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APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 23, 2014
From	Theresa M. Michele, MD Director, Division of Nonprescription Clinical Evaluation
Subject	Division Director Summary Review
NDA/BLA #	205,434
Applicant Name	GlaxoSmithKline Consumer Healthcare
Date of Submission	September 23, 2013
PDUFA Goal Date	July 23, 2014
Proprietary Name / Established (USAN) Name	Flonase Allergy Relief/ fluticasone propionate
Dosage Forms / Route of Administration / Strength	Nasal spray/ 50 mcg
Proposed Indication(s)	Temporary relief of symptoms due to hay fever, other respiratory allergies, (b) (4)
Recommended Regulatory Action	Approval (SAR and PAR indications only)

1 INTRODUCTION

GlaxoSmithKline Consumer Healthcare (GSK) submitted this 505(b)(1) new drug application seeking approval for fluticasone propionate aqueous nasal spray (FPANS; proposed trade name Flonase Allergy Relief), at a once daily dose of 50 mg for OTC use for the temporary relief of symptoms due to hay fever, other respiratory allergies, and (b) (4) including nasal congestion, runny nose, itchy, watery eyes, sneezing, and itching of the nose.

FPANS (trade name Flonase) is approved under NDA 20-121 as a prescription product for the management of the nasal symptoms of seasonal and perennial allergic (SAR/PAR) and nonallergic rhinitis (NAR) in adults and pediatric patients 4 years of age and older. The prescription dosage is 200 mcg daily in adults and 100 to 200 mcg daily in pediatric patients.

The indication that the sponsor is proposing "relief of symptoms due to hay fever or other respiratory allergies in adults" is consistent with other OTC products available for treatment of allergic rhinitis. However, the sponsor is also proposing to include "itchy, watery eyes", the claim for the treatment of ocular allergy symptoms, which would represent a new claim for FPANS and the first OTC approval of this claim for a nasal steroid. The current prescription labeling does not include a claim for ocular symptoms. (b) (4)

(b) (4)

GSK's OTC development program for FPANS relies on the safety and efficacy established for the prescription product. To support the new claim for ocular allergy symptoms, GSK submitted the results of three SAR trials, which were not previously reviewed as part of the prescription AR program.

The allergic rhinitis indications of SAR and PAR are considered to be similar for both prescription and OTC use, and consumer ability to understand and use products in this category is well established. (b) (4)

In the initial submission, GSK requested a partial switch for adults only. However, potential safety issues related to growth affects in children are insufficient to warrant the proposed age restriction. At FDA's request, GSK modified their application to request a full switch of all age groups.

This summary review provides an overview of the application with a focus on the new ocular claims (b) (4)

2 BACKGROUND

2.1 Allergic rhinitis (seasonal and perennial)

Allergic rhinitis is a common IgE-mediated inflammatory condition characterized by one or more of the following symptoms: congestion, rhinorrhea (anterior and posterior), sneezing, and itching. Symptoms may significantly affect quality of life, and may be associated with sleep disturbance, fatigue, headache, cognitive impairment. Traditionally, allergic rhinitis is divided into two subsets, SAR and PAR, depending on the aeroallergens involved and persistence of symptoms. Although estimates vary, allergic rhinitis may affect as many as 30-60 million people in the US, including 10-30% of adults and up to 40% of children.[1]

Allergic rhinitis is a well-established OTC indication, with both monograph and NDA OTC products available in a variety of intranasal and oral formulations. These include first and second generation oral antihistamines, oral antihistamine/decongestant combination products, intranasal decongestants, and intranasal cromolyn. In addition, in October 2013, FDA approved the first intranasal corticosteroid as a prescription to OTC switch [Nasacort Allergy 24 HR (triamcinolone acetonide) nasal spray; NDA 20,468]. Professional guidelines for the treatment of adults with allergic rhinitis recommend nasal steroids as first line therapy for moderate-severe disease with or without a second generation antihistamine.

