CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

MEDICAL REVIEW(S)

120-day Safety Report:

An overview of all spontaneous reports (regardless of source) received in association with

intranasal fluticasone propionate aqueous nasal spray (FPANS) is presented. This includes a total

of 245 cases describing 501 adverse events received between the time period January

01, 2013 and October 31, 2013.

This report is covered in my NDA Review

Reference ID: 3591334

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/s/

STEVEN F OSBORNE
07/14/2014

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205-434

Submission Date(s): received 9/21/13, stamp date 9/23/13, PDUFA 7/23/14

Applicant: GlaxoSmithKline Consumer Healthcare

Product: Flonase Allergy Relief

Reviewer: Steven Osborne

Date of Review: June 2, 2014

Covered Clinical Study (Name and/or Number): see list below

Was a list of clinical investigators provided: N/A	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 3		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 3		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): three (3)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: three (3) Significant payments of other sorts: None reported Proprietary interest in the product tested held by investigator: None reported Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Summary
The sponsor appears to have done an appropriate due diligence process, as per GSK's internal SOPs. They documented up to three attempts to collect data regarding any potential financial conflicts of interest for investigators. They documented their findings in the Sponsor Study Record.

All investigators have supplied information upon commencement of their participation in the study. No investigator had a financial interest in GSK at the time they started their participation in the covered study. If GSK has been unable to collect financial information at the end of the study, then these investigators are included in listing 3454b Data Not Obtained.

GSK states that it is their policy to not to allow the participation of investigators in a clinical study if they, their spouse or dependent children have proprietary interest in the tested product. It is also the policy of GSK not to compensate Investigators in a way that the amount of compensation received could be affected by the outcome of the study. The questionnaire does include collection of this information since these GSK policies are in place.

Financial interest information is not collected from investigators who are also GSK employees during the conduct of the study. Investigators who become GSK employees during the one year period following their completion of the study are instructed to report changes in financial interest information, within the 1 year period following completion of the study.

Current or Former employees of the Sponsor
From the data collected, there has not been any reported case of any current or former GSK employees being used as an investigator in the covered studies.

Significant payments of other sorts

From the data collected, there has not been any Significant Payments of Other Sorts reported from the sponsor of the covered study as per 21 CFR 54.4(a)(3)(ii), 54.2(f).

Proprietary interest in the tested product

From the data collected there has not been any Proprietary Interest reported as per 21 CFR 54.4(a)(3)(iii), 54.2(c).

Significant equity interest in Covered Clinical Studies

From the data collected, there were three (3) Investigators/sub-investigators within the covered clinical studies for this NDA (see Appendix below) with significant equity interest reported as per 21 CFR 54.4(a)(3)(iv), 54.2(b).

- In Study (b) (6), site number (b) (6) recruited (b) (6) subjects from a total of (b) (6) subjects which was (b) (6)% of the total recruitment. Additionally, sub-investigator (b) (6) reported $103,500.00 in equity. An impact analysis was carried out and GSK concluded that the results of the study were not impacted by the data generated by the subjects recruited by site (b) (6).

- In Study (b) (6), sub-investigator (b) (6) within site number (b) (6) (b) (6), MD - Principal Investigator) reported an equity interest of $148,707. (b) (6) of the (b) (6) subjects (b) (6) were enrolled in (b) (6) site. An impact analysis was carried out and GSK concluded that the results of the study were not impacted by the data generated by the subjects recruited by (b) (6) site.

- In Study (b) (6), investigator (b) (6) (site number (b) (6)) reported $60,000 in equity during the study. (b) (6) of the (b) (6) subjects (b) (6) were enrolled in (b) (6) site. No impact analysis was performed as the percentage of subjects enrolled in site number (b) (6) were less than (b) (6) and unlikely to impact overall study outcome.

Appendix:

This appendix lists the Flonase Covered Clinical Studies Included Within NDA 205-434, Covered Under the Financial Disclosure Rule (Protocol No., Title, Sponsor). These studies were:

- Conducted by either GSK Pharmaceuticals or GSK Consumer Healthcare;
- Initiated after the Final Rule came into effect;
- Have not been submitted in a previous marketing application for Flonase.

