CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 30, 2014
From	Narayan Nair, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	205434
Related INDs **Related Rx NDA**	109805, 28636 20121
Applicant	GlaxoSmithKline Consumer Healthcare ("GSK")
Date of Submission	23-Sep-13
PDUFA Goal Date	23-Jul-13
Proprietary Name / Established (USAN) names	Flonase Allergy Relief/fluticasone nasal spray
Dosage forms / Strength	Spray, metered/50 mcg
Proposed Indication(s)	Temporarily relieves the symptoms of nasal congestion, runny nose, sneezing, itchy nose, itchy and watery eyes due to hay fever, other respiratory allergies, (b) (4)
Recommended:	*Approval pending satisfactory negotiation of labeling*

Table of Contents

1. Introduction 3
2. Background....3
3. CMC/Device....6
4. Nonclinical Pharmacology/Toxicology....7
5. Clinical Pharmacology/Biopharmaceutics 8
6. Clinical Microbiology....9
7. Clinical/Statistical- Efficacy....9
7.1 Seasonal and Perennial Allergic Rhinitis....9
7.2 (b) (4) 10
7.3 Ocular Symptoms....10
8. Safety....13
8.1 Safety in Clinical Trials 14
8.2 Postmarketing Safety 16
8.3 Effect on Growth....19
9. Advisory Committee Meeting 20
10. Pediatrics....20
11. Other Relevant Regulatory Issues....21
12. Labeling 21
12.1 Consumer Studies 22
12.2 DMEPA's Labeling Review 25
12.3 DNRD's Labeling Review....26
13. Recommendations/Risk Benefit Assessment....26
13.1 Recommended Regulatory Action....26
13.2 Risk Benefit Assessment....27
13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies 27
13.4 Recommendation for other Postmarketing Requirements and Commitments....27
13.5 Recommended Comments to Applicant 27
14. Appendix – Recommendations for Drug Facts Labeling 28

1. Introduction

This is a summary review of an application that proposes switching fluticasone propionate aqueous nasal spray (FPANS) metered nasal spray ("Flonase") from prescription (Rx) to over-the counter (OTC) status for individuals 4 years and older. If approved, FPANS will be the second nasal spray containing a glucocorticoid on the OTC market in the United States. The first, Nasacort Allergy 24HR (NDA020468), was approved on October 11, 2013.

Although FPANS and Nasacort share many similarities, in several respects the proposed FPANS OTC label differs from the approved Nasacort label. GSK is seeking the addition of ocular symptoms (b) (4) to the indication.

Relief of ocular symptoms is a new claim for an OTC nasal spray drug label. During the development program, FDA asked GSK to address the potential issue of consumers mistakenly spraying into the eyes rather than the nose. In response, GSK conducted two small human factors studies involving a total of 55 subjects in which no one deliberately sprayed the product in his or her eyes.

A problematic feature of FPANS compared with Nasacort is the drug-drug interaction (DDI) that is noted on Rx labeling: concomitant use with strong CYP 3A4 inhibitors is likely to lead to adrenal suppression. The applicant attempted to address the issue with a self-selection study involving HIV infected subjects taking ritonavir, a strong CYP 3A4 inhibitor. However the results of this study were disappointing with less than half of the subjects making a correct self-selection decision. (See section 12.1, below.)

In the original submission, GSK proposed to keep FPANS a prescription product for children ages 4 to 17 years old (b) (4). FDA expressed concerns about this approach during the development program and a mid-cycle teleconference with the GSK. Subsequently, the GSK amended their submission to include children 4 years and older to align the age range with what is currently in the Rx label.

FDA has already determined that the risk/benefit profile of FPANS is favorable in the prescription setting. This review will focus on changes in the risk/benefit assessment related to availability in the OTC setting.

2. Background

FPANS is approved for treatment of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and children 4 years of age and older. The applicant's proposed OTC dosing regimen is consistent with the dosing regimen on prescription labeling for patients 4 years and older.

Numerous prescription and over-the-counter (OTC) drug therapies are available to treat allergic rhinitis. OTC drug therapies include oral antihistamines, oral/intranasal decongestants, and cromolyn sodium nasal spray. There are no OTC products specifically labeled for nonallergic rhinitis.

Fluticasone propionate is a mid-potency trifluorinated glucocorticoid. FPANS was approved in the United States as a prescription product for allergic rhinitis in adults and children 12 years of age and older on October 19, 1997. The indication was expanded on October 31, 1997 to include pediatric patients 4 years of age and older. The indication was further expanded on December 11, 1998 to patients with perennial non-allergic rhinitis and on May 23, 2002 for as-needed use (PRN).

FPANS is sold for nonprescription use in thirteen countries: UK, Ireland, Denmark, Finland, Sweden, Latvia, Estonia, Slovenia, South Africa, Singapore, China, Australia, and New Zealand. Three countries (the UK, Finland, and Latvia) have labels for 18 years of age and over; the remaining countries restrict labeling to 12 years of age and older. Six countries have labeling that includes eye symptoms, and three countries have language on labeling that suggests nonallergic rhinitis. The earliest nonprescription approvals occurred in 2002 (UK, Australia, and New Zealand). It should be noted however that the experience overseas may not be analogous to the US OTC process. In some nations an interaction with a pharmacist is required to obtain a nonprescription product.

Regulatory interactions in the development phase for FPANS included six advice letters and five meetings:

- May 2001 – This PIND meeting covered general advice about the proposed development program and labeling. At this point, GSK proposed labeling for consumers (b) (4); FDA did not object. Concerns about DDIs and HPA axis suppression were discussed. At this point an actual use study was planned. Subsequent to this meeting, GSK conducted a label comprehension study and an actual use study in 2003. However, they decided to place the development program on hold for business reasons. They re-initiated the development program in 2011.

- Feb 2011 – This PIND meeting covered general advice about the proposed development program and proposed labeling. GSK's labeling was for consumers (b) (4) FDA advised that the proposed (b) (4) was problematic. GSK indicated that the results of their 2003 actual use study (AUS) suggested that noncompliance with dosing instructions was an issue in adolescents. FDA noted that the list of specific triggers "pollen, dust, mold, and pets…." on the proposed label was not warranted as the rhinitis caused by specific allergens had not been studied. FDA expressed concern about drug-drug interactions at this meeting. In addition, the Agency requested that GSK conduct targeted analysis for several safety concerns including HPA axis suppression, effects on growth, effects on bone metabolism, bacterial sinusitis, and perforation of the nasal septum.

- Oct 2012 – At this guidance meeting, GSK sought advice about the content and format of the future NDA submission, and for the first time, proposed expanding the uses of

FPANS to include the symptoms of "itchy, watery, eyes." FDA provided advice about the type of study needed to support the eye indication, FDA also expressed concerns that consumers might put the product in the eye rather than the nose and told GSK that the issue would need to be addressed in label comprehension study (LCS) and either an AUS and/or an AUS/Human Factors Study hybrid. (b) (4) SK was also told again that, to include individual triggers in the label, they would need to provide data to support each trigger. (b) (4) . Finally, GSK was reminded to address the DDI potential of FPANS with potent CYP 3A4 inhibitors.