The standard OTC indication language for allergic rhinitis, covering the prescription indications for both SAR and PAR, is derived from the OTC monograph indication for first

[1] The diagnosis and management of rhinitis: An updated practice parameter, Joint Task Force on Practice Parameters for Allergy and Immunology. 2008

generation antihistamines "temporarily relieves runny nose and sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies.[2]" For products that are approved via the NDA pathway, ocular symptoms are considered to be a separate claim for allergic rhinitis, as the primary endpoint for allergic rhinitis trials focuses on total nasal symptom scores. FPANS was approved for SAR and PAR based on nasal symptoms and does not carry a claim for ocular symptoms in the prescription label.

(b) (4)

[2] 21 CFR 341.72 Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Labeling of antihistamine drug products (1992, as amended Dec 6, 2002).

[3] NDA 205,434, Clinical Overview, Section 2.5.4.3.

(b) (4)

(b) (4)

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

Fluticasone propionate, the active component of FPNAS, is a synthetic corticosteroid that is practically insoluble in water. (b) (4)

For OTC use, the proposed configurations contain (b) (4) 60, (b) (4), 120 (b) (4) spray counts. Stability data support the proposed expiration dating period of (b) (4) 24 months for the other configurations. Manufacturing facilities inspections were found acceptable, and there are no outstanding CMC issues.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical data were submitted as part of this application. As the OTC product is the same as the prescription product, there are no new excipients or impurities. There are no outstanding nonclinical pharmacology/toxicology issues.

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

No new clinical pharmacology data were submitted as part of this application. According to the prescription label, FPANS has an absolute bioavailability averaging less than 2%. Fluticasone propionate is metabolized via the cytochrome P450 3A4 pathway. It has demonstrated clinically important drug-drug interactions (DDI) with ritonavir and ketoconazone. In a clinical study of FPANS coadministered with ritonavir, plasma FPANS levels significantly increased accompanied by a significant (86%) decrease in plasma cortisol area under the plasma concentration versus time curve (AUC). When orally inhaled fluticasone propionate was coadministered with ketoconazole, increased fluticasone propionate exposure and reduced plasma cortisol AUC were also observed. These findings will be reflected in the OTC label, with exact language guided by the consumer self-selection study. There are no outstanding clinical pharmacology issues.

6 CLINICAL MICROBIOLOGY

Not applicable.

7 CLINICAL AND STATISTICAL EFFICACY

A large number of clinical trials have been conducted with FPANS, including a number of trials supporting the SAR and PAR, as well as pediatric dosing. This summary will focus on studies related to ocular symptom relief, since new data was submitted to support that claim. The efficacy of FPANS for SAR and PAR has been previously established for the prescription product, so efficacy will be reviewed only briefly here, as the OTC indication is similar. (b) (4)

7.1 Seasonal and perennial allergic rhinitis

According to the prescription label, a total of 13 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials were conducted in the United States in adults and children 4 years of age and older. The trials included 2,633 adults, 440 adolescents (range 12 to 17 years), and 500 children (range 4 to 11 years). Total nasal symptom scores (TNSS), a composite symptom score of rhinorrhea, nasal obstruction, sneezing, and nasal itching, were evaluated over treatment periods of 2 to 24 weeks. Subjects treated with FPANS exhibited significantly greater decreases in TNSS than placebo-treated patients (see product prescription labeling). In studies evaluating onset of action, a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with 200 mcg FPANS, although maximal effect may take several days. This finding supports the statements in the Drug Facts label on onset of action "you may start to feel relief the first day and full effect after several days of regular, once-a-day use".

7.2 Ocular symptoms related to allergic rhinitis

GSK submitted three multicenter, randomized, placebo-controlled SAR trials not previously reviewed by FDA in support of the OTC ocular indication. Two trials were 4-week pivotal trials also including a third active control arm (loratadine 10 mg), and the third was a 2 week supportive trial in adult and adolescent patients with SAR. All 3 trials were conducted in the U.S., with a primary endpoint of daytime eye symptoms score (average of tearing, itchy, red and puffy eyes).

Two of the three trials demonstrated a statistically significant difference from placebo on reflective total ocular symptom scores (rTOSS). The third trial showed borderline significance, but had a larger placebo effect, so is not inconsistent with the other trials. The numerical effect size appears larger in the two 4 weeks trials because ocular symptom scores were measured on a 300 point scale instead of the more common 4 point scale (0-3) typically used. See Table 1 taken from Dr. Stacy Chin's clinical review. Overall, these data are sufficient to support efficacy of the claim that FPNAS relieves allergy symptoms related to itchy, watery eyes.