FNM30033

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy of a Four-Week Course of Fluticasone Propionate Aqueous Nasal Spray (200mcg QD) on Ocular Symptoms Commonly Associated with Allergic Rhinitis GlaxoSmithKline

FNM30034
A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy of a Four-Week Course of Fluticasone Propionate Aqueous Nasal Spray (200mcg QD) on Ocular Symptoms Commonly Associated with Allergic Rhinitis
GlaxoSmithKline

R1810198
An Actual Use Study in Support of the Over-the-Counter Switch of Flonase® Allergy
GlaxoSmithKline Consumer Healthcare

R1810220
An Efficacy and Safety Study of Fluticasone Propionate Aqueous Nasal Spray in Subjects with Perennial Allergic Rhinitis
GlaxoSmithKline Consumer Healthcare

R1810221
An Efficacy and Safety Study of Fluticasone Propionate Aqueous Nasal Spray in Subjects with Seasonal Allergic Rhinitis
GlaxoSmithKline Consumer Healthcare

RH01619
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multi-center Study to Assess the Efficacy of once daily Fluticasone Propionate Aqueous Nasal Spray 200mcg for 14 Days on Ocular Symptoms Associated with Allergic Rhinitis
GlaxoSmithKline Consumer Healthcare

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/s/

STEVEN F OSBORNE
06/18/2014
Flonase Financial Disclosure Form

NARAYAN NAIR
06/18/2014

Division of Pulmonary, Allergy, Rheumatology Products Summary Review

Date	June 12, 2014
From	Stacy Chin, MD, Medical Officer, DPARP
Through	Anthony Durmowicz, MD, Clinical Team Leader, DPARP
Through	Badrul Chowdhury, MD, PhD, Division Director, DPARP
Subject	Division Director Summary Review for prescription to OTC switch for fluticasone propionate nasal spray in patients ≥ 4 years of age with allergic rhinitis (b) (4)
NDA#	205434
Applicant Name	GlaxoSmithKline (GSK)
Date of Submission	September 23, 2014
PDUFA Goal Date	July 23, 2014
Proprietary Name / Established Name	Flonase® (fluticasone propionate nasal spray)
Dosage Forms/Strength	Nasal Spray (50 mcg fluticasone propionate/spray)
Proposed Indication(s)	Temporary relief of symptoms due to hay fever, other respiratory allergies (b) (4) nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes in adults and children ≥ 4 years of age.
Action/Recommended Action	Approval for allergic rhinitis indication, including relief of ocular symptoms

1. Introduction and Regulatory Background

1.1 Product Information

Fluticasone propionate aqueous nasal spray (FPANS) was approved on October 19, 1994, (NDA 20-121) for the management of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Supplemental NDAs extended the indication to children 4 to 11 years of age on October 31, 1997 (supplement 005), to the management of perennial nonallergic rhinitis on December 11, 1998 (supplement 009), and for use on an as needed (PRN) basis on May 23, 2002 (supplement 023). The prescription dosages for each age group are summarized in Table 1. The 200 mcg daily dose may be administered as 2 sprays in each nostril once daily or as 1 spray in each nostril twice daily. Once adequate control is achieved, the dosage is recommended to be decreased to 100 mcg (1 spray in each nostril) daily.

Table 1. Approved FPANS Prescription Dosing

Age Range	Starting Dose	Maximum Dose
Adult patients	200 mcg daily	200 mcg daily
Pediatric patients (≥ 4 years of age)	100 mcg daily	200 mcg daily
Source: Flonase® Prescribing Information		

1.2 Currently Available Nonprescription Treatments for the Proposed Indications

While numerous intranasal corticosteroids are available by prescription for the treatment of allergic rhinitis, there is currently one approved OTC intranasal corticosteroid product in the United States, Nasacort® Allergy 24HR (NDA 20-468). Nasacort® Allergy 24HR was approved on October 11, 2013, for the relief of nasal symptoms of hay fever or other upper respiratory allergies in children 2 years and older.

