house dust mite. Some patients with PAR have coexistent SAR leading to seasonal exacerbations of the condition. The pathophysiology of SAR and PAR are viewed as similar in terms of the chemical mediators produced in end organ manifestations, with the difference between the two entities primarily based on the causes and duration of the disease.

The diagnosis of allergic rhinitis is usually based on a medical history that includes nasal and/or ocular allergy symptoms occurring on a seasonal and/or perennial basis in response to specific allergen triggers. The diagnosis is further supported by the presence

m2.2 Introduction to Summary
of positive skin prick and/or intradermal skin tests to at least one specific allergen or by the detection of specific IgE antibodies on *in vitro* testing.

The goal of allergic rhinitis therapy is to manage both the acute and chronic manifestations of the disease by minimizing the associated symptoms and improving quality of life. To achieve this, current treatment recommendations include allergen avoidance, immunotherapy and/or pharmacotherapy. Avoidance is difficult to achieve for the most common allergens (e.g., pollen, dust mites). Immunotherapy is an effective chronic therapy in some patients but it is time-consuming, inconvenient, and has potential, albeit rare, serious adverse effects (such as large local reactions and anaphylaxis). Current pharmacotherapy options include intranasal corticosteroids, antihistamines, non-steroidal anti-inflammatory agents and decongestants. Of these, intranasal corticosteroids provide the broadest relief of the symptoms of allergic rhinitis and offer the only therapeutic option with proven anti-inflammatory activity.

Fluticasone furoate (GW685698X) is a new corticosteroid developed as a nasal spray and is a white, uniform suspension contained in an amber glass bottle, closed with a metering spray pump and incorporated into a plastic device with a dose indicator window and side-actuated lever. The novel delivery system was designed for self-administration by children from the age of 7 years as well as adults, and for third party administration to very young children. It incorporates features that are designed to ensure that a consistent dose is delivered and that the product has a reduced need for re-priming. The device also incorporates a shorter nozzle than other marketed products. Compared with other intranasal corticosteroids, such as mometasone furoate and fluticasone propionate, the volume per actuation is lower, which may result in a reduction in post nasal run-off. In

An extensive global clinical trial program was undertaken by GSK to study the safety and efficacy of fluticasone furoate nasal spray in the treatment of SAR and PAR in adults and adolescents (12 years of age and older) and children (2 to <12 years of age). The program comprised 22 Clinical Pharmacology studies in healthy volunteers and subjects with allergic rhinitis or asthma, and 12 Phase 2b/3 studies in adults, adolescents and children with SAR or PAR. A total of 3954 adult, adolescent, and pediatric subjects participated in the Phase 2b and Phase 3 clinical studies, with approximately 60% of these subjects (2359) treated with fluticasone furoate 100mcg (1990) or fluticasone furoate 50mcg (369). Overall, the numbers of subjects exposed to fluticasone furoate met or exceeded the International Conference on Harmonization (ICH) Guidance E1 for extent of population exposure to assess clinical safety, where total population exposure is recommended to be 500 to 1500 subjects, with 300 to 600 subjects exposed for 6 months and 100 subjects exposed to investigational drug for a minimum of one year.

Throughout development the spray content of Fluticasone Furoate Nasal Spray has been approximated as 25mcg/actuation in the clinical trial documentation pending final confirmation of the spray content. The proposed label dose for the commercial product is the overall mean of the spray content database for clinical batches at release and long term stability. The actual dose delivered from the product is 27.5mcg/actuation, which is

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therefore proposed as the label claim. Based on this spray content assessment, the doses examined in the clinical program were actually 55mcg, 110mcg, 220mcg, and 440mcg rather than the 50mcg, 100mcg, 200mcg, and 400mcg doses indicated in the clinical documentation of this dossier.

As a result, the recommended starting dosage for adults and adolescents 12 years of age and older is 110mcg once daily (administered as two sprays in each nostril). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose to 55mcg (one spray in each nostril) once daily may be effective in maintaining control of allergic rhinitis symptoms. This will allow an individual patient to titrate to the minimum effective dose.

In children, the recommended starting dosage is 55mcg once daily with the option to increase the dosage to 110mcg once daily in children not adequately responding to the lower dose. Once adequate control is achieved, the dosage may be decreased to 55mcg once daily.

Based upon the clinical data that is presented in this NDA, it is proposed that fluticasone furoate nasal spray will be indicated for the treatment of the symptoms of seasonal and perennial allergic rhinitis in patients 2 years of age and older.

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT B

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m1.3.5.3 Exclusivity Request

STATEMENT OF CLAIMED EXCLUSIVITY

We submit this statement, pursuant to 21 C.F.R. §§ 314.50(j) and 314.108(b)(2), to explain why "5-year" market exclusivity should be awarded for fluticasone furoate nasal spray. In short, the fluticasone furoate molecule is both a "new chemical entity" and a new "active moiety" as those terms have been interpreted and applied by the FDA.

No drug product containing fluticasone furoate has been approved previously. Fluticasone furoate, an ester, is a unique molecular entity that exhibits distinct functional effects. In comparison, fluticasone propionate is a different ester and is the active ingredient in various inhaled and dermal drug products. The two esters exhibit quite distinct functional characteristics, as detailed below. The distinctive ester groups – which remain appended as the two drugs exert their therapeutic effect – are responsible for the functional differences, and they are essential contributors to efficacy at the drugs' local site of action.

FDA has made clear its position that eligibility for 5-year exclusivity depends on whether the same "active moiety" has been approved previously. See 21 C.F.R. § 314.108(b)(2):

If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the chemical entity for a period of five years from the date of approval of the first approved new drug application . . ."

(Emphasis added.)

See also 21 C.F.R. §314.108(a), in which FDA defines a "new chemical entity" as "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act," and defines "active moiety" as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."¹

¹ In establishing the parameters of what constitutes an active moiety, FDA has concluded that the term is synonymous with the term, "active ingredient". 59 Fed. Reg. 50338, 50368 (October 3, 1994). GSK notes that neither the term "new chemical entity" nor the term "active moiety" is defined in the FDCA, and that FDA's interpretation of these terms and the active moiety test is subject to challenge as a matter of law. See *Abbott Labs v. Young*, 920 F.2d 984 (D.C. Cir. 1990), cert. denied, 502 U.S. 819 (1991). GSK reserves the right to raise such a challenge. However, even under FDA's regulatory interpretation, fluticasone furoate constitutes a new active moiety, as explained in this statement.

m1.3.5.3 Exclusivity Request

As noted above, this is not the usual case in which an appended ester group is cleaved *in vivo* to liberate the active moiety after administration of a drug, prior to exertion of its therapeutic effect at the local site of action. To the contrary, neither fluticasone furoate nor fluticasone propionate is metabolized to fluticasone. As will be discussed below, here it is the entire molecule, *including* the ester group, that is the active moiety because the ester group is an essential part of "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance."

Fluticasone Furoate Functions as a Unique Active Moiety.

Fluticasone furoate is a unique molecular entity that exhibits functional effects that are distinct from those of fluticasone propionate. These functional differences bear significantly on the molecular (and thus therapeutic) activity of the two molecules. The structural difference between fluticasone furoate and fluticasone propionate lies in the identity of the ester group at the 17 α position.² This variation changes and improves the overall activity of fluticasone furoate³ at the glucocorticoid receptor relative to that of fluticasone propionate with regard to potency, binding affinity. The *entire fluticasone furoate* molecule is thus the active moiety, with the furoate ester group contributing essentially to the characteristics and activity of the drug molecule. Without the furoate ester group, the functional activity of the fluticasone furoate molecule and its interaction with the target receptor and target tissue would be less effective.