Table 1: Change from baseline in rTOSS across 3 ocular studies in SAR

	Study FNM30033	Study FNM30034	Study RH01619
Change from baseline (SE): Placebo	-59.9 (5.4)	-72.0 (5.7)	-0.61 (0.08)
Change from baseline (SE): FPANS	-88.7 (5.3)	-86.7 (5.8)	-0.97 (0.08)
Change from baseline (SE): Loratadine	-72.5 (5.4)	-81.4 (5.7)	---
Difference of FPANS from placebo, LS mean change from baseline (95% CI)	-28.8 (-43.2, -14.4)	-14.7 (-29.6, 0.3)	-0.36 (-0.59, -0.13)
p value (FPANS vs placebo)	<0.001	0.055	0.0024

rTOSS=reflective Total Ocular Symptom Score (sum of ocular itching, tearing, and redness)
FPANS=fluticasone propionate nasal spray 200 mcg daily
Loratadine = loratadine 10 mg oral daily
Baseline defined as the average rTOSS over the 7 days (Studies FNM30033 and FNM30034) or the 5 days (Study RH01619) immediately preceding treatment start date.
Change from baseline over Days 1-28 in Studies FNM30033 and FNM30034
Change from baseline over Days1-14 in Study RH01619
Source: Statistical Review by David Hoberman, CSR for FNM30033 and FNM30034 p38

8 SAFETY

The safety profile of FPANS is well-characterized, including a large clinical trial database (primarily in SAR and PAR), and post-marketing data from prescription approval in over 140 countries worldwide and in 13 countries as a non-prescription drug. The U.S. prescription label contains warnings and precautions related to corticosteroid effects, including hypercorticism, HPA axis suppression, immunosuppression, and reduction in growth velocity as well as immediate hypersensitivity reactions. Local effects including

nasal septal perforation, cataracts, increased intraocular pressure, and nasal *Candida albicans* infection were specifically evaluated.

8.1 Safety in clinical trials

GSK provided an analysis of 43 clinical trials conducted to support the prescription NDA. A pooled database from 28 of these trials included more than 8000 patients 4 years of age and older, 4999 of whom received FPANS. Four-hundred-sixty-two (462) patients were exposed to FPANS for 3 months or more. The most common adverse events in the clinical trial program were headache, epistaxis, upper respiratory tract infections, oropharyngeal pain, sinus headache, nasal discomfort, chough, and sinusitis. The sponsor also provided targeted analyses for adverse events of special interest, including HPA axis suppression, growth effects, ocular effects, local nasal adverse events, effect on glucose metabolism, bacterial rhinosinusitis, and potential drug-drug interactions. The most common local effects occurring more often in the FPANS group than placebo were epistaxis, nasal discomfort, and nasal dryness. There were 4 cases of nasal septal perforation, which did not occur in the placebo group. These patients were noted to have underlying risk factors including previous sinus/nasal surgery or cocaine abuse. This is a known effect of nasal steroids, and is unlikely to occur with greater frequency in the OTC setting compared to use in the prescription setting. The OTC package insert contains instruction to aim the spray slightly away from the center of the nose to avoid spraying FPANS directly onto the nasal septum.

Effect on growth

Like other orally inhaled and nasal steroids, the prescription label for FPANS includes a class-specific precaution regarding a potential for the reduction in growth velocity in children, and a clinical trial was completed to evaluate the effect of FPANS on growth. The following summary is taken from the Flonase prescription label.

> *A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients 344 (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray and 52 receiving placebo, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted with placebo (95% confidence interval ranging 348 from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.*

These results are consistent with growth effects demonstrated in dedicated linear growth effects with other marketed nasal steroids, which range from +0.61 cm/year to -1.45 cm/year difference from placebo.

8.2 Consumer studies

GSK conducted five consumer studies, all in adults, in support of the OTC use of FPNAS: two label comprehension studies (one pilot and one pivotal), one self-selection study, and two human factors studies. In addition, the sponsor provided the results of a legacy actual use study. This study was reviewed for safety only given that it was conducted more than 10 years ago (2003) using a previous version of the label, and is not generally applicable to the current label proposed for marketing.