Other over-the-counter products to treat symptoms associated with allergic rhinitis have been available for many years and include both oral and intranasal products: first and second generation oral antihistamines, oral antihistamine/decongestant combination products, intranasal decongestants, and intranasal cromolyn. In addition to oral antihistamines, several over-the-counter eye drops are available for the relief of allergic conjunctivitis symptoms: intraocular decongestants, intraocular antihistamine/decongestant combination products, and intraocular antihistamine/mast cell stabilizer products.

The OTC oral antihistamines are indicated to temporarily relieve symptoms of allergy and hay fever including sneezing, itchy watery eyes, runny nose and itchy throat. The OTC intraocular antihistamine/mast cell stabilizer products are indicated to temporarily relieve itchy eyes due to pollen, ragweed, grass, animal hair, and dander. Many of the antihistamine products are also marketed in combination with decongestants, which adds the relief of nasal congestion to the OTC indication of oral antihistamines and the relief of red eyes to the OTC indication of intraocular antihistamines.

1.3 Summary of Presubmission Regulatory Activity Related to Submission

Discussions regarding an OTC switch for FPANS occurred on May 2, 2001; November and December 2001; February 22, 2011; October 22, 2012; March 29, 2013; and May 16, 2013 between participants from GlaxoSmithKline, the Division of Nonprescription Clinical Evaluation (DNCE), and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Major discussion points from the most recent interactions are outlined below.

February 22, 2011:

- No additional trials to support the efficacy of FPANS in allergic rhinitis are required, provided that the OTC indications correspond to the approved prescription indications.
- The Agency was unaware of data that should definitely preclude the labeling of the proposed OTC product down to age of 4 years like the prescription product. (b) (4)
- Since the efficacy of FPANS for managing allergic rhinitis caused by specific allergens has not been specifically studied, listing symptom relief from specific allergens in the Drug Facts label would not be warranted.

October 22, 2012:

- The Agency expressed safety concerns with the proposal to add ocular symptoms to the FPANS over-the-counter indication since nasal sprays, which are non-sterile products, have not been approved for simultaneous topical ophthalmic use or for relief of ophthalmic symptoms. Furthermore, the Drug Facts label is not conducive to conveying data on ocular symptom relief.
- The use of "non-nasal symptoms" would be too broad and confusing to consumers.

(b) (4)

March 29, 2013:

- While the use of TOSS was deemed acceptable to evaluate ocular symptoms as part of the efficacy assessment in their allergic rhinitis development program, the Agency continued to express concerns regarding the proposal to include ocular symptoms in the Rx-to-OTC switch for Flonase.

May 16, 2013:

- Regarding the proposed ocular claim, (b) (4), and labeling restriction (b) (4), the Agency referenced previous responses and discussions from February 2011, October 2012, and March 2013.
- The Agency stated that expanding the approved indication to include ocular symptoms may trigger PREA and, if so, a Pediatric Study Plan would be required.

May 27, 2014:

- The Applicant agreed to amend the proposed labeling to expand the OTC population down to 4 years of age, consistent with the approved Rx population.

2. Overview of Clinical Trial Database

The OTC switch application seeks to include a claim for improvement in ocular symptoms associated with allergic rhinitis, and, since the composite endpoint used as the basis for approval of intranasal corticosteroid products (total nasal symptom score or TNSS) does not assess ocular symptoms, data from 3 clinical trials in SAR that evaluated for relief of eye symptoms (two 4-week pivotal studies and one 2-week supplementary study) were submitted. As additional support, the Applicant has pooled results from seven previously submitted studies that were designed to show efficacy with nasal symptoms, but also evaluated individual ocular symptoms. Clinical trial data to support the dose selection and efficacy and safety of fluticasone propionate for the management of nasal symptoms of seasonal and perennial allergic rhinitis (b) (4) in adults and pediatric patients 4 years of age and older have already been reviewed in detail by the Agency and are summarized in the current approved product label. Details of the individual trial designs are summarized in Table 2 and the efficacy data are summarized in Section 3.