The distinctive identity of fluticasone furoate is clearly demonstrated by the molecule's physical properties, functional activity within tissue, interaction with the target receptor, and ultimate metabolism of the molecule.

The Physical Properties of Fluticasone Furoate are Distinct from the Properties of Fluticasone Propionate.

Fluticasone furoate differs from fluticasone propionate in its molecular weight,⁴ melting point⁵ and crystalline structure.⁶ Differences in such fundamental physical properties mirror the functional differences detailed below.

² Report SR2006/00001/01-The in vitro preclinical pharmacology of GW685698X, a potent and selective Glucocorticoid Receptor agonist, page 9.

³ See Footnotes 9 and 10.

⁴ Fluticasone furoate's molecular weight is 538.6 and the molecular weight of fluticasone propionate is 500.6.

⁵ The melting point for fluticasone furoate is approximately 280°C and the melting point for fluticasone propionate is 261°C.

The Functional Activity of Fluticasone Furoate Differs from Fluticasone Propionate.

Studies in respiratory tissue indicate that the fluticasone furoate and fluticasone propionate molecules interact differently with target tissue. In *in vitro* studies involving cultured human bronchial epithelial cells, the duration of the functional activity of fluticasone furoate is longer than that of fluticasone propionate. In addition, there is greater accumulation of the fluticasone furoate in the epithelial cells.⁷ Furthermore, after intratracheal dosing in the isolated perfused rat lung and, more significantly, after inhaled dry powder dosing in man, fluticasone furoate is absorbed more slowly than fluticasone propionate.⁸

The Interaction of Fluticasone Furoate with the Target Receptor is Different from that of Fluticasone Propionate as a Result of Distinct Esters.

The presence of the furoate ester group results in an improved interaction of the entire molecule with the target receptor site compared to the propionate ester group.

As glucocorticoids, both fluticasone propionate and fluticasone furoate exert their therapeutic activity by binding to the glucocorticoid receptor site in target tissue. X-ray crystal structures of the two fluticasone esters in the glucocorticoid receptor show that the furoate ester more fully occupies a lipophilic pocket in the receptor than the propionate ester (which is smaller). This additional and stronger binding with the target receptor is reflected in the higher receptor affinity of fluticasone furoate when compared to fluticasone propionate.⁹ In fact, fluticasone furoate displays a higher affinity for the glucocorticoid receptor site than all other clinically available glucocorticoids.¹⁰

⁷ Report SH2005/000036/00-Characterisation of Binding to the Glucocorticoid Receptor, Inhibition of the NFkB Pathway, Association with Lung Cells and Tissue and *in vitro* Duration of Action for GW685698X

⁸ Memorandum CMD/04/162-The transpulmonary transport of FP and GW685698X in the isolated perfused respiring rat lung following instillation into the trachea; Report GM2003/00388/00-A part-randomised, single dose, open label, 6-way cross-over study to assess the relative systemic pharmacokinetics and absolute bioavailability of 2 and 3 µm GW685698X (2000µg), FTIM GW685698X material (2000µg) and FP (1000µg) administered via Diskhaler in healthy male subjects.

⁹ Report SR2006/00001/01-The *in vitro* preclinical pharmacology of GW685698X, a potent and selective Glucocorticoid Receptor agonist.

¹⁰ Report SH2005/000036/00; Based upon a reference standard of 100 for Dexamethasone, fluticasone furoate exhibits a glucocorticoid receptor affinity of 2989, while fluticasone propionate's affinity is

m1.3.5.3 Exclusivity Request

Fluticasone Furoate and Fluticasone Propionate Have Distinctive Metabolic Pathways.

The differences in metabolism of fluticasone furoate and fluticasone propionate further demonstrates their status as separate molecular entities, and establishes fluticasone furoate's status as a unique active moiety. Fluticasone furoate and fluticasone propionate are metabolized to different inactive acid metabolites¹¹ and share no common metabolites. Neither fluticasone furoate or fluticasone propionate is metabolized to fluticasone. The unique properties of fluticasone furoate are due to the entire molecule with the furoate ester being the key contributor to the molecule's properties.

FDA Has Granted Exclusivity to Esters When, as Here, the Ester is a Distinct and Stable Active Moiety.

Precedent exists for the designation of fluticasone furoate as a new chemical entity. FDA previously has granted five years of marketing exclusivity to a therapeutically active, stable ester of a previously approved molecule. Specifically, in 1991, FDA granted 5-year exclusivity to isosorbide mononitrate in spite of the prior approval of products containing isosorbide dinitrate. This previous determination by FDA establishes precedent supporting GSK's request for a 5-year marketing exclusivity for fluticasone furoate.

Once GSK receives notification that this application has been accepted for review by FDA, GSK intends to furnish a courtesy copy of this statement of claimed exclusivity to John K. Jenkins, M.D., Robert J. Temple, M.D., and Elizabeth H. Dickinson, Esq.

1775. See also, Attachment ___ (table showing relative receptor binding affinities for fluticasone furoate versus other inhaled steroids).

¹¹ Fluticasone furoate is metabolized into (6 alpha, 11 beta, 16 alpha, 17 alpha)-6, 9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxoandrosta-1,4-diene-17-carboxylic acid. Fluticasone propionate is metabolized into (6 alpha, 11 beta, 16 alpha, 17 alpha)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(propanoyloxy)androsta-1,4-diene-17-carboxylic acid. See Report WD2005/01496/00 - Characterisation of the Major Metabolites of GW685698X following a Single Oral Administration and a Single Intravenous Administration of [14C]GW685698 to Healthy Adult Male Subjects; Report WD2004/00004/00 - In vitro investigations into the metabolism of [14C]GW685698 and [3H]GW685698 in human, mouse, rat, female rabbit and dog (Study No. B30977).

EXCLUSIVITY SUMMARY

NDA # 22-051

SUPPL #

HFD # 570

Trade Name Veramyst Nasal Spray

Generic Name fluticasone furoate nasal spray

Applicant Name GlaxoSmithKline

Approval Date, If Known April 27, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?
YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-120

21-433

NDA# 20-549

20-833

NDA# 20-548

21-077, NDA 21-254, NDA 20-770

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES

NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

FFR20001
FFR30003
FFR103184
FFR104861
FFR30002
FFR102123
FFR20002
FFR101816
FFR100010
FFR30008
FFR100012
FFR101747

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

FFR20001

FFR30003

FFR103184

FFR104861

FFR30002

FFR102123

FFR20002

FFR101816

FFR100010

FFR30008

FFR100012

FFR101747

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 48,647

YES

! NO

! Explain:

Investigation #2

IND # 48,647

YES

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Ladan Jafari
Title: Regulatory Health Project Manager
Date: April 25, 2007

Name of Office/Division Director signing form: Dr. Badrul Chowdhury
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Badrul Chowdhury
4/27/2007 02:58:57 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-051 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: June 29, 2006 Action Date: PDUFA DATE: April 29, 2007

HFD-570 Trade and generic names/dosage form: fluticasone furoate nasal spray

Applicant: GlaxoSmithKline Therapeutic Class: Respiratory

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Seasonal allergic rhinitis

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

—XNo: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. <24 _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