Label comprehension

The pilot label comprehension study enrolled 130 adult subjects with a history of allergy symptoms, including 30 subjects with low literacy. The pivotal study enrolled 607 subjects with and without allergy symptoms, 153 of whom were low literacy. Key messages tested were uses, warnings (do not use to treat asthma, DDI with ritonavir, symptoms not better in 7 days, and new symptoms), and directions for use. Overall, subjects did well on most items tested. In the pilot study, subjects did poorly on the instruction to "stop use and ask a doctor if your symptoms do not get better with 7 days of starting use," for which only 79.2% of normal literacy and 54.8% of low literacy subjects answered correctly. After refinement of the label, subjects in the pivotal label comprehension study did better on this item, with 91.0% [lower bound of the 95% Confidence Interval (LCB) 88.2%] of the normal literacy and 93.5% (LCB 88.3%) of the low literacy population answering correctly after mitigation. (b) (4)

Self selection

GSK submitted a targeted self-selection study focusing on the safety concern related to the DDI with ritonavir, which increases fluticasone levels when taken concomitantly. The study enrolled 399 subjects taking ritonavir for HIV, 92 of whom had low literacy. The self-selection study tested the initial, proposed label warning (b) (4)

These results were used to modify labeling to "Ask a doctor before use if you are taking a medicine for HIV infection (such as ritonavir)," although this warning was not retested. FDA reviewers requested to add the text "(such as ritonavir)" in order to help guide consumers and health care professionals to the DDI of interest since other drugs used to treat HIV are not known to interact with FPANS.

Human factors

The sponsor submitted two human factors studies in healthy adults, one in 40 subjects with normal literacy and one in 15 subjects with low literacy. Over ½ of the normal literacy and 1/3 of the low-literacy populations reported eye symptoms. The primary objectives were to understand the consumer's ability to clean and prime the nasal spray apparatus correctly,

and to demonstrate that the consumer understands how to use the nasal spray, including the correct route of administration of the product (intranasal versus intraocular).

Subjects did very well on the route of administration of the product, with 100% of subjects in both studies correctly administering the product to the nose rather than the eyes, although a single participant accidentally sprayed himself in the face while replacing a nozzle incorrectly after cleaning. Overall, these results address a key safety concern for this product for ocular administration.

Subjects did generally poorly on cleaning and priming of the device, with only 67% (LCB 53%) of normal literacy subjects performing adequately on initial use and 46% (LCB 30.5%) performing adequately 2 weeks later. Low literacy subjects generally did worse on these tasks. However, all subjects improved significantly on these tasks on retry when prompted to consult the package insert. Based on these findings, the sponsor modified labeling to provide additional emphasis on problem areas in instructional materials.

If a consumer were to fail to clean or prime the device, it is possible that the device may fail to deliver a dose or deliver an incorrect (lower) dose. Given that FPANS is a symptomatic therapy and failure to deliver a dose is unlikely to result in significant serious adverse events for consumers, the FDA clinical review teams determined that the concern regarding proper cleaning does not constitute a substantial safety risk for the treatment of SAR and PAR. I concur with this assessment.

8.3 Post-marketing data

As part of this application, post-marketing safety data for FPANS were submitted and reviewed from the following sources: the sponsor's pharmacovigilance database, FDA's Adverse Event Reporting System (FAERS), the World Health Organization (WHO Vigibase), the American Association of Poison Control Centers' National Poison Data System (NPDS), the Drug Abuse Warning Network (DAWN), and the published literature. All of these sources are subject to a number of limitations, primarily due to issues inherent in spontaneous reporting. Overall, the adverse events reported in the post-market setting are consistent with the clinical trials database and the known adverse event profile of nasal steroids.

Ocular safety

One potential concern regarding granting a claim for the treatment of "itchy, watery eyes" with a nasal spray product in the OTC setting is that consumers may spray the product directly into the eyes, either inadvertently or intentionally. GSK identified 35 reports of erroneous application in the eye in the GSK postmarket database of 8041 reports. Of these 35 reports, only 4 involved intentional eye applications, 19 were accidental and 23 were of unclear intention. No reports of erroneous application in the eye were identified in the FAERS database. In addition, two human factors studies demonstrated that 100% of subjects in both the normal and low literacy groups correctly applied the product to the nose rather than the eyes. Overall, these data do not suggest that erroneous application of FPNAS in the eye is likely to be a significant issue in the OTC setting. To help consumers understand proper application of FPNAS, the package insert will contain instructions not to spray into the eyes along with a graphic illustration. In addition, the Drug Facts Label will

contain the following Warning "Only for use in the nose. Do not spray into your eyes or mouth."