A review of the safety data, with a focus on class specific risks, is presented in Section 4. In addition to the clinical trial database, the safety information for the application is supplemented by postmarketing data for FPANS, which is reviewed in-depth by the DNCE medical officer, Dr. Steven Osborne.

Table 2. Efficacy and Safety Trials

Trial	Design	Age (yrs)	Treatment (mcg): N	Duration	Population	Study Objectives	Relevance to Review
Ocular studies							
FNM30033*	R, DB, DD, PC, PG	≥ 12	FP200 qd: 158 LOR qd: 158 Placebo: 155	4 weeks	SAR, US	Safety and efficacy (TOSS300)	Pivotal ocular claim study
FNM30034*	R, DB, DD, PC, PG	≥ 12	FP200 qd: 158 LOR qd: 163 Placebo: 161	4 weeks	SAR, US	Safety and efficacy (TOSS300)	Pivotal ocular claim study
RH01619	R, DB, PC, PG	≥ 12	FP200 qd: 314 Placebo: 312	2 weeks	SAR, US	Safety and efficacy (rTOSS)	Supplemental ocular claim study
Supportive ocular studies							
FLN-401*	R, DB, DD, PG	≥ 12	FP200 qd: 78 TERF bid: 77 Placebo: 77	2 weeks	SAR	Safety/HPA axis and efficacy (TNSS, TOSS)	Ocular claim and safety
FLN-402*	R, DB, DD, PG	≥ 12	FP200 qd: 117 TERF bid: 116 Placebo: 115	4 weeks	SAR	Safety/HPA axis and efficacy (TNSS, TOSS)	Ocular claim and safety

FLN-411*	R, DB, DD, PG	≥ 12	FP200 qd:105 AST qd: 102 Placebo: 106	2 weeks	SAR	Safety/HPA axis and efficacy (TNSS, TOSS)	Ocular claim and safety
FLN-412*	R, DB, DD, PG	≥ 12	FP200 qd:102 AST qd: 100 Placebo: 102	4 weeks	SAR	Safety/HPA axis and efficacy (TNSS, TOSS)	Ocular claim and safety
FLTA4004*	R, DB, DD, PG	≥ 12	FP200 qd:109 LOR qd: 112 Placebo: 112	4 weeks	SAR	Safety and efficacy (TNSS, TOSS)	Ocular claim and safety
FLTA4006*	R, DB, DD, PG	≥ 12	FP200 qd:150 LOR qd: 150 FP + LOR: 150 Placebo: 150	2 weeks	SAR	Safety and efficacy (TNSS, TOSS)	Ocular claim and safety
FLTA4024*	R, DB, DD, PG	≥ 12	FP200 qd:161 LOR qd: 166 FP + LOR: 164 Placebo: 164	2 weeks	SAR	Safety and efficacy (TNSS, TOSS)	Ocular claim and safety
Pooled safety studies*							
FLN-202	R, DB, PC, PG	≥ 18	FP400 bid: 106 FP100 bid: 103 FP25 bid: 112 Placebo: 102	2 weeks	SAR	Safety and efficacy	Safety
FLN-203	R, DB, PC, PG	≥ 18	FP200 bid: 77 FP100 bid: 75 Placebo: 75	2 weeks	SAR	Safety/HPA axis and efficacy	Safety
FLN-204	R, DB, PC, PG	≥ 18	FP200 bid: 101 FP100 bid: 100 Placebo: 100	4 weeks	PR	Safety/HPA axis and efficacy	Safety
FLN-261	R, DB, PC, PG	≥ 18	FP200 qd: 42 Placebo: 38	52 weeks	PR	Safety/HPA axis	Long-term safety
FLN-270	R, DB, PC, PG	≥ 12	FP200 qd: 204 Placebo: 97	4 weeks	SAR	Safety and efficacy	Safety
FLN-306	R, DB, PC, AC, PG	≥ 12	FP200 qd: 55 FP100 bid: 64 BDP[1] bid: 61 Placebo: 58	4 weeks	SAR	Safety/HPA axis and efficacy	Safety
FLN-310	R, DB, PC, PG	≥ 12	FP200 qd: 128 FP100 bid: 121 Placebo: 116	26 weeks	PAR	Safety/HPA axis and efficacy	Long-term safety
FLN-311	R, DB, PC, AC, PG	≥ 12	FP200 qd:118 FP100 bid: 119 BDP bid: 116 Placebo: 113	26 weeks	PAR	Safety/HPA axis and efficacy	Long-term safety
FLN-320	R, DB, PC, PG	4-11	FP200 qd: 81 FP100 qd: 84 Placebo: 85	2 weeks	SAR	Safety/HPA axis and efficacy	Safety
FLN-321	R, DB, PC, PG	4-11	FP200 qd: 83 FP100 qd: 83 Placebo: 85	4 weeks	SAR	Safety/HPA axis and efficacy	Safety
FLN-350	R, DB, PC, PG, SC	≥ 18	FP200 bid: 22 FP100 bid: 23 Placebo: 23	4 weeks	PNAR	Safety/HPA axis and efficacy	Safety