- May 2013 - At this preNDA meeting, discussion focused on content and format of the NDA submission. FDA again stated its concern with GSK's plan to only include (b) (4) in the OTC label. The sponsor was told that since the prescription product was indicated for 4 years and older it was likely the OTC product would be used by children also. The sponsor stated it would provide a justification (b) (4) in the OTC label.

In addition, to the above meetings a teleconference was held with GSK on March 2014. This meeting was held as a follow-up to the internal FDA mid-cycle meeting and was intended to provide early feedback to GSK regarding their NDA submission.

The NDA contains:

- Clinical data from 10 clinical studies in support of adding ocular symptoms to the OTC indication.
- Consumer studies including two label comprehension studies, a targeted self-selection study, and two human factors studies.
- CMC information to support the introduction of (b) (4) .
- An integrated summary of safety including an analysis of data from 43 clinical studies, postmarketing safety databases, published literature, and behavioral studies.

In writing this review, I considered the following reviews:

- Clinical review by Dr. Steven Osborne, Division of Nonprescription Clinical Evaluation (DNCE)
- Clinical review by Dr. Stacy Chin/Dr. Anthony Durmowicz, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
- Statistical review of the clinical trials by Dr. David Hoberman, Office of Biostatistics
- Statistical review of the LCS by Dr. Scott Komo, Office of Biostatistics
- Social science review by James Stansbury Social Scientist (DNCE)
- Pharmacology/toxicology review by Dr. Wafa Harrouk/Dr. Paul Brown, (DNCE)
- Clinical pharmacology review by Dr. Yunzhao Ren/Dr.Satjit Brar, Division of Clinical Pharmacology-2
- Labeling and proprietary name reviews by Dr. Chi-Ming (Alice) Tu, Division of Medication Error Prevention and Analysis (DMEPA)
- Labeling review by Dr. Elaine Abraham/Dr. Steven Adah, Division of Nonprescription Clinical Evaluation (DNRD)
- Chemistry review by, Dr. Nina Ni, the Office of New Drug Quality Assessment (ONDQA)
- CMC microbiology review by Dr. John Metcalfe

In addition, I relied on a draft Cross-Discipline Team Leader (CDTL) Review authored by Dr. Lesley Furlong, the former CDTL for this NDA until her departure from DNCE on February 28, 2014. Some of the language of her draft has been incorporated into this review with her permission.

3. CMC/Device

This CMC review concluded that this NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

New CMC elements of the submission include a new type of glass bottle ("Type III" in addition to the "Type I" glass bottles currently used for the prescription product) and new spray-count configurations. In addition, the dust cover will be (b) (4) green and carry a debossed logo, compared with the (b) (4) green and logo-less Rx product. The material for the dust cover remains the same. Figure 1 shows the container with dust cover pulled off.

.

Figure 1. Graphic of Product to From Proposed "Quick Start Guide"

Source: Submission Module 1, section 1.14.1.3

Although the container is changed, the drug product itself is the same as the prescription product: a suspension of (b) (4) fluticasone propionate (b) (4) delivered with a metered, atomizing spray pump. GSK cross- referenced information for the drug substance with the approved FPANS Nasal Spray NDA 20121, which has been reviewed and found satisfactory.

GSK proposed configurations of sprays with (b) (4), 60, (b) (4), 120, (b) (4) spray counts. (The prescription product is sold with 120 spray counts and 50 counts) As it requires six actuations to prime the pump, the configurations roughly correspond to (b) (4) 13.5, (b) (4), 28.5, (b) (4) treatment days at the maximum proposed dose of product.

Stability data was provided for the (b) (4), 60, 120, (b) (4) spray configurations and was found to be satisfactory. This included both long term and accelerated stability data packaged in the Type I and the Type III glass bottles. The stability data support the proposed expiration dating period of (b) (4) 24 months for the other actuation configurations when stored at 4 to 30 C (39 to 86 F).

Regarding the facilities involved in this NDA, the Office of Compliance evaluation is still pending and they have not made an overall "Acceptable" recommendation at this time. However, they have given a preliminary indication that there are no outstanding issues which should affect the approvability of this NDA from a GMP standpoint.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data in the submission. The pharmacology/toxicology review team have stated that no Pharmacology/Toxicology issues were identified for this NDA and the NDA can be approved from their perspective.

Prescription labeling indicates that FP is not a known carcinogen or mutagen. FP is labeled as Pregnancy Category C; Rx labeling indicates that FP should be used in pregnancy only if the potential benefit justifies the potential risk. Proposed OTC labeling includes the statement, "if pregnant or breast-feeding, ask a health professional before use."

Comment: The proposed Drug Facts labeling is consistent with Nasacort and labeling of other Pregnancy Category C drugs that are available OTC (for example, ibuprofen, naproxen, and omeprazole).

5. Clinical Pharmacology/Biopharmaceutics

Office of Clinical Pharmacology/Division of Clinical Pharmacology II reviewed this NDA and and found the proposed drug product acceptable from a clinical pharmacology perspective.

The following summary comes from prescription labeling:

> The activity of FPANS is due to the parent drug, which has an absolute bioavailability when delivered by the intranasal route averaging less than 2%. Following intravenous dosing, the terminal elimination half-life is 7.8 hours, and more than 95% of FP is excreted in feces as FP or metabolites. A trial comparing FPANS to 5 and 10 mg of oral FP demonstrated that the FPANS exerts its therapeutic effect on allergic rhinitis topically.
>
> While the bioavailability of FP at recommended doses by the intranasal route is low, systemic exposure to FP can become significant in the present of a strong Cytochrome P450 3A4 inhibitor. In a drug-drug interaction (DDI) study with the Cytochrome P450 3A4 inhibitor ritonavir, the Cmax of FP increased approximately 30-fold and the AUC increased approximately 400-fold when administered with ritonavir. This resulted in an 86% decrease in the AUC of plasma cortisol. FP has also been shown to significantly interact with ketoconazole, another Cytochrome P450 3A4 inhibitor.
>
> FP was not studied in hepatic or renal impairment.

The Clinical Pharmacology Review address issues related to effects on hypothalamic-pituitary-adrenal (HPA) axis, effects on the growth rate in children and drug/drug interactions. They conclude that FPANS does not suppress the HPA axis. They also note that there were no statistical differences in HPA axis suppression in children. They recommend longer term treatment in children should be avoided. With regard to drug/drug interactions they note the above mentioned interaction with ritonavir and ketoconazole. They suggest this be addressed in labeling.