—X Other: Disease does not exist in children < 2 years of age.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. > 24 months _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-051
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Perennial allergic rhinitis

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo < 24 months. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. > 24 months _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 22-051
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Ladan Jafari

7/31/2006 02:44:56 PM

CONFIDENTIAL

m1.3.3 Debarment Certification

NDA 22-051, fluticasone furoate nasal spray
Treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in
adults and children aged 2 years and older

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller or Mertie V. Snead
Director, North America Clinical Compliance
Worldwide Regulatory Compliance



Date

MEMORANDUM

To: Ladan Jafari
Division of Pulmonary and Allergy Products

From: Iris Masucci, PharmD, BCPS and Jeanne Delasko, RN, MS
for Study Endpoints and Label Development (SEALD) Team, OND

Date: April 17, 2007

Re: Comments on draft labeling for Veramyst (fluticasone furoate) nasal
spray
NDA 22-051

We have reviewed the proposed label for Veramyst (FDA version dated 4-5-07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Throughout the label, doses are sometimes expressed as "110-mcg" or "50-microliter." The preferred formatting for doses is to use no hyphenation (e.g., "110 mcg") in order to avoid misreading of dosing. FDA has recently begun a joint effort with the Institute for Safe Medication Practices to avoid using abbreviations and terminology that may contribute to medication errors, including deleting them from approved labeling.

HIGHLIGHTS

Required Statement

- *"These highlights do not include all the information needed to use VERAMYST safely and effectively. See full prescribing information for VERAMYST."*

Is the trade name for this product "VERAMYST" or "VERAMYST Nasal Spray"? If the latter is true, then "Nasal Spray" should be added in both places in this statement at the beginning of Highlights. We note that throughout the label, the product is called "VERAMYST Nasal Spray."

Indications and Usage

- "VERAMYST Nasal Spray is a _____ corticosteroid indicated for..."

The term " _____ " from the indication statement. The pharmacologic class is "corticosteroid," not " _____ corticosteroid." If the trade name is "VERAMYST Nasal Spray," it is unnecessary to say " _____ corticosteroid." If the trade name is "VERAMYST" and you want to emphasize that this product is for intranasal use, you could rewrite this statement to say, "VERAMYST is a corticosteroid indicated for _____ treatment of..."

Warnings and Precautions

- "Systemic and local corticosteroid use _____."

Please consider if this introductory sentence is truly necessary here in Highlights. Its use implies that all of the risks listed below are class effects, and not necessarily attributable to VERAMYST use. The full description of some of these risks in the Full Prescribing Information (FPI), however, seems to say that some have specifically been seen with VERAMYST (e.g., epistaxis, *Candida* infection). Would it be more appropriate to delete this statement, and let the full discussion in the FPI clarify which are class effects?

If this sentence remains in the label, please consider rewording. Use of the phrase "associated with" is currently being discouraged in labeling because it is vague and has legal implications when included in labels.

- "Development of glaucoma or posterior subcapsular cataracts."

When possible, each warning/precaution should state the problem and what to do about it (e.g., monitor, discontinue, etc.). Please revise this bullet (and subsequent ones) as appropriate.

- "Potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. More serious or even fatal course of chickenpox or measles in _____ susceptible patients."

As above, can we give advice here? Should we not use VERAMYST? Monitor?

Can we find another term for " _____ susceptible patients"? This one seems awkward.

- "Hypercorticism and adrenal suppression with very high dosages or _____ at regular dosage."

As above, can we rephrase " _____"?

Adverse Reactions

- "The most common adverse reactions (>1% incidence) included epistaxis (6%) and nasal ulceration (1%)."

In the version of the label used for this review, there is a second "Table 1" in "6 Adverse Reactions" that has a different list of the most common reactions (headache, epistaxis, and pharynolaryngeal pain as the most common) than is seen in the first "Table 1" (that lists only epistaxis and nasal ulceration). Please be sure that the list used for Highlights reflects the reactions from the proper table.

When the list is created, the incidence rate for each reaction need not be included. Instead, only the cut-off rate used for the entire list should appear.

- "Localized infections of the nose with *Candida albicans* (—————)." ."

We recommend deletion of this bullet from Highlights. The risk of *Candida* infection is adequately noted under Warnings and Precautions and does not need to be repeated here.

Drug Interactions

- To avoid redundancy, the introductory "CYP3A4 Inhibitors" can be deleted. Instead, the item could be revised to read, "Potent inhibitors of CYP3A4 (e.g., ritonavir): May increase exposure..."

Use in Specific Populations

- As above, the introductory "Hepatic Impairment" can be deleted from this item.

Patient Counseling Statement

- Will there be FDA-approved labeling for this product (e.g., a PPI or Patient Instructions for Use)? If not, this statement should read simply, "See 17 for PATIENT COUNSELING INFORMATION."

Revision Date

- Please ensure that the lettering that currently appears under the revision date (VRM:1PI) at the end of Highlights will not appear in the final version of the labeling.

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.
-

FULL PRESCRIBING INFORMATION

1.1 Treatment of Allergic Rhinitis

Because the product has only one indication, the subheading "1.1 Treatment of Allergic Rhinitis" can be deleted. The indication itself can appear directly under "1 Indications and Usage." If this change is made, it should also be corrected in Contents and any cross-referencing throughout the label (including the Indications and Usage section of Highlights).

2.2 Children 2 to 11 Years of Age

- "~~_____~~"

We suggest deletion of this sentence from this section of "Dosage and Administration." It is unnecessary here because it is not relevant for Dosage and Administration and because it is adequately addressed in the indication and Pediatric Use sections.

5 Warnings and Precautions

- Please review the list of Warnings/Precautions in this section to ensure that they are in decreasing order of importance. If any changes are made to the ordering, please make the corresponding changes to Highlights and Contents.

- "Systemic and local corticosteroid use ~~_____~~"

As mentioned under Highlights, please consider deletion of this sentence.

5.1 Local Nasal Effects

- "~~_____~~ instances of nasal septal perforation have been reported in patients following the intranasal application of corticosteroids."

Can this sentence be revised to avoid use of the word "~~_____~~"? Vague terms such as this should generally not be used in labeling and may be seen as minimizing the risks of VERAMYST use.

- "Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred."

We suggest revising this sentence to, "... should not use VERAMYST until healing has occurred."

5.2 Glaucoma and Cataracts

- "Nasal and inhaled corticosteroids ~~_____~~ the development of glaucoma and/or cataracts."

As noted above, please revise this sentence to avoid use of "_____."

5.3 Immunosuppression

- *"If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated."*

These sentences should each be revised for grammatical correctness to, "If a patient is exposed to..."

- *"If chickenpox develops, treatment with antiviral agents may be considered."*

Should the package insert for a nasal corticosteroid be making recommendations on how to treat chickenpox? Is it beyond the scope of this document? Additionally, if a patient using VERAMYST develops chickenpox or measles, should VERAMYST be discontinued?

5.4 Hypothalamic-Pituitary-Adrenal Axis Effects

- *"When intranasal steroids are used at higher than recommended dosages or in individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear."*

As above, please consider rewording "→ individuals."

6 Adverse Reactions

- *"Systemic and local corticosteroid use t _____ the following:"*

As above, please revise to avoid "_____ ' in this sentence.