FLN-351	R, DB, PC, PG	≥ 12	FP200 bid: 95 FP100 bid: 98 Placebo: 93	4 weeks	PNAR	Safety/HPA axis and efficacy	Safety
FLTA3010	R, DB, PG	≥ 12	FP200 bid: 207 FP100 bid: 211 FP50 bid: 207 Placebo: 210	4 weeks	PNAR	Safety/HPA axis and efficacy	Safety
FNM30030	R, DB, DD, AC, PG	≥ 12	FP200 prn: 121 LOR prn: 125 Placebo: 122	4 weeks	SAR	Safety and efficacy	Safety
FNM30031	R, DB, DD, AC, PG	≥ 12	FP200 prn: 121 LOR10 prn Placebo: 119	4 weeks	SAR	Safety and efficacy	Safety
FNM40184	R, DB, PG	≥ 12	FP200 qd: 98 Placebo: 97	2 weeks	AR	Safety and efficacy	Safety
FNM40185	R, DB, PG	≥ 12	FP200 qd: 101 Placebo: 105	2 weeks	AR	Safety and efficacy	Safety
R1810220	R, DB, PG	≥ 12	FP100 qd: 184 Placebo: 177	4 weeks	PAR	Safety and efficacy	Safety
R1810221	R, DB, PG	≥ 12	FP100 qd: 205 Placebo: 206	2 weeks	SAR	Safety and efficacy	Safety
Non-pooled safety studies							
FLIT08	OL, SC	≥ 18	FP200 bid: 60	52 weeks	PR	Safety and efficacy	Long-term safety
FLIT11	R, DB, AC, PG	≥ 18	FP200 bid: 159 BDP[2] bid: 83	52 weeks	PR	Safety/HPA axis and efficacy	Long-term safety
FLIT22	R, DB, PG, SC	≥ 16	FP100 bid: 21 Placebo: 21	52 weeks	PR	Safety/HPA axis and efficacy	Long-term safety
FLN-230	R, DB, DD, PG	≥ 12	FP200 qd: 77 FP[3] 5mg qd: 73 FP[3] 10mg qd: 77 Placebo: 77	2 weeks	SAR	Safety/HPA axis and efficacy	Safety
FLN-260	R, DB, DD, AC, PG	≥ 18	FP200 qd: 20 FP400 qd: 23 PSN 7.5 qd: 21 PSN 15 qd: 21 Placebo: 21	4 weeks	AR	HPA axis	Adult HPA axis study
FLTA3010E	OL	≥ 12	FP200 bid: 289	26 weeks	PNAR	Safety/HPA axis and efficacy	Long-term safety
FLTA4025	R, DB, PG	≥ 12	FP200 qd: 185 Placebo: 186 (CEF bid x 20d)	48 days	Sinusitis + SAR, PAR, or PNAR	Safety and efficacy	Safety
FLTA4033	R, DB, PG	≥ 12	FP200 qd: 165 Placebo: 168 (CEF bid x 20d)	48 days	History + current sinusitis	Safety and efficacy	Safety
FLTB1009	R, OL, XO, SC	18-50	FP800 tid: 12	4 days	Healthy volunteer	PK	Safety
FLTB3052	R, DB, PG	≥ 18	FP200 qd: 270 Placebo: 274 (AUG tid x 14d)	50 weeks	History + current sinusitis	Safety and efficacy	Safety
FLTB3053	R, DB,	≥ 18	FP200 qd: 219	50 weeks	History +	Safety/HPA axis	Safety