Comment: The interactions with ritonavir and ketoconazole are concerning because concomitant use may put the user at risk adrenal suppression. In the prescription setting, the

prescriber can screen for drug/drug interactions and avoid complications. In the OTC setting, the burden of recognizing a potential drug/drug interaction falls to the consumer.

It is not clear if the risk of adrenal suppression could occur with other CYP 3A4 inhibitors. However, existing data suggest that the risk of HPA axis suppression is increased in the presence of strong CYP 3A4 inhibitors. Chronic users of potent CYP 3A4 inhibitors may experience significant systemic effects from concurrent use of FPANS. The applicant proposes to address this in labeling by including a (b) (4) *warning "if you are taking medicine for HIV infection" and "ask a doctor before use if you are taking ketoconazole pills." While this labeling may alleviate the concern, this issue is problematic in that other CYP 3A4 inhibitors that have not been studied may have significant effects as well. This would only be an issue if these medications are taken chronically concurrently with FPANS.*

Should FPANS be approved for OTC use, I recommend adding general language advising the consumer to "remember to tell your doctor about all the medicines you take, including this one". This language appears on the Nasacort Allergy 24HR labeling, too. While it is a physician's responsibility to manage (or prevent) acute adrenal crisis, the consumer should tell the doctor if he or she is taking this medicine so that the doctor is aware of the possibility of adrenal suppression.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The proposed OTC indication is to "temporarily relieve the following symptoms due to hay fever, other respiratory allergies (b) (4) nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes". Efficacy for the nasal symptoms of seasonal and perennial allergic rhinitis for adults and pediatric patients 4 years of age and older was established in the clinical program leading to Rx approval and was not resubmitted for this NDA. Each component of the efficacy claim is discussed below.

7.1 Seasonal and Perennial Allergic Rhinitis

Clinical trials have shown that FPANS is effective at relieving the nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). These studies utilized the total nasal symptom score (TNSS) as the primary endpoint. TNSS includes the symptoms rhinorrhea, nasal obstruction sneezing, and nasal itching. Efficacy for rhinitis has been demonstrated for adults and children four years of age and older in 13 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials. These trials included 2,633 adults as well as 440 adolescents aged 12 to 17 years, and 500 children aged 4 to 11 years.

Comment: The efficacy data supporting the use of FPANS in both SAR and PAR is robust and has been thoroughly reviewed previously. Allergic rhinitis has long been recognized as a

condition appropriate for OTC use. I do not expect OTC use of FPANS to alter the efficacy in a significant manner.

(b) (4)

(b) (4)

7.3 Ocular Symptoms

In the current submission, the applicant proposed adding labeling language addressing ocular symptoms, specifically, temporary relief of "itchy, watery eyes." Several oral OTC products (including monograph, and NDA drugs) indicated for allergic rhinitis contain similar language in their DFL. Oral antihistamines that were approved under an NDA evaluated ocular symptoms in their Phase 3 trials as part of the symptoms score which served as their primary endpoint. However, intranasal corticosteroid products work predominantly though local action on the nasal passages. The primary endpoints in their Phase 3 trials were the TNSS which did not evaluate ocular symptoms. To obtain the ocular claim GSK has submitted 3 studies evaluating ocular symptoms using the Total Ocular Symptoms Score (TOSS) These studies

were designated as FNM30033, FNM30034, and RH01619. The salient features of the studies are briefly discussed below. For additional details please see Dr. Chin's review.

FNM3033 and FNM30034

These trials were designed to assess the efficacy of FPANS on relief of ocular symptoms from allergic rhinitis. The studies were randomized, double-blind, double-dummy, parallel group studies comparing FPANS 200 mcg daily to placebo, and oral loratadine 10 mg as an active comparator. The studies were conducted in 2001 and included subjects 12 years and older with a minimum of a 2 year history of SAR. The study began with a 7-14 day baseline period during which ocular symptoms of itching tearing and redness were assessed daily using a 100 point visual analog scale. The TOSS was derived from a sum of the individual ocular symptom scores. The TOSS could range from a minimum of 0 to a maximum of 300 (100 for each symptom of redness, itching and tearing).

After the baseline period, subjects with moderate and severe ocular symptoms were randomized to one of the following groups:

- FPANS 200 mcg + placebo capsule,
- placebo nasal spray + placebo capsule
- placebo nasal spray + loratadine 10 mg.

The medication was taken daily in the morning for 28 days, and each evening subjects recorded the severity of their ocular symptoms using the VAS score. Subjects met with investigators at screening and at Days 1, 14, and 28. At the final visit, subjects self-assessed their overall treatment response. The subjects rated their response using a 7-point categorical scale, ranging from significant improvement (1) to significant worsening (7).

The primary endpoint was the mean change in baseline in rTOSS (rTOSS is reflective TOSS, the TOSS score over a particular time period rather than a single point in time) averaged over days 1-28 for FPANS vs. placebo. Study FNM 3033 enrolled 471 subjects among 14 centers in the United States. Study FNM 3034 randomized 482 subjects among 14 centers. Both studies had high completion rates.

Table 1 displays the results from the trials. As seen in the table, both trials revealed an improvement in the primary endpoint.

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: From Dr. Chin's DPARP Review/Statistical Review by David Hoberman, CSR for FNM30033 and FNM30034

Comment: It should be noted that the P -value for FNM30034 was 0.055. This is likely due to the large effect seen in the placebo group during week 4 of this study. Dr. Hoberman notes in his statistical review, the mean change from baseline in the FPANS group in both studies was nearly identical (-88.7 vs -86.7). However, this was offset by the greater placebo response in Study in FMN30034 (-59.9 vs -72.0) leading to a borderline P-value. He also points out the P-values for itching, tearing, and redness were 0.032, 0.210, and 0.037, respectively when averaged over days 1-28. This suggests that the trial FNM30034 does demonstrate efficacy in relieving ocular symptoms from SAR although the results were less impressive than trial FNM30033.

Study RH01619

This was a 2-week randomized, double-blind, parallel group, multi-center trial designed to demonstrate the superiority of FPANS 200 mcg daily to placebo in relieving ocular symptoms associated with allergic rhinitis. It included patients older than 12 years of age with minimum of a 2 year history of SAR with moderate to severe symptoms, and a positive skin test to Mountain Cedar. Patients were randomized to receive FPANS 200mcg daily for 2 weeks. The primary endpoint was the mean change from baseline in subject-rated rTOSS compared to placebo over the entire treatment period of 2 weeks. The point scale used to derive the rTOSS was different from the pivotal trials in that it ranged from 0-3 for ocular symptoms. The

maximum TOSS score in this trial was 9 as opposed to 300 in the pivotal trials. The trial met its primary endpoint as can be seen in Table 1.

Additional Data
In addition to the 3 clinical trials described above, the applicant submitted data pooled from seven pooled studies (FLN-401, FLN-402, FLN-411,FLN-412, FLTA4004, FLTA4006, and FLTA4024).
This data was limited in its applicability in assessing ocular symptoms. The data was originally submitted to support the original NDA, hence it focused on nasal symptoms. Furthermore the methodology used to score ocular symptoms differed from the current standard. For these reasons this data was not formally evaluated by DPARP or DNCE.