6.1 Clinical Trials Experience

- Throughout this section, the term "adverse events" is often used. When possible, the label should present "adverse reactions," not all "adverse _____" seen in the trials. Please ensure that the proper term is used in the text and tables when describing the data presented.
- *"Epistaxis tended to be more severe in patients treated with VERAMYST. All 17 reports of epistaxis that occurred in patients who received placebo were of mild intensity, while 83, 39, and 1 of the total 123 epistaxis events in patients treated with VERAMYST were of mild, moderate, and severe intensity, respectively."*

Are the categories of mild/moderate/severe intensity for epistaxis widely agreed upon? Do they need defining here?

Does this section about hypercorticism belong in the Adverse Reactions section? It seems redundant with the Warning about this risk and does not seem to fit in the Adverse Reactions section.

8.4 Pediatric Use

- We suggest that the first sentence in this section conclude with a cross-reference to the Clinical Studies section
- We suggest that the discussion of reduction in growth velocity have an underlined subheading title to increase its prominence.
- *"To minimize the systemic effects of intranasal corticosteroids, including VERAMYST Nasal Spray, each patient should be titrated to the lowest dosage that effectively controls his/her symptoms."*

We suggest this sentence be revised to say, "... each patient's dose should be titrated..." instead of "each patient should be titrated."

8.6 Hepatic Impairment and 8.7 Renal Impairment

- In general, these sections under "Use in Specific Populations" should include the broad clinical recommendations on using the drug in these patients. The actual pharmacokinetic findings should appear in "12.3 Pharmacokinetics" and cross-referencing used as needed.

12.2 Pharmacodynamics

- *"In a 6 week randomized, double blind, parallel group study in adult and adolescent patients 12 years of age and older with perennial allergic rhinitis, VERAMYST Nasal Spray 110 mcg was compared to both placebo nasal spray and prednisone in a positive control group that received prednisone 10 mg once daily for the final 7 days of the treatment period."*

We suggest that this sentence specify the dosage form for prednisone (presumably oral) used in this study.

- *"Based on a thorough QTc study, there is no evidence that fluticasone furoate has an effect on QTc interval."*

We suggest deletion of the word "thorough" from this study description because it is promotional in tone and may imply that more is known about effects on QT interval than is really true.

12.3 Pharmacokinetics

- “

”
- Is this first sentence truly necessary under “Absorption”? Unless there is a reason to expect that the parent drug would not be responsible for its activity, we suggest it be deleted.
- *“Fluticasone furoate is typically not quantifiable in plasma following intranasal dosing of 110 mcg once daily with the exception of isolated cases of very high plasma levels (see Absorption).”*
- Is the subheading “Population Pharmacokinetics” truly necessary? Is there a reason that the information presented here should not just be incorporated into the “Absorption” section instead?

14 Clinical Studies

- As with the lone indication, the subheading “14.1 Seasonal and Perennial Allergic Rhinitis” can be deleted because it is the only indication for the product. If it is deleted, please make the corresponding changes in Contents and throughout the label as well.

14.1 Seasonal and Perennial Allergic Rhinitis

- This section presents data on numerous endpoints. Do the study design and data analysis plan allow for the evaluation of multiple endpoints? Any findings that are not adequately supported should not appear in labeling.
- Please consult Laurie Burke of OND’s SEALD team for an evaluation of any patient-reported outcomes (e.g., RQLQ findings) and their appropriateness for inclusion in the label.
- Should the “dose ranging trial” even be included in the label? Unless there is a compelling reason to include it, please consider its deletion. The discussion can imply benefits of “off-label” dosing regimens, namely higher doses than those recommended in the label. If the presentation of the higher doses remains in the label, should we add explanatory language why they are not recommended (e.g., either no additional benefit seen or more toxicities reported)?
- In each of the sections describing the study findings, the text summarizes the findings that are subsequently presented in the tables. Is it necessary to present both? Would it be sufficient to say simple, “Study results are presented in Table X”?
- *“Table 4 displays the efficacy results from a representative trial in patients with seasonal allergic rhinitis.”*

Are these results truly "representative," or is this a selective presentation of the data? Would pooling the data instead be more appropriate (if the study designs and populations allow)?

- *"Onset of action was evaluated by frequent instantaneous TNSS assessments after the first dose in the clinical trials in patients with seasonal allergic rhinitis and perennial allergic rhinitis. Onset of action was generally observed within 24 hours in patients with seasonal allergic rhinitis. In patients with perennial rhinitis, onset of action was observed after 4 days of treatment. Continued improvement in symptoms was observed over approximately 1 and 3 weeks in patients with seasonal and perennial allergic rhinitis, respectively."*

Are these "onset of action" and "continued improvement" claims adequately supported? They will likely be used promotionally. We note that similar statements also appear in "17 Patient Counseling Information."

16 How Supplied/Storage and Handling

- We suggest that information on proper storage that is currently in bold type be unbolded. Bold type should be used for emphasis sparingly in labels.

17 Patient Counseling Information

- The reference to the approved patient labeling should specify " _____" instead of the broader term "FDA-approved Patient Labeling." The recommended formatting for these references to patient labeling is: " _____."
- For the remainder of section 17, it is your choice whether to give each topic its own numbered subheading or to just make each of these a bullet under "17 Patient Counseling Information." Most PLR labels that have included such a list have used bullets, but either way is acceptable.

Revision Date

- The date ("2007") should be deleted from the label. The revision date at the end of Highlights is intended to replace the data that has traditionally appeared at the end of the label.

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/s/

Iris Masucci
4/24/2007 11:25:48 AM
DDMAC REVIEWER

Laurie Burke
4/24/2007 05:54:14 PM
INTERDISCIPLINARY



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 23, 2007

To: Munir Abdullah	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-9318	Phone number: 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 30

Comments: labeling

Document to be mailed: YES NO

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Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate and we have the following comments with regard to the labeling. We ask that you provide draft labeling incorporating our comments and respond to our questions and comments by the close of business on April 24, 2007.

Highlights

- We deleted the introductory statement under the warnings and precautions because it implied that all the risks were class effects and not necessarily attributable to Veramyst.
- We added recommendations regarding monitoring based upon the warnings and precautions.
- The Adverse Reactions section was expanded to reflect the table in the Adverse Reactions section.

FPI

Adverse Reactions (6)

- We decided upon option two for the Adverse Reactions section; however, we have maintained use of the term "Adverse Reaction" throughout the section. We refer you to the Guidance for Industry: Adverse Reaction Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, Section IV (A), which describes selection of adverse events for inclusion. Decisions regarding a causal relationship include factors, such as: (1) the frequency of reporting and (2) whether the adverse event rate for the drug exceeds placebo rate. On the basis of these two factors, we used the term adverse reactions throughout this section.
- Include racial distribution in the safety database description.
- We removed the last paragraph because it seemed redundant with the Warnings and Precaution Section.

Special Populations – Pediatric Use (8.4)

- We deleted the _____ study because we typically do not include this information in product labels.

Special Populations – Renal and Hepatic Impairment (8.6 and 8.7)

- We moved the detailed PK information to Section 12.3 and just included the broad clinical recommendations in Sections 8.6 and 8.7.

Pharmacodynamics (12.2)

- Clarify what conversion factor you used and how you arrived at the conversion factor to convert the data from nmol/24 hour to mcg/24 hour in the HPA axis section.
- There appears to be an extra return in this section (Line 394). Please remove.
- We updated the section with new language regarding the QT study.