9 ADVISORY COMMITTEE MEETING

An advisory committee meeting was not held for this application (b) (4)

10 PEDIATRICS

FPANS is approved in the prescription setting down to age 4 years. Because this product was approved prior to many of the pediatric rules, it was not tested in children younger than 4 years. Prescription dosing for children aged 4-11 years is 100 mcg (1 spray each nostril once daily), but may be increased to 200 mcg (2 sprays in each nostril once daily or 1 spray in each nostril twice daily). FPANS, like other nasal steroid products, contains a precaution regarding potential reduction in growth velocity in children.

Evaluation of the ocular claim by DNCE in collaboration with DPARP determined that this is not, in fact, a new indication, but rather additional language being added to the OTC allergic rhinitis indication. Therefore, PREA is not triggered by this application. The product label will include precautionary language regarding growth in children consistent with the approved label for Nasacort Allergy 24HR (triamcinolone acetonide), which is another recently approved OTC nasal steroid.

11 OTHER RELEVANT REGULATORY ISSUES

11.1 OSI Audits

OSI site inspections were not conducted for this application.

11.2 Financial Disclosure

Financial disclosure statements for investigators in clinical trials for this application were deemed acceptable.

11.3 Environmental Assessment

A categorical exclusion was granted for this application.

12 LABELING

12.1 Proprietary name

The proposed proprietary name, Flonase Allergy Relief, was deemed acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). Of note, the clinical review team considered this name in the context of using the product to treat allergic rhinitis (SAR and PAR). (b) (4)

(b) (4)

12.2 Consumer labeling

GSK submitted Drug Facts label, outer carton labels, immediate container label for the 60 and 120 count bottles, and the package inserts (Quick Start Guide, Question & Answer Book). (b) (4)

Labeling reviews consults were completed by DMEPA, DRISK, and DNRD in addition to labeling reviews completed by the various review disciplines. The Drug Facts label contains warnings not to spray in the eyes, and "Do not use" instructions for children under 4 years of age, to treat asthma, if you have an injury or surgery to your nose that is not fully healed, or if you ever had an allergic reaction to this product or any of the ingredients. The Drug Facts label also contains instructions regarding glaucoma, cataracts, and DDIs with ritonavir, other steroids, and ketoconazole. Specific language regarding growth effects is as follows: "The growth rate of some children may be slower while using this product. Children should use for the shortest amount of time necessary to achieve symptom relief. Talk to your child's doctor if your child needs to use the spray for longer than two months a year." (b) (4)

13 DECISION/ACTION/BENEFIT RISK ASSESSMENT

13.1 Regulatory action

GSK has submitted adequate data to support approval of Flonase Allergy Relief (FPANS) for OTC use for seasonal and perennial allergic rhinitis. (b) (4) As such, this approval will constitute a partial switch of just the SAR and PAR indications from the prescription setting.

13.2 Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Flonase Allergy Relief (FPANS) under the indication "temporarily relieves these symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes." The efficacy and safety of allergic rhinitis indications (SAR and PAR) have been established for prescription use. It is expected that the product would have similar nasal efficacy in the OTC setting, as the allergic rhinitis indication is similar for both prescription and OTC. The additional claim for relief of ocular symptoms is supported by three dedicated ocular symptom trials, which show statistically significant benefit in two trials in the patient reported reflective total ocular symptom score. No new safety signals were identified as part of this application, including evaluation of the safety database of 43 clinical trials and an extensive post-marketing database. The new ocular symptom claim raises the concern of whether consumers would inappropriately spray the product into the eyes in the OTC setting. The limited number of post-marketing reports of erroneous eye

application as well as the human factors studies demonstrating that consumers could correctly apply the product to the nose adequately addresses this concern.

(b) (4)

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

13.4. Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

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