Comment: DPARP reviewed the 2 pivotal and 1 supportive studies and concluded that the data sufficed to support the ocular claim. They recommended that the relief of eye symptoms be listed under "Uses" in the OTC Drug Facts Label under the broader indication of "hay fever and other respiratory allergies." After reviewing the data submitted by the applicant, Dr. Chin's and Dr. Hobermans's reviews, I concur with DPARP's conclusion and believe that the applicant has demonstrated sufficient evidence to support an ocular claim for inclusion in the label. While it is true the pivotal studies only enrolled subjects with SAR, with regard to ocular symptoms PAR and SAR share similar pathophysiology. Thus, it is reasonable to extend this claim for both SAR and PAR. Furthermore, children aged 4 years old to less than 12 would be expected to respond similarly to ages 12 and greater.
Another issue during the review cycle that arose was a safety concern that patients would misinterpret labeling relating ocular symptoms and spray the product in their eyes. However, safety data does not support this (see the review of Human Factors Study).
Previously, the Agency has viewed the ocular symptoms associated with allergic rhinitis as a separate indication. For other nasal steroids that have shown improvement in eye symptoms of allergic rhinitis, this information has been included only in the clinical studies section of prescription drug labeling. However, after internal discussion among DPARP and DNCE, this thinking has shifted. Currently, the ocular symptoms as proposed in the applicant's DFL for OTC FPANS is considered a claim rather than a separate indication. This approach reflects the pathophysiology of allergic rhinitis. The ocular symptoms associated with SAR and PAR do not represent a distinct disease entity but rather are part of the constellation of symptoms related to allergic rhinitis and are recognized by consumers as such.

8. Safety

The safety concerns for FPANS fall under two categories: local effects on the nasal passages and systemic effects related to exposure to corticosteroids. FDA has previously determined that the risk/benefit profile of FPANS is favorable for Rx marketing. The issue for the NDA submission is whether the absence of a learned intermediary shifts the risk/benefit profile to an unacceptable degree.

The occurrence of local adverse effects (AEs), such as nosebleeds and nasal perforations, will not likely be impacted by the absence of a prescriber. The prescriber would not play a role in preventing these types of events and management of these AEs is reactive. Thus, switching FPANS to OTC should not affect occurrence nor severity of local AEs to a significant degree.

However, the systemic effects of FPANS are more relevant in the context of OTC availability. The potential systemic effects (class effects) that appear on Rx current labeling include:

- Glaucoma and cataracts
- Immunosuppression
- Hypothalamic-pituitary adrenal axis effects
- Effect on growth in children
-

Consumers may not be readily familiar with these types of AE's as they are not commonly seen in OTC medications. Among these potential class effects, only the effect on growth in children has been demonstrated in the clinical trial database for FPANS. Rx labeling notes that the use of intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. In a clinical trial that enrolled children 3 to 9 years of age who used FPANS or placebo for a year, the point estimate for height velocity was 0.14 cm/year lower in the FPANS group (n=56) compared with the placebo group (n=52). However, this difference was not statistically significant and the dosing for FPANS was 200 mcg/day, the maximum labeled dose in this age range. The study did not detect clinically relevant changes in HPA axis function or bone mineral density as assessed by 12-hour urinary cortisol excretion and dual energy x-ray absorptiometry.

Concerns about the effect of intranasal corticosteroids on growth in the pedicatric population are not new. Nasacort was approved for OTC use in October 2013 as and has a similar effect on growth. After review and discussion at an Advisory Committee, FDA approved Nasacort with labeling for children. Ultimately, FDA decided that the growth issue could be managed adequately in the consumer setting with appropriate labeling. The growth issues are the same for FPANS. I believe the precedent established with Nasacort should be followed with FPANS and the labeling should be similar.

The following sections briefly summarize the safety findings. The reader is referred to Dr. Chin's and Dr. Osborne's reviews for more detailed safety information.

8.1 Safety in Clinical Trials

The applicant provided an analysis of safety information from 43 clinical trials conducted to support the original NDA. Data from 28 of these trials was pooled and consisted of 4999 patients over 4 years of age who received FPANS. For three of these studies, the duration of treatment was 26 weeks or more. The fifteen remaining trials were designed to address various safety issues such as growth velocity, ocular effects, oral effects and HPA axis suppression.

Table 2 displays the safety data related to local nasal effects derived from the 28 pooled safety studies.

Table 2- Local nasal effects: Pooled safety studies

	Placebo	FPANS
N	3160	4999[a]
Epistaxis	122 (3.9)	321 (6.4)
Nasal discomfort	57 (1.8)	114 (2.3)
Nasal dryness	17 (0.5)	42 (0.8)
Nasal congestion	17 (0.5)	21 (0.4)
Nasal ulcer	1 (<0.1)	8 (0.2)
Nasal septum ulceration	1 (<0.1)	4 (<0.1)
Nasal septum perforation	0	4 (<0.1)
Nasal edema	1 (<0.1)	2 (<0.1)
Nasal mucosal disorder	1 (<0.1)	2 (<0.1)
Nasal inflammation	0	2 (<0.1)
Nasal abscess	0	1 (<0.1)
Nasal candidiasis	0	1 (<0.1)
Application site pain	0	1 (<0.1)
Nasal cyst	0	1 (<0.1)
Nasal polyps	3 (<0.1)	1 (<0.1)
Nasal mucosal discoloration	1 (0.1)	1 (<0.1)
Nasal turbinate hypertrophy	1 (<0.1)	0

Source: ISS Table 14.5.5.1
[a] Includes doses less than 200 mcg/day

Comment: As seen in the table, patients treated with FPANS demonstrated a higher rate of epistaxis, nasal septum ulcers/ulcerations, and nasal septum perforations compared to those treated with placebo. Local nasal effects can be addressed in labeling. The cases of nasal septal perforation are concerning. However the case histories of these subjects revealed underlying risk factors which suggest that FPANS was not the causative agent. These risk factors included previous nasal surgery and cocaine abuse. It is notable that no nasal perforations were seen in the non-pooled studies.

Ocular effects and risk of immunosuppression have also been of concern with the use of corticosteroids. The prescription FPANS label mentions these potential AE's. The pooled clinical studies did not demonstrate significant number of cases of cataracts, or glaucoma in the FPANS group versus placebo. Systemic immunosuppression as manifested by worsening or reactivated serious infections was not seen in either the pooled or non-pooled safety studies. Five cases of oropharyngeal fungal infections in FPANS treated subjects were seen in 5 of the non-pooled sties.
Comment: Neither the pooled nor non-pooled clinical trials reveal a significant safety signal related to systemic immunosuppression. There were small numbers of oropharyngeal candidiasis but these did not occur in frequency or severity to a degree that alters the risk/benefit profile in an OTC setting.