Clinical Studies (14)

- We deleted the ~~_____~~, for the following reasons:
 - As discussed in the Pre-NDA meeting, we prefer the onset of action in an individual study be defined as the time point from where statistical significance is maintained from that hour onwards rather than allowing one non-significant assessment.
 - Using the above definition, the onset of action in Study FFR30003 onset may be as late as Day 6.
 - Although the onset of action in Study 20001 (dose ranging) could be considered to be 8 hours, the frequency of assessment was less than the pivotal studies (no 10 hour assessment). In addition, in the same study the 220 mcg group did not show onset of action until 24 hrs.
 - Your allergen challenge onset of action study failed to demonstrate an onset of action within 12 hours.

How Supplied (16)

- We removed unscented and alcohol-free because the label should describe what is in the product, not what is not in the product.

Carton and Container

- Submit copies of the mock up container and carton labels because the labels are difficult to read without significant (200%) magnification.
- Increase the size and prominence of “Nasal Spray” in the drug product name.
- Remove the information about “special offers and savings” from the carton labels.
- Emphasize the phrase “For Intranasal Use Only”

27 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓
_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Ladan Jafari
4/23/2007 04:45:39 PM
CSO

April 11, 2007



Badrul A. Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products
Food and Drug Administration
Center for Drug Evaluation and Research
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Beltsville, MD 20705-1266

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

**Re: NDA 22051; Fluticasone Furoate Nasal Spray
General Correspondence: Phase IV Commitment
Resubmission**

Dear Dr. Chowdhury:

Reference is made to our NDA 22-051 for fluticasone furoate nasal spray submitted on June 28, 2006. Reference is also made to the fax dated March 27, 2007, from the Division of Pulmonary and Allergy Drug Products (DPADP) providing post-marketing study commitments. Reference is further made to GlaxoSmithKline's (GSK) letter dated April 6, 2007, acknowledging agreement to the DPADP proposed post-marketing (Phase IV) commitments and providing brief study proposals seeking comments from the Division on the two proposed post-marketing studies. As requested in a telephone conversation today (April 11, 2007) by Ms. Ladan Jafari, Project Manager, to resubmit the Phase IV commitment agreement letter without the study proposals, this letter is to acknowledge GSK's agreement to the following post-marketing (Phase IV) commitments as proposed by DPADP:

- 1. To conduct a one-year linear growth study in children with fluticasone furoate using a dose that is relevant to the proposed fluticasone furoate nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation. Submit a labeling supplement reflecting the results of the study.**

GSK agrees to this post-marketing study commitment and will conduct a growth study in children with fluticasone furoate nasal spray according to the following dates:

Final Protocol Submission Date: August 2007

Study Start Date: November 2007

Final Report/Labeling Supplement Submission Date: November 2011

Badrul A. Chowdhury, M.D.

April 11, 2007

Page 2

- 2. To conduct a 2-year safety study to assess the long-term effects of fluticasone furoate nasal spray on ocular safety, including cataract formation and the development of elevated intraocular pressure/glaucoma. Submit a labeling supplement reflecting the results of this study.**

GSK agrees to this post-marketing study commitment and will conduct a 2-year safety study with fluticasone furoate nasal spray to assess the ocular safety according to the following dates:

Final Protocol Submission Date: October 2007

Study Start Date: January 2008

Final Report/Labeling Supplement Submission Date: February 2011

The final protocols for the above Phase IV studies will be filed to IND 48,647; GW685698X (fluticasone furoate) Nasal Spray according to the above listed dates and GSK will initiate the studies after receiving comments and agreement with the Division on the study protocols.

This submission is being provided electronically in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format-NDAs, January 1999*. Please see Guide to Reviewers for detailed information about this electronic submission.

If you have any questions regarding this submission, please contact me at (919) 483-9318 or via secure email at munir.a.abdullah@gsk.com.

Sincerely,



Munir Abdullah, Ph.D.

Director

Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2007

To: Munir Abdullah	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-9318	Phone number: 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 3

Comments: labeling comments

Document to be mailed: YES NO

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NDA 22-051

Dear Dr. Abdullah:

We are reviewing the labeling that you submitted on April 5, 2007, and we have the following requests for information.

• ✓

- J
- Explain why in Tables 2 and 5 the change from baseline differences in the tables does not represent the numerical difference between baseline and end of the treatment period.
 - Provide the summary data (as you did for Tables 2 and 5) for the analyses of urine and serum cortisol levels found in Tables 1, 3, 4, 6, 7, and 8.

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/s/

Ladan Jafari
4/11/2007 01:33:33 PM
CSO

Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate nasal spray submitted on June 28, 2006. We also refer to your submission dated February 22, 2007, which contained updated labeling for this application. We have made significant changes to the label to be consistent with the published guidances on the new label format. Please note that the attached label may not include all of our labeling recommendations and that additional comments may be forthcoming.

Submit revised draft labeling incorporating our comments listed below as well as in the attached package insert and patient information sheet.

PI: General Comments

The following are general comments regarding the PI:

- The trade name should not be in all capital letters throughout the label. Revise the label accordingly.
- Note that in final format the label will have 2 columns of text per page. Since, according to new guidelines, 8 font is the smallest to be used, ensure that tables are formatted such that they will fit into the final 2-column label as 8 font text.
- Include demographic information in the Clinical Studies (14) section in the discussions of the clinical trial database for the adults and pediatrics sections.
- Include information regarding subgroup analysis (age, race, gender) in the Adverse Reactions (6) section.
- Highlights should be limited to a half-page.

PI: Footnoted Comments

The PI contains superscripts that correspond to the following comments:

1. Update the Warnings and Precaution Highlights to reflect changes in the order and title of subheadings in the Warnings and Precautions FPI.
2. Include the incidences. This list may change when the adverse event table is updated.
3. Use in special populations added to reflect section 8.6.

4. Update table of contents to reflect addition of subheadings and changes to proposed subheadings.
5. Onset of action and efficacy information deleted from the Dosage and Administration and Mechanism of Action Sections. Onset of action information is included in the Clinical Studies Section (14).
6. The number of patients in the adult safety study who developed elevated IOP and cataracts were included. We have concerns regarding the quality of the fundoscopic exams performed in these studies; therefore, the fundoscopic findings were deleted. The values for the 12 week children study have not been included as the study is too short to adequately determine the risk of increased IOP/cataracts.
7. Revise Table 1 to include the AEs for only the adults and adolescents trials. Include AEs with incidence >1% and more common than placebo. This would also include headache, pharyngolaryngeal pain, and back pain for adults (see Table 26 ISS.pdf, page 82 of 1692).

Clarify the nasal ulceration AEs in Table 1. In Table 26 (pg. 82) of the ISS, there are 9 nasal ulceration AEs in the FF group and 2 nasal ulceration AEs in the placebo group. In the source table, Table 14.20, there are 13 nasal ulcerations in the FF group and 4 nasal ulcerations in the placebo group.

8. Insert Table 2 displaying the AEs for the pediatric studies. Use the cutoff of >3% incidence and more common than placebo.
9. Insert subgroup analysis information (race, gender) for the pediatric population. For age, insert subgroup analysis information for children 2 to < 6 years and children to 6 to <12 years.
10. "Rapidly" was deleted throughout the FPI because it is an ambiguous term that is promotional in tone.

The number of subjects enrolled in each study has been included as a placeholder. Revise the numbers to show the number of subjects that the results are based upon.