	PG		Placebo: 212 (CEF bid x 14d)		current sinusitis	and efficacy	
FNM40017	R, DB, PG	3.5-9.5	FP200 qd: 74 Placebo: 76	52 weeks	AR	Safety/HPA axis and growth effects	Pediatric growth velocity study
FNM40181	R, DB, XO, SC	4-12	FP100 qd: 28 Placebo: 28	2 weeks per tx	AR	Safety/growth effects	Pediatric knemometry study
FNM40183	R, DB, PG	2-4	FP200 qd: 33 Placebo: 32	6 weeks	AR	Safety/HPA axis and PK	Pediatric HPA axis study
FNS30003	R, DB, PG	12-16	FP200 qd: 75 Placebo: 82 (CEP bid x 15d)	6 weeks	Rhino-sinusitis	Safety/HPA axis and efficacy	Safety

Abbreviations: R=randomized, DB=double-blind, DD=double dummy, PC=placebo-controlled, AC=active control, OL=open-label, PG=parallel group, XO=cross-over, SC=single center, qd=daily, bid=twice daily, tid=three times daily, FP=fluticasone propionate, LOR=Loratadine 10 mg, TER=terfenadine 60 mg, AST=astemizole 10 mg, BDP=beclomethasone dipropionate, PSN=prednisone, CEF=Ceftin 250 mg, AUG=Augmentin 625 mg, CEP=cephalosporin 250 mg, AR=allergic rhinitis, SAR=seasonal allergic rhinitis, PAR=perennial allergic rhinitis, PR=perennial rhinitis, PNAR=perennial nonallergic rhinitis, US=United States

* Also included in pooled safety studies

[1] beclomethasone dipropionate 168 mcg

[2] beclomethasone dipropionate 200 mcg

[3] oral fluticasone propionate

Source: ISS Table 1, Table 14.1.1.2

3. Review of Efficacy

The proposed OTC dosing and indication for FPANS are consistent with the dosing and indications approved for the prescription product with the exception of a new ocular claim for the OTC product. 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". The efficacy data to support the nasal components of the OTC indication were reviewed as part of the Rx clinical development program and were not resubmitted to this NDA. Following are summaries of the clinical data used to support efficacy labeling in the OTC Drug Facts Label.

3.1 Seasonal and Perennial Allergic Rhinitis

The efficacy of FPANS in the management of nasal symptoms of SAR and PAR was supported by 13 randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials conducted in patients 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).

3.3 Relief of Ocular Symptoms Associated with Allergic Rhinitis

The Rx to OTC switch application includes clinical data to support the addition of relief of ocular symptoms ("temporary relief of itchy, watery eyes") for the OTC product. It should be noted that other OTC systemically active products for management of allergic rhinitis, such as oral antihistamines, already contain relief of ocular symptoms in their Drug Facts Label, based on the Total Symptom Score (TSS) primary endpoint used in their Phase 3 trials, which included an evaluation of ocular symptoms as part of the TSS. This is in contrast to nasal corticosteroid products for management of allergic rhinitis, which, because of their presumably local action specific to the nose were approved initially for management of the nasal symptoms of allergic rhinitis based on the Total Nasal Symptom Score (TNSS) as the primary endpoint in their Phase 3 trials. As such, when Sponsors sought to extend the indication for prescription intranasal allergic rhinitis products to include relief of ocular symptoms associated with allergic rhinitis, additional studies utilizing an ocular symptom score (Total Ocular Symptom Score or TOSS) as the primary endpoint were necessary (see Veramyst and Zetonna product labels as examples). With that as background, to support the additional ocular claim, the Applicant conducted three dedicated ocular studies to evaluate the efficacy of FPANS 200 mcg daily for the treatment of ocular symptoms associated with allergic rhinitis. There were two 4-week pivotal studies (FNM30033 and FNM30034) and a supplementary 2-week study (RH01619), all of which

evaluated patients ≥ 12 years of age with SAR. Each of these studies will be described in detail below.