Corticosteroids have potential to affect the hypothalamic-pituitary adrenal (HPA) axis. There were no treatment related adverse events related to effects on the HPA axis in the pooled studies. GSK also conducted nine non-pooled safety studies assessing adrenal suppression. Four of these studies assessed the HPA axis by adrenal stimulation, the remaining five studies by morning plasma and/or urinary cortisol. The exposure of FPANS did not have clinically significant effect on HPA axis function.

Comment: This data demonstrates that the systemic effects of FPANS are minimal when taken as directed. However, as previously discussed, when FPANS is co-administered with ritonavir, systemic exposure increases dramatically.

Table 3 displays the TEAEs of special interest including patients who experienced sinusitis. It shows that with regard to these AEs rates between FPANS and placebo are comparable.

Table 3. TEAEs of special interest: 28 pooled studies

	Placebo (N=3,160) n (%)	**All FPANS (N=4,999) n (%)**
TEAE	82 (2.6%)	119 (2.4%)
HPA Axis Suppression		
Blood cortisol increased	1(<0.1%)	0
Glucose Metabolism		
Hyperglycaemia	0	1(<0.1%)
Fungal Infection (overall)	10 (0.3%)	18 (0.4%)
Nasal candidiasis	0	1 (<0.1%)
Oral candidiasis	1 (<0.1%)	0
Oropharyngeal candidiasis	0	3(<0.1%)
Eye Disease (all)[2]	2 (<0.1%)	3 (<0.1%)
Cataract	0	2 (<0.1%)
Cataract subcapsular	1 (<0.1%)	0
Lenticularopacities	1(<0.1%)	1(<0.1%)
Bacterial Rhinosinusitis (all)	72 (2.3%)	95 (1.9%)
Acute sinusitis	7 (0.2%)	5 (0.1%)
Chronic sinusitis	1 (<0.1%)	0
Sinusitis	64(2.0%)	91(1.8%)
Nasal septum perforation	0	4 (<0.1%)

[1] Includes FPANS 200 mcg QD and 100 mcg BID, 2 different regimens both equal in total mcg FPANS
[2] There were no occurrences of glaucoma
Source: Dr. Osborne's review/Sponsor's submission ISS Section 14, Table 14.5.4.1

8.2 Postmarketing Safety

The applicant provided safety data from the following sources:

- Sponsor's Pharmacovigilance Database (OCEANS)
- FDA AERS
- World Health Organization (WHO)
- Drug Abuse Warning Network (DAWN)
- National Poison Data System (NPDS)
- 2 large epidemiology studies

GSK estimates the cumulative exposure to FPANS to be 31.2 million patient years. From 2008-2012 approximately 10.5% of the exposure was OTC in countries where it is approved in that setting.

Sponsor's Pharmacovigilance Database (OCEANS)

The OCEANS database contained 8041 spontaneous AE reports with the use of intranasal fluticasone propionate from 1996 to the end of 2012. This includes AEs related to the use of fluticasone propionate nasal drops (although these are used much less frequently than the nasal spray). Of the 8041 reports, 726 were serious and 203 were related to OTC use. The largest number of reports was related to local nasal effects. The second largest category of AEs was related to the drug being ineffective, or product quality issues.

Table 4 shows AEs of interest from the GSK database

Table 4 AEs from GSK pharmacovigilance database 1994-2012

Event (Preferred Term)	Number of PTs
Epistaxis	1101
Nasal discomfort	358
Glaucoma or Intraocular pressure increased	118
Candidiasis	100
HPA Axis Disorders / Growth Delay	75 (53 and 22 respectively)
Cataract	83
Nasal Ulcer or ulceration	72
Nasal Septum Perforation	68
Blood Glucose Increased	30
Growth Retardation	22

Source: Dr. Osborne's review/sponsor's Postmarketing data, p.18

With regard to the cases of epistaxis nearly all of them (95.5%) were non-serious. Of the serious cases of epistaxis, half likely were due to co-morbid conditions. Nasal septum perforation was also seen in the GSK database but nearly a third of these had underlying conditions which suggest the perforation was not caused by FPANS. There were AEs related to glaucoma and cataracts. While many of these reports provided limited information, there were a small number of cases where it appeared the cataracts and glaucoma were related to administration of FPANS. There were 53 reports of HPA axis disorders. Twenty-nine of these 53 reports were confounded as the patients were using other corticosteroid medications or were taking ritonavir in addition to FPANS. Three reports were from patients who likely

had an underlying medical condition which caused the HPA axis disorder. There were nine reports of Cushing's syndrome and three of these were considered serious.

Comment: Spontaneous adverse event reports can be difficult to interpret. Often times the details provided are scant and causality is challenging to establish. I reviewed Dr. Osborne's description of the serious cases of most concern and reviewed the information GSK provided. AEs related to local nasal effects or ocular conditions can be addressed in labeling. Of the AEs related to HPA axis disorders the three cases, the three cases involving ritonavir are most troubling. As previously discussed ritonavir dramatically increases the amount of FPANS absorbed. This issue should be able to be addressed with careful labeling.

WHO Database

The data submitted related to WHO does not provide any new safety information. The AEs in this data are already captured in the proposed label.

National Poison Data System

No deaths have been reported to US poison control centers related to the use or misuse of FPANS.

Drug Abuse Warning Network (DAWN)

The DAWN is a public health surveillance system that monitors hospital visits to US emergency departments that are deemed related to drug use. This data revealed a few cases of emergency room visits by individuals using FPANS. Since up to 22 drugs can be listed related to each visit, it is not clear what role, if any, FPANS played.

Epidemiology Studies

The applicant submitted data from two epidemiology studies:

- GSK study: WWE113666/WE50001 (study report February 15, 2006)
- GSK study WWE111983/WE50002 (study report April 19, 2010)

These studies were designed to determine rates of steroid related AEs among patients using FPANS compared to patients using other intranasal steroids (INS). WWE113666/WE50001 revealed slightly higher rates of nasal septum perforation, sinusitis and abscess. Patients taking FPANS were less likely to be diagnosed with cataracts versus users of other INS. WWE111983/WE50002 suggested a weak association with higher rates of chronic sinusitis but otherwise did not reveal significant differences in the AE profile for FPANS as opposed to other INS.

Comment: The higher rate of septal perforation was modest and not to a degree that would impact approval. WWE111983/WE50002 had a higher rate of chronic sinusitis in the FPANS cohort. This may have been confounded as it seemed that this group was prescribed FPANS after multiple acute events suggesting the patients had an underlying condition prior to treatment initiation.