11. The Adrenal Function section has been expanded to better describe the results of the studies. Include the change from baseline in each treatment group and the difference between treatment and placebo. Based upon the distribution of the data, use the most appropriate values (mean, geometric mean, median) and include the 95% CI for the difference between treatment groups. The number of subjects enrolled in each study has been included as a placeholder. Revise the numbers to show the number of subjects that the results are based upon. We realize this section is very lengthy with a lot of data and we would be open to other presentations of the data, including a table.
12. Although no changes were made to the Cardiac Effects section, there will be labeling recommendations forthcoming.
13. The dose-ranging study FFR20001 should be discussed separately in this section. A table showing the dose-ranging results should be included.
14. Since all SAR studies demonstrated efficacy, the results of one representative study in tabular format is adequate. FFR104861 was chosen as it is most representative of the United States population. Table 4 in the Clinical Trials section should contain the results from Study FFR104861 to represent the SAR data and the results of FFR30002 for PAR. The table should include the change from baseline, difference from placebo with confidence intervals for rTNSS, AM iTNSS, rTOSS, and RQLQ for both studies.

We suggest a table layout similar to the following example to be consistent with a recently approved nasal corticosteroid spray for SAR and PAR; however, we recognize with the two column format, this table layout may not be feasible. We are open to other similar type table formats that can display the data.

Adult SAR and PAR Studies						
Treatment	n	Baseline	Change from Baseline – LS Mean	Difference from Placebo		
				LS Mean	95% CI	p-value
Reflective TNSS						
SAR Study						
Fluticasone Furoate 110 mcg	151	9.6	-3.55	-1.47	-2.01, -0.94	<0.001
Placebo	148	9.9	-2.07			
PAR Study						
Fluticasone Furoate 110 mcg	149	8.6	-2.78	-0.71	-1.20, -0.21	0.005
Placebo	153	8.7	-2.08			
Instantaneous TNSS, AM Score						
SAR Study						
Fluticasone Furoate 110 mcg	151	9.4	-2.90	-1.38	-1.90, -0.85	<0.001
Placebo	148	9.3	-1.53			
PAR Study						
Fluticasone Furoate 110 mcg	149	8.2	-2.45	-0.71	-1.20, -0.21	0.006
Placebo	153	8.3	-1.75			

15. Overall response to therapy was removed because it is not an acceptable validated endpoint.
16. Table 5 in the Clinical Trials section should contain the results from the pediatric SAR and PAR studies for 6-11 year olds. The table should include the change from baseline, difference from placebo and confidence intervals for rTNSS, AM iTNSS, and rTOSS for both studies, similar in format to Table 4.
17. Update the Patient Counseling Information to reflect the Warnings and Precautions section.

Patient Information Sheet

The following are general comments about the Patient Information Sheet:

- Note that there are some comments in brackets within the document.
- What you should know about allergic rhinitis was moved to the end because the most important information should go at the beginning.

- Change “doctor” to “health care provider”.
- Include Warnings and Precautions bullets in consumer friendly language.

Comments on the Carton/container label

The following are specific comments about the carton/container labeling:

- Include the following statements:
 - “Keep out of reach of children”
 - “Do not refrigerate or freeze”
 - “Store with the cap and in an upright position”
- Remove the “ — ” from over the drug product proprietary name.
- Ensure the font size of the letters comprising the established name is at least half as large as the letters comprising the proprietary name. We refer you to 21 CFR 201.10(g)(2) for guidance.
- Relocate the strength (27.5 mcg per spray) to immediately follow the established name. Additionally, increase the prominence of the strength so it is the same size as the proprietary and established names.
- Ensure the net quantity is located away from the expression of strength. Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength.
- Increase the prominence of the statement “FOR INTRANASAL USE ONLY” and remove the word “Spray” preceding the statement.
- Relocate the statement “Shake well before each use” to the principle display panel and increase its prominence.
- Revise the statement “See prescribing information...” to read “Usual Dosage: See prescribing information...”
- Provide a heading for the statement “TRADENAME™ Nasal Spray should be primed...”. A heading will draw attention to this statement and stress its importance.
- Only use “new” for 6 months.

33 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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Ladan Jafari
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 27, 2007

To: Munir Abdullah	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-9318	Phone number: 301-796-1231
Subject: NDA 22-051	

Total Number of Pages Including Cover: 3

Comments: Post-marketing commitments

Document to be mailed: YES NO

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NDA 22-051

Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate nasal spray and we ask that you submit post-marketing study commitments as listed below:

- To conduct a one-year linear growth study in children with fluticasone furoate using a dose that is relevant to the proposed fluticasone furoate nasal spray dose in children. A linear growth study conducted with a formulation other than the nasal formulation may be adequate provided the systemic exposure from that formulation is higher than the systemic exposure from the nasal formulation. Submit a labeling supplement reflecting the results of the study.

Protocol Submission Date:

Study Start Date:

Final Report Submission Date:

- To conduct a 2-year safety study to assess the long-term effects of fluticasone furoate nasal spray on ocular safety, including cataract formation and the development of elevated intraocular pressure/glaucoma. Submit a labeling supplement reflecting the results of the study.

Protocol Submission Date:

Study Start Date:

Final Report Submission Date:

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
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Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 22, 2007

To: Michael Golden

From: Ladan Jafari

Company: GSK

Division of Pulmonary and Allergy
Products

Fax number: 919-483-5381

Fax number: 301-796-9728

Phone number: 919-483-3692

Phone number: 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 6

Comments: CMC Questions

Document to be mailed:

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Dear Mr. Golden:

We are reviewing your NDA for fluticasone furoate nasal spray and we have the following requests for information. We ask that you submit your response by March 26, 2007.

Submit revised Specifications, Stability Protocols and Agreements to comply with the following comments.

1. The statistical analysis of the —month stability data collected for the Process — drug substance batches supports your proposal for the — months retest period. However, you have only submitted 3 month data using the Process — drug substance, which is the current process. In addition you plan additional changes to the manufacturing process identified as Process —. Provide an agreement to continue the ongoing stability studies for the drug substance and report comparative side-by-side data for batches manufactured with Processes ' — and —, in the forthcoming annual reports. In particular, include the following:
 - a. Updated report on the mass imbalance and formation of the “ ——— ——— ” for drug substance batches manufactured with processes ' — and —
 - b. A study report to re-evaluate the proposed acceptance criteria for drug substance and drug product impurities as more process knowledge is gained in manufacturing campaigns. Refer to your agreement provided on page 13 of your submission dated January 26, 2007. Submit results in the annual report before July 2009.

Any further extension of the drug substance retest period should be supported by real time data collected on batches manufactured by a corresponding manufacturing process.

2. Stability data for the drug product supports the requested 24 month expiry period. However, these data do not support recent changes to the container-closure design and the assembly process. Provide an agreement to submit the following in the forthcoming annual reports:
 - a. Additional release and stability data on the drug product batches manufactured with the fully representative commercial process. Provide comparative analyses of the dose performance parameters to the drug product batches used in stability studies and in the clinical trials. To assure consistency of the results assessment, provide data collected by conventional testing methods, and proposed parametric tolerance intervals testing (PTIT) method where available.

- b. Updated results for the current stability studies, with data analysis and graphical summaries. Refer to the 18-months stability data submitted on January 26, 2007, in response to Comment 2f, in the Agency letter dated December 20, 2006. Address noticeably different profiles of the pH changes for different orientations of the container closure, differences in the droplet size distribution (stability trend versus new analytical instrument), and changes in viscosity, observed upon storage.
3. We have evaluated the proposed alternate approaches (conventional and PTIT) for testing of the drug product spray weight (SW), spray content uniformity (SCU) and droplet size distribution (DSD), and have the following comments:
 - a. Limit the testing for the droplet size distribution to the proposed conventional method BC-AM0000/00117662, as specified in the currently proposed drug product specifications. The applicability of the PTIT approach for the droplet size distribution attributes has not been determined by the Agency yet. Refer to the OPS Advisory Committee meeting regarding the PTIT methodology for the inhalation and nasal spray products (October 2005).
 - b. Revise the proposed PTIT methods for testing the spray weight and spray content uniformity to include the revisions outlined below (see comment #4 and #5 in this letter.). State which analytical approach (conventional or PTIT) will be used as the regulatory acceptance criteria for SW and SCU testing. Outline what rules of batch pass or fail will apply during the transitional period when both methods will be in use, e.g., bridging data to support recent drug product changes.
4. Revise the PTIT analysis of Spray Weight to assert the following: with a

value is used. Please refer to the PTI methods for inhalation and nasal spray products that were presented by the Agency in October 2005, at the OPS Advisory Committee meeting (public domain). Note that the mean of life stages is within 90%-110% label claim.

2 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

Ladan Jafari
3/22/2007 08:45:41 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 9, 2007

To: Michael Golden	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-483-5381	Fax number: 301-796-9728
Phone number: 919-483-3692	Phone number: 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 3

Comments: CMC Questions

Document to be mailed: YES NO

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NDA 22-051

Dear Mr. Golden:

We are reviewing your NDA for fluticasone furoate and we have the following requests for information. We ask that you respond by the Close of Business on March 16, 2007.

Provide the levels of impurities _____ and _____
in the drug product batches used for studies listed below:

1-mon dog inhalation: E01B280

3-mon dog inhalation: E02B87

9-mon dog inhalation: E02B240, BVR/H/1001/03

3-mon rat inhalation: E02B87

6-mon rat inhalation: E02B87, E02B139

2-yr rat inhalation: E02B348, E02L2040, E02B347

2-yr mouse inhalation: E02B348, E02L2040, E02B347

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
3/9/2007 01:50:00 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 7, 2007

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Products

VIA: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Products

FROM: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCs Review of Patient Labeling for TRADE NAME (fluticasone furoate), NDA 22-051.

Background and Summary

The sponsor submitted a new NDA for TRADE NAME (fluticasone furoate), a synthetic trifluorinated corticosteroid proposed as a treatment for symptoms of allergic rhinitis, on June 28, 2006.

We have been asked to review Patient Information/Patient Instructions for Use for TRADENAME (fluticasone furoate), under "FDA-Approved Patient Labeling," in section 17.6 of the PI for NDA 22-051. OSE/DMETS recommended against the use of the trade name Allermist, and is currently reviewing the trade name Veramyst. Thus, we have used the term TRADENAME throughout this review.

See the attached Patient Labeling (Patient Information/Patient Instructions for Use) for our recommended revisions to the proposed Patient Information/Patient Instructions for Use submitted for TRADENAME (fluticasone furoate), NDA 22-051. The purpose of patient information is to enhance appropriate use and provide important risk information about

medications. We have simplified the wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information.

Comments and Recommendations

1. The sponsor's approved Patient Instructions for Use for Flonase (fluticasone propionate) Nasal Spray was used as a comparator in our review. Patient Information/Patient Instructions for Use are voluntary for TRADE NAME. The sponsor submitted the proposed TRADE NAME Patient Information/Patient Instructions for Use in a format similar to what we recommend for other types of patient labeling materials (PPIs); however, it is not presented in a question and answer format. We have reorganized some of the content and put the Patient Information/Patient Instructions for Use into the patient-friendly question and answer-type format as described in 21 CFR 208.20 for Medication Guides. Research and experience support the communication effectiveness of the Medication Guide format.
2. Patient Information should provide patients with the most important information up front in order to use the product safely and appropriately. The section "What you should know about allergic rhinitis" is not the most important information for patients to know. The section has therefore been moved to the end of the Patient Information.
3. A list of active and inactive ingredients in TRADE NAME should be in the Patient Information. This has been added to the end of the Patient Information, just before the Patient Instructions for Use.

Comments to the review division are **bolded, underlined and italicized**. We are providing a marked-up and clean copy of the revised document in Word to the review division.

Please call us if you have any questions.

18 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Sharon Mills
2/7/2007 05:45:13 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/8/2007 01:47:24 PM
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 1, 2007

To: Munir Abdullah	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-315-0033	Fax number: 301-796-9728
Phone number: 919-483-9318	Phone number: 301-796-1231
Subject: NDA 22-051	

Total Number of Pages Including Cover: 3

Comments: Device questions

Document to be mailed: YES NO

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NDA 22-051

Dear Dr. Abdullah:

We are reviewing your NDA for fluticasone furoate nasal spray and have the following request for information. We ask that you provide this information by close of business on February 9, 2007.

Submit a summary of the reasons given for the malfunctioning of devices returned to GSK during Phase 3 clinical trials, including those found to be malfunctioning by investigator site personnel at the time of initial priming of the device.

I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager

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/s/

Ladan Jafari
2/1/2007 01:13:40 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: January 29, 2007

To: Michael Golden	From: Ladan Jafari
Company: GSK	Division of Pulmonary and Allergy Products
Fax number: 919-483-5381	Fax number: 301-796-9728
Phone number: 919-483-3692	Phone number: 301-796-1231

Subject: NDA 22-051

Total Number of Pages Including Cover: 4

Comments: Meeting minutes

Document to be mailed: YES NO

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NDA 22-051

Drug: fluticasone furoate nasal spray

Applicant: GSK

Date of teleconference: January 16, 2007

IMTS: 21030

Page 1

GSK Representatives:

Michael Golden, Director, Global CMC New Submissions

Sandra Kite, Director, Global CMC New Submissions

Anna Slater, Director, Intranasal Product Development

Andrew Grant, Director, World Wide Device Technology

Jim Godfrey, Manager, World Wide Device Technology

Division of Pulmonary and Allergy Products (DPAP) Representatives:

Eugenia Nashed, Ph.D., CMC Reviewer

Prasad Peri, Ph.D., ONDQA Assessment Lead

Meiyu Shen, Ph.D., Biometrics Reviewer

Tsong Yi, Ph.D., Biometrics Team Leader

Ladan Jafari, Regulatory Health Project Manager

Background: The Division is currently reviewing GSK's fluticasone furoate nasal spray. The Division sent a telephone facsimile dated December 21, 2006, which contained a list of questions to be addressed by GSK. GSK submitted a meeting request dated January 8, 2007, to discuss the response to the Divisions' questions. GSK also submitted a briefing package dated January 10, 2007, which contained additional information for this teleconference. Specifically, this submission contained information that described improvements that have been made to the device since the NDA was submitted.

The Division initiated the teleconference by stating that this teleconference is scheduled to clarify any issues that GSK has with regard to the information request the Division sent on December 21, 2006. This teleconference is not to be used as a forum to reach any agreements as all issues need to be discussed with the rest of the review team.

- The Division asked that GSK clarify as to why it was necessary to modify the device after the submission of the NDA. The Division notes that our advice to all sponsors is to have all Phase 3 studies with the to-be-marketed formulation.
 - GSK indicated that their intention for modifying the device was to assure patients easy use of the side actuated device and to minimize variability in actuation parameters across different patient groups. GSK had identified two potential risks which were identified as "accidental or premature release of a dose during dose" and "leakage from the pump if the pump is partially actuated".