8.3 Effect on Growth

The effect of intranasal steroids on growth in pediatric patients has long been recognized by the Agency. Following a 1998 Advisory Committee meeting addressing this topic all intranasal steroids have labeling mentioning a potential reduction in growth velocity. The current label for prescription FPANS states in the Pediatric Use section:

> Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including FLONASE Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

The effect of FPANS was evaluated in Study FNM400017. This study was conducted as part of a postmarketing commitment in 150 prepubescent children age 3.5 to 9.5 year of age with PAR. The primary endpoint was growth velocity over one year of treatment. A total of 56 patients received FPANS and were compared to 52 patients who received placebo. The following table shows the results of FNM40007 and growth studies related to other INS.

Table 5- Growth Study Results of Intranasal Corticosteroids

Drug	Age (years)	N	Dose (mcg/day)	Δ from placebo (cm/year)	95% CI
Beclomethasone dipropionate[1,2]	6-9.5	100	336	-1.45	not available*
Triamcinolone acetonide aqueous	3-9	299	110	-0.45	- 0.78, -0.11
Budesonide[3]	4-8	229	64	-0.25	-0.59, 0.08
Fluticasone furoate[4]	5-8.5	474	110	-0.27	-0.48, -0.06
Fluticasone propionate[5]	3-9	150	200	-0.14	-0.54, 0.27
Mometasone furoate[2,6]	3-9	82	100	+0.61	0.11,1.10

* p value < 0.01
[1] Beconase AQ prescribing information accessed May 6, 2013
[2] Slide 13, "Lessons Learned from Growth Studies with Orally Inhaled and Intranasal Corticosteroids" Joint Dermatologic and Ophthalmic Drugs Advisory Committee with Nonprescription Drugs Advisory Committee, March 24, 2005. Website: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4099S1_04_FDA-Wilson_files/frame.htm
[3] Rhinocort Aqua prescribing information accessed May 6, 2013
[4] Veramyst prescribing information accessed May 6, 2013
[5] FPANS prescribing information accessed May 6, 2013
[6] Nasonex prescribing information accessed May 6, 2013
Source: Dr. Chin's review/ NDA 20-468, primary medical officer review by Sofia Chaudhry, MD

In addition, to the information from FNM40007, GSK submitted postmarketing data that indicated 22 reports of growth retardation. Sixteen of these reports either lacked enough detail to assess causality or were confounded with other medical conditions. The remainder of these reports were from consumers.

Comment: As seen in the table above, FPANS appears to have less effect on growth velocity than Triamcinolone acetonide (Nasacort 24 hour Allergy) which has been approved for OTC use in children 2 years and older. The study FNM4007 was conducted prior to the release of FDA Guidance addressing the evaluation of the INS effects on growth in children. Thus, it may be underpowered and lacks other features desirable for this type of trial. However, the data has been evaluated by FDA and found to be robust. Initially, GSK stated that the results from a clinical study of intranasal fluticasone furoate (FFNS) led it to request labeling for ages 18 and older for this NDA. They have since amended their application and requested approval to ages 4 years and older. FFNS is a distinct molecular entity with different properties than FPANS and the results of studies involving FFNS cannot automatically be extrapolated to FPANS. After reviewing the data, I believe there is no evidence that FPANS affects growth velocity to a larger degree than Triamcinolone acetonide. I believe the precedent established with Triamcinolone acetonide intranasal spray can be followed with FPANS and this issue can be addressed with labeling.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

This application does not trigger the Pediatric Research Equity Act (PREA) since there are not any new indications in the submission. The language in the proposed label related to the ocular claim is not viewed as a new indication but rather a claim.

Although FPANS has been studied down to age 2 as part of a fulfilled written request (WR) the prescription product is labeled only down to 4 years of age. The WR study[1] was a six-week HPA axis study in approximately 33 patients between 24 and 47 months of age. The

[1] Study FMN40183 submitted to NDA 20121 on 27-Sep-2001

study did not collect efficacy data. Prescription labeling notes that 650 patients aged 4 to 11 and 400 patients aged 12 to 17 years were studied in U.S. clinical trials with FPANS.

On 1/7/14, the applicant submitted an updated pediatric plan. They requested a waiver of pediatric studies because of the small, but statistically significant observed effect on the use of corticosteroids in general and fluticasone furoate sprays in particular on growth. They propose to label OTC FPANS for use in (b) (4) years and older. DNCE advised GSK that this was not optimal and suggested they extend the age to 4 years and older to align with the current prescription label. Subsequent to the mid-cycle meeting, GSK agreed and amended their application to extend the age to 4 years and older.

Comment: I concur with labeling OTC FPANS for ages 4 years and older. As Dr. Osborne notes in his review, approximately 19.38% of prescriptions for FPANS were written for ages 0-11, and 8.99% for ages 12-17. Limited the age range for OTC FPANS would likely lead to confusion among consumers and off-label use with possible incorrect dosing. The growth velocity issue can be addressed with labeling as it was with the approval of Nasacort. It is reasonable to extend the ocular claim to (b) (4) age range as there is no reason to suspect FPANS would be less efficacious for this age range.

11. Other Relevant Regulatory Issues

The application includes a signed debarment certificate stating that no one involved in the development program has been debarred.

Evaluation of financial interests revealed 3 investigators who had significant equity interests in three different studies supporting the ocular indication. The three investigators enrolled (b) (6) of subjects in the respective trials. The applicant performed an impact analysis and found that the results of the study were not impacted by the data generated by the subjects. The investigators with equity interest in the clinical studies are listed below:

- Study (b) (6), (b) (6) subjects subjects, (b) (6) indication)
- Study (b) (6), (b) (6) subjects (b) (6)
- Study (b) (6) 1, (b) (6) subjects. (b) (6)

DPARP determined that site inspections were unnecessary for the ocular claim, noting that two of the pivotal trials were conducted over 10 years ago.

12. Labeling

The proposed name is Flonase Allergy Relief, which DMEPA found acceptable. DPARP recommended against including the language that attempts to capture (b) (4) (b) (4).

Comment: I concur with all of these recommendations.

Data support that the risk of HPA axis suppression is increased in the presence of strong CYP 3A4 inhibitors. Chronic users of potent CYP 3A4 inhibitors who also use FPANS may experience a substantial increase in systemic exposure to triamcinolone (for example, a 300-fold increase in AUC for triamcinolone when used with ritonavir). The applicant proposes to address this in labeling by including a [redacted] (b) (4) " warning "if you are taking medicine for HIV infection" and "ask a doctor before use if you are taking ketoconazole pills." One drawback to this approach is FPANS does not interact with all the HIV medications. [redacted] (b) (4)

Comment: I favor the revised language. As noted there were three individuals in the postmarketing data who experienced HPA axis related AE while taking FPANS with ritonavir.

The DFL for OTC Nasacort contains language advising the consumer to "remember to tell your doctor about all the medicines you take, including this one". It would be prudent to add this type of language to the FPANS DFL to help alleviate drug-drug interactions.

The following subsections summarize the consumer studies and the DNRD and the DMEPA labeling reviews. Consumer studies included two label comprehension studies (LCS), a self-selection study (SSS), and two human factors studies (HFS), all reviewed by the FDA Social Scientist, James Stansbury. The Drug Facts label (DFL), consumer package insert (CPI), the principal display panel (PDP), and other carton labeling were reviewed in detail by the DNRD and DMEPA review teams.

12.1 Consumer Studies

12.1.1 RH01305 Pilot Label Comprehension Study (16Aug2011-19Aug2011)

This pilot study was performed at four market research sites in the United States, and tested aspects of Uses, Warnings, and Directions on the proposed DFL prior to fielding a larger study. Subjects were 18 years of age and older with a history of nasal allergy symptoms. A total of 130 subjects were interviewed. The applicant concluded that the tested messages were reasonably well understood, and no changes were made to the DFL before performing the pivotal LCS. Low literate respondents did not score well when asked what to do if the product was ineffective in reducing their symptoms. Low literate respondents also tested poorly on the directions to consult a physician about continued use after 3 months of daily use and the direction to use the product once a day.

12.1.2 RH01318 Targeted Label Comprehension Study (27Aug2012-7Sep2012)

This study was a multi-site LCS study performed at nine market research facilities in the United States. Two sites exclusively recruited low-literate subjects. A total of 607 subjects, including 153 low literate subjects, were evaluable. All subjects were over 18 years of age.

The primary objects were to measure consumers' understanding of the following elements of Drug Facts labeling:

1. Warnings: Stop use and ask a doctor if
   - Your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.
   - You get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.

2. Directions
   - 12 years of age and older, Week 1, use 2 sprays in each nostril once daily
   - 12 years of age and older, Week 2 onwards, use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms

Approximately 25.2% of subjects tested as low literate; 53.9% had a history of nasal allergies; 17.7% had previously used FPANS in the past year.

Results are reported as the lower bound of the 95% confidence interval. Dosing directions were well understood at 98.9% at week 1 and week 2. Stop use and ask a doctor if you get new symptoms was well understood at 92.8%. The warning to stop use and ask a doctor if your symptoms do not get better within 7 days of starting use had a comprehension rate of 88.2%.

The low literate population performed well: 95.4% and 93.4% understood dosing directions for week 1 and week 2; 88.3% understood the stop use and ask a doctor if symptoms did not get better within 7 days of starting use; 78.3% understood the stop use and ask a doctor if you get new symptoms.

Comment: Subjects showed a reasonable understanding of the dosing directions and the stop use directions in this LCS. The performance of low literate consumers was lower, but not unexpected for this type of study.

12.1.3 RH01442 Targeted Self-Selection Study (05Dec2012-05Feb2012)

This was a multicenter single visit study conducted in HIV clinics in the United States. The objective of the study was to show that subjects who are taking ritonavir make a correct self-selection decision. Heeding this warning is important because subjects who concurrently use both medications will experience a markedly elevated serum concentration of FPANS which will in turn markedly reduce serum cortisol concentrations.

Three hundred ninety-nine subjects were included in the analysis; 399 subjects completed the study by answering all questions. 23.2% of subjects tested as low literacy.

Of 399 subjects, only 174 (43.6%) made the correct self-selection decision. (b) (4)

Comment: The problem of inadvertent concomitant use is significant. The interaction may involve other CYP 3A4 inhibitors, which haven't been studied. It is conceivable this may lead to more adrenal suppression in the OTC setting compared to prescription setting because the use of OTC drugs may not be reported to the provider who is managing the HIV infections. I believe this potential safety issue can be addressed with the proposed labeling but should be monitored in postmarketing. Also, I recommend DNCE coordinate with the Office of Communications to release a Consumer Update discussing potential interactions with OTC medicines and HIV drugs.

12.1.4 RH01801 Human Factors Study (April 2013)

The objectives of this study were evaluation of the consumer's ability to clean and prime the apparatus and to show that the consumer understands use, including the correct route of administration (intranasal and not intraocular). The study was a single center, open label study using a placebo nasal spray (120-meatered dose size). Subjects were 18 years of age and older. Subjects were given the placebo spray in packaging and asked to use the product with only the instructions on labeling. Subjects were told to imagine they were suffering from nasal congestion, runny nose, sneezing, itchy nose and itchy watery eyes, and they were to use the product. The subjects were in a room with a sink, counter, scissors, mirror and medicine cabinet. Initial use was observed. The investigator then told that subject to imagine it was two weeks later, and they had new symptoms. The subject was asked to show what he/she would do. Subjects who failed tasks were interviewed about the reasons for failure.

Forty subjects were included in the analysis. Twenty-four subjects reported prior experience with nasal sprays; twenty-three subjects reported ocular symptoms; twenty-five subjects had seasonal nasal allergies.

No subject tried to use the product in his or her eyes; 27 of 40 subjects correctly primed the pump; 21 of 40 subjects correctly cleaned the pump after use. However, 21 of 40 subjects inadvertently discharged product when replacing the spray nozzle on the bottle in the cleaning step at the two week simulation. During one of these discharges, the discharge went into the participant's face. During initial use, 13 out of 40 (33%) of participants failed to view the Quick Start Guide. Twenty seven of 39 (69%) of participants at the two week use session did not read the Quick Start Guide.

Comment: Failure to read instructions and inadvertent discharge of the product are problems are not unique to the OTC setting as there is no reason to think that healthcare providers demonstrate use of the device when they write a prescription in the office setting.
While none of the subjects deliberately tried to spray FPANS in the eyes, only 16 of 40 subjects were naïve users of nasal sprays. Failure to adequately clean the product is unlikely to raise a significant safety issue. There was one subject who sprayed the product in the face In reviewing the Quick Start guide, I recommend GSK modify the schematic to emphasize consumers should hold the spray at distance and pointed away from the face.

12.1.5 RH01929 Human Factors Study (July 2013)

This study had the same objectives and design as the previous HFS (RH01801) except that it recruited low literacy consumers. Low literacy was defined as a score of 60 or below on the Rapid Estimate of Adult Literacy in Medicine (REALM) test, a standard test for consumer studies. Labeling was modified in response to findings in the previous HFS.

The study enrolled 16 participants; one was excluded from the analysis as a protocol deviation because he did not bring his reading glasses and was unable to read the Quick Start Guide. Eight subjects reported experience with nasal sprays and five subjects reported ocular symptoms.

No subject tried to use the spray in the eyes. Six of 15 subjects (40%) appropriately primed the pump. Five of 15 (33%) of subjects appropriately cleaned the pump. At the simulated two-week use, none of the subjects passed on the clean step that involved cleaning the pump and correctly answering a question regarding what to do if the actuator was clogged.

Eight of 15 subjects inadvertently discharged spray when replacing spray nozzle on the bottle. Per the applicant, the root cause was applying too much pressure and pressing through the "soft click" when replacing the spray nozzle.