NDA 22-051

Drug: fluticasone furoate nasal spray

Applicant: GSK

Date of teleconference: January 16, 2007

IMTS: 21030

Page 2

- The Division raised concerns that any change in the device could have a big impact on the device performance (e.g., change in actuation force, plume characterization, droplet size distribution, etc.). The Division asked if GSK had any data to link the old device to the modified one. The Division is particularly interested to see if GSK has any clinical data with the new device.
 - GSK explained that they have obtained analytical data throughout the development of this device, however, they do not have any clinical data with the new device.
- The Division stated that we are very concerned with this new information and need to discuss it further with the rest of the review team. The Division asked that GSK provide a response to the Division's information request as soon as possible.
 - GSK indicated that due to the problems observed with the old device, they thought it is best to modify the device at this point rather than post approval. GSK confirmed that the NDA stability studies are currently being done with the old device.
- The Division stated that GSK should submit any data they have at this point as soon as possible. The Division would discuss the review of any information with the rest of the review team once it is submitted.

Action:

- GSK agreed to provide the responses to the Division's information request by January 26, 2007. GSK also acknowledged the Division's second information request dated January 16, 2007, and indicated that they should be able to respond by the requested time.
- The Division would have to discuss the acceptability and review of the new data once they are received.

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/s/

Ladan Jafari
1/29/2007 08:59:07 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: January 22, 2007

To: Ladan Jafari, Regulatory Project Manager
Division of Pulmonary and Allergy Products

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

Subject: NDA 22-051
DDMAC labeling comments for TRADENAME (fluticasone furoate)
Nasal Spray, 27.5 mcg

Per your consult request dated August 3, 2006, DDMAC has reviewed the proposed product labeling (PI), proposed patient labeling (PPI), and proposed carton and container labeling for fluticasone furoate, and we offer the following comments.

PI

Highlights

1. Per the Physician Labeling Rule, we recommend limiting this section to a half-page in the final product labeling.
2. "The most common adverse reactions were epistaxis and nasal ulceration."

We recommend providing the _____

2 Dosage and Administration

1. "Onset of action has been observed within _____ 24 hours _____" (Please see similar statements under **12.1 Mechanism of Action**, **14 Clinical Studies**, and **17.6 FDA-Approved Patient Labeling**).

Is this statement accurate, as it has major promotional implications?

5.5 Risk of Systemic Corticosteroid Effects

1. "Based on data with another glucocorticoid metabolized by CYP3A4, co-administration with ritonavir is not recommended because of the risk of systemic effects secondary to increased exposure to fluticasone furoate" (emphasis added). (Please see similar statement under **7 Drug Interactions**).

Would it be possible to specify what the other glucocorticoid was?

6.1 Short-term Clinical Studies Experience

1. "_____..." (emphasis added).

This phrase is promotional in tone; we recommend deletion.

6.2 Long-Term Clinical Study Experience

1. This section discusses epistaxis of mild, moderate, and severe intensity.

Would it be possible to provide context for "mild," "moderate," and "severe"? The Adverse Events guidance of the Physician Labeling Rule suggests avoiding vague terms such as the ones above.

7 Drug Interactions

1. "Fluticasone furoate is '_____ cleared..." (emphasis added).

'_____' is promotional in tone; would it be possible to provide context? If not, we recommend deletion.

12.3 Pharmacokinetics – Absorption

1. "...at least 30% of fluticasone furoate is absorbed and then rapidly cleared from plasma" (emphasis added).

"Rapidly" is promotional in tone; would it be possible to provide context? If not, we recommend deletion.

14 Clinical Studies

1. This section discusses total nasal symptoms score (TNSS), reflective total nasal symptoms score (rTNSS), and instantaneous total nasal symptoms score (iTNSS).

Since results for rTNSS and iTNSS are given, should results for TNSS also be presented? While TNSS is a validated scale for this patient population, are rTNSS and iTNSS adequately validated instruments in this patient population to include them in labeling?

2. This section also discusses total ocular symptoms score (TOSS), reflective total ocular symptoms score (rTOSS), and instantaneous total ocular symptoms score (iTOSS).

Since results for rTOSS and iTOSS are given, should results for TOSS also be presented? Are TOSS, rTOSS, and iTOSS adequately validated instruments in this patient population to include them in labeling?

3. Furthermore, this section discusses the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

Is the RQLQ an adequately validated instrument in this patient population to include it in labeling? While the proposed PI states that an absolute difference of ≥ 0.5 in mean change in baseline is considered clinically meaningful improvement, does DPAP consider this a clinically meaningful change?

17.6 FDA-Approved Patient Labeling

1. We recommend referring to DSRCS for their review of this proposed PPI for comments on formatting, order of presentation, consistency, and readability.
2. We recommend revising “doctor” throughout this proposed PPI to “health care provider” to reflect the variety of health care providers (i.e., nurse practitioners, physician assistants) who may treat patients with seasonal and perennial allergic rhinitis.

What you should know about allergic rhinitis

1. “You may also have...an itchy throat; and blocked, itchy ears.”

While a patient with allergic rhinitis may have these symptoms, to include them in this proposed PPI broadens the indication for TRADE NAME, as the Clinical Studies section discusses only nasal and ocular symptoms. Therefore, we recommend deletion of these symptoms.

Important points about TRADE NAME Nasal Spray

1. We recommend including the **Warnings and Precautions** section in consumer-friendly language for consistency with the proposed PI.

Patient's Instructions for Use

1. "TRADE NAME Nasal Spray comes in an amber glass bottle inside an _____ nasal device" (emphasis added).

"_____" is promotional in tone and appears to be an unsubstantiated patient-reported outcome claim. Unless there is adequate evidence to support that TRADE NAME is " _____ ," we recommend deletion.

PPI

(Please see comments under **17.6 FDA-Approved Patient Labeling**).

Carton and Container Labeling

1. For consistency with **17.6 FDA-Approved Patient Labeling** of the proposed PI, we recommend including the following statements:
"Keep out of reach of children."
"Do not refrigerate or freeze."
"Store with the cap and in an upright position."
2. We recommend that the term "NEW!" be used only for six months from the time TRADE NAME is initially marketed; this should be distinguished from the time TRADE NAME is approved.
3. Because the product logo makes an (accurate) representation about TRADE NAME's formulation, we recommend adding appropriate balancing risk information to the proposed carton and container labeling.

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/s/

Michelle Safarik
1/22/2007 10:35:38 AM
DDMAC REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: Ladan Jafari, Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
301-796-1231

DATE
January 18, 2007

IND NO.

NDA NO.
22-051

TYPE OF DOCUMENT
New Correspondence

DATE OF DOCUMENT
January 16, 2007

NAME OF DRUG

Veramyst or _____

PRIORITY CONSIDERATION

S

CLASSIFICATION OF DRUG

Respiratory

DESIRED COMPLETION DATE

February 9, 2007*

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the alternative names proposed by GSK for this application. Your office originally objected to _____. This correspondence contains two additional names for consideration : Veramyst and _____. This is an all electronic submission available in the EDR dated January 16, 2007. We are requesting this consult to be completed by February 9, 2007, because we will have our Wrap-up meeting for this application on February 13, 2007.

PDUFA DATE: April 29, 2007

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 21-251

HFD-570/Division File

HFD-570/RPM

HFD-570/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

Ladan Jafari 301-796-1230

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

5/28/05

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