Three of 15 subjects did not consult the Quick Start Guide at the initial use; 9 of 15 subjects did not consult the Quick Start Guide at the simulated two week use.

Comment: It is hard to make generalizations from a study involving only 15 subjects, only seven of whom were naïve users of nasal sprays.

Of all the observed behaviors, only the inadvertent spraying problem raises a safety issue, and only if the spraying results in unintended dosing in the user's (or a bystander's) eyes. In this second study, the applicant claimed that the minor labeling changes helped keep respondents from spraying in their eyes, although inadvertent spraying continued. The report suggests potential labeling changes that could mitigate the problem, such as inserting the word "gently" in the text "Aim away from your face and gently *replace spray nozzle until you hear a soft click."* (b) (4) *In the proposed Quick Start Guide, GSK added "gently"* (b) (4) *Ideally, since subjects do not routinely consult the Quick Start Guide; it would be better to engineer the spray nozzle so that replacing it doesn't cause the product to discharge.*

The inadvertent discharge issue is a problem regardless of Rx or OTC marketing status.

12.2 DMEPA's Labeling Review

DMEPA reviewed the label and concluded that the proposed container labels and carton labeling were acceptable from a medication error perspective.

12.3 DNRD's Labeling Review

Elaine Abraham from DNRD conducted the labeling review. Details can be found in her review as I will only discuss the highlights.
DNRD had the following comments on the PDP:

- The drug class "glucocorticoid" should follow the established name of the drug

(b) (4)

DNRD had the following recommendations related to the DFL:

- The purpose should be changed from "Allergy symptom relief" to "Nasal allergy symptom reliever".
- Remove bolding from the statement "Only for use in the nose. Do not spray into your eyes or mouth" .
- The statement which advises consumers to read the Quick Start Guide should be revised to include abbreviated instructions on using the product.

Comments: It may be difficult to capture the important elements of priming, shaking before use, and cleaning the spray in an abbreviated fashion on the DFL.

13. Recommendations and Risk/ Benefit Assessment

13.1 Recommended Regulatory Action

I recommend FPANS be approved for a switch to OTC status for SAR and PAR, for adult and pediatric patients 4 years and older, contingent on final agreement on labeling. (b) (4) I also recommend the applicant be allowed to include a statement in their label regarding the relief of ocular symptoms under the "Uses" section of the DFL.

The Code of Federal Regulations 21CFR310.200 states:

> Any drug limited to prescription use under section 503(b)(1)(B) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.

GSK has provided sufficient information in this NDA submission to meet this legal standard for an OTC drug product.

13.2 Risk Benefit Assessment

FPANS has already been determined to have a favorable risk /benefit profile in the prescription setting. The question is whether if it were to be available OTC would its risks be enhanced or benefits diminished to a significant degree?

The benefit of FPANS is related to relief of symptoms of SAR and PAR. Allergic rhinitis is an extremely common condition afflicting a large segment of the population. It has long been recognized as an OTC condition. Current OTC drug treatments for allergic rhinitis include oral antihistamines, nasal and oral decongestant, and cromlyn sodium nasal spray. In addition in 2013, triamcinolone acetonide was the first nasal spray containing a corticosteroid approved in the US for OTC treatment of allergic rhinitis. Although allergic rhinitis rarely leads to serious sequelae, it certainly can impact quality of life. Providing consumers an additional OTC treatment option for this prevalent condition would be beneficial. Label comprehension studies and self-selection studies demonstrated that consumers can understand key concepts in the label. Overall, GSK has provided adequate data to indicate that these benefits would not be lessened should FPANS be made available OTC.

The risks of FPANS include local nasal effects, possible reduction in growth velocity in pediatric patients and drug-drug interactions in certain populations. The local effects are not likely to occur more frequently or with greater severity with OTC use. The prescriber does not have a preventative role in making local nasal effects less likely to occur. The various class systemic effects associated with the use of corticosteroids have been evaluated by the applicant and are not likely to lead to AEs. One of the issues around adding the ocular claim to labeling is the possibility of a consumer mistakenly spraying FPANS into the eyes. Human factors studies showed that this is unlikely to occur. The issues of potential effects on growth velocity in children and drug-drug interaction for patients on ritonavir can both be adequately addressed in the labeling of this product.

In summary, FPANS has an acceptable risk/ benefit profile for nonprescription marketing, contingent on adequate labeling.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable

13.4 Recommendation for other Postmarketing Requirements and Commitments

No postmarketing recommendations are made at this time.

13.5 Recommended Comments to Applicant

No comments to the applicant at this time

14. Appendix – Recommendations for Drug Facts Labeling

Comments on GSK's proposed labeling can be found in the footnotes, the relevant sections are highlighted.

Drug Facts	
Active ingredient *(in each spray)*	***Purpose***
Fluticasone propionate 50 mcg	Allergy symptom relief

Uses

- temporarily relieves these symptoms due to hay fever, other upper respiratory allergies (b) (4)
  - nasal congestion • runny nose • sneezing • itchy nose • itchy, watery eyes

Warnings

Only for use in the nose. Do not spray into your eyes or mouth.

Do not use

- to treat asthma
- (b) (4)
- if you have an injury or surgery to your nose that is not fully healed
- if you have ever had an allergic reaction to this product or any of its ingredients

Ask a doctor before use if you have

- glaucoma

Ask a doctor or pharmacist before use if you are taking

- (b) (4) ketoconazole pills (medicine for fungal infection)

When using this product[2] [3]

- stinging or sneezing may occur for a few seconds right after use
- (b) (4)

Stop use and ask a doctor if

- your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.
- you get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.
- you get a constant whistling sound from your nose. This may be a sign of damage inside your nose.[15]
- you get an allergic reaction to this product. Seek medical help right away.
- you get new changes to your vision that develop after starting this product.

(b) (4)

[2] Language should be added "Remember to tell you doctor about all the medicines you take including this one"
[3] Language should be added the growth rate of some children may be slower (this mirrors language used in the Nasacort DFL)

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of [redacted], get medical help or contact a Poison Control Center right away.

Directions

- read the Quick Start Guide for how to [redacted]
- use this product only once a day

[redacted]	Week 1	Use 2 sprays in each nostril once daily
	Week 2 [redacted]	Use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms
	After 6 months of daily use	Ask your doctor if you can keep using

[redacted]

Other information

- you [redacted] start to feel relief [redacted] the first [redacted] and full effect after several days of regular, once-a-day use
- store between 4 [redacted] and 30°C (39°F and 86°F) • keep this label and the enclosed materials, they contain important additional information.

Inactive ingredients benzalkonium chloride, dextrose, microcrystalline cellulose, phenylethylalcohol, polysorbate 80, purified water, sodium carboxymethylcellulose

Questions or comments?

Call toll-free 1-xxx-xxx-xxxx (English/Spanish) weekdays 9:00am - 5:00pm EST

[redacted]

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

/s/

NARAYAN NAIR
07/01/2014