The Applicant also submitted data from seven pooled studies (FLN-401, FLN-402, FLN-411, FLN-412, FLTA4004, FLTA4006, and FLTA4024) that were previously submitted to support the indication of treatment of nasal symptoms of allergic rhinitis in the original NDA, but which also included ocular symptom assessments. Because the primary objective of these studies was to demonstrate efficacy in nasal symptoms and the ocular symptom scoring differed from the currently preferred method, the pooled post-hoc analysis of these studies was not evaluated in depth and will not be discussed any further in this review.

3.3.1 Ocular Studies

FNM30033 and FNM30034

The Applicant conducted two pivotal trials FNM30033 and FNM30034 to assess efficacy of FPANS on ocular symptoms in subjects with SAR. The studies were similar in design and thus will be described jointly with differences noted where relevant. Both trials were randomized, double-blind, double-dummy, parallel group studies comparing FPANS 200 mcg daily to placebo. Oral loratadine 10 mg was included as the active comparator. The studies were each conducted at 14 investigation sites during the spring allergy season in 2001. Subjects ≥ 12 years of age with a positive skin test, history of SAR for a minimum of 2 years, and meeting other eligibility criteria entered a 7-14 day baseline period to assess the severity of ocular symptoms (itching, tearing, redness) and nasal congestion. Each symptom was scored based on a 100-point visual analog scale (VAS) to represent the reflective symptom severity experienced over the entire day. The total ocular symptom score (TOSS) was the sum of individual symptom scores for ocular itching, tearing, and redness; thus, the TOSS could range from 0 to 300, with 300 representing maximum severity. Subjects with moderate to severe ocular symptoms and nasal congestion during the baseline period[1] were randomized to one of three treatment groups: FPANS 200 mcg + placebo capsule, placebo nasal spray + placebo capsule, or placebo nasal spray + loratadine 10 mg. Study medication was taken every morning for 28 days; no rescue medication was permitted. Every evening, subjects recorded the severity of four symptoms (nasal congestion, ocular itching, ocular tearing, and ocular redness) using the 100-point VAS score. Subjects attended study visits at screening and at Days 1, 14, and 28. At the final visit, subjects self-assessed their overall treatment response using a 7-point categorical scale, ranging from significant improvement (1) to significant worsening (7).

Efficacy assessments were measured by the change in subject-rated ocular symptoms from baseline averaged over time. The primary endpoint was the mean change from baseline in reflective TOSS (rTOSS) averaged over Days 1-28 for FPANS compared with placebo.

[1] Defined as a TOSS of ≥ 120 out of 300 and nasal congestion ≥ 50 out of 100 on at least 4 of the 7 preceding days before randomization

Secondary endpoints included the mean change from baseline in the weekly averaged individual ocular symptom scores and rTOSS for FPANS compared with placebo. The comparisons of FPANS with loratadine and loratadine with placebo were considered exploratory.

Results of the rTOSS for each treatment group over the entire 4 week treatment period are shown in Table 3. Both trials demonstrated a statistically significant greater decrease (improvement) in the primary endpoint of mean change from baseline in rTOSS compared to placebo over the 4 week treatment period. Although the p value for the entire treatment period in Study FNM30034 was borderline statistically significant (p=0.055), the mean change from baseline in rTOSS over Days 1-28 was similar in magnitude to the results from Study FNM30033. The larger treatment effect in the placebo group during Week 4 of Study FNM30034 appears to be the main factor accounting for a difference in p values between the two pivotal studies. Furthermore, both trials demonstrated a statistically significant decrease in the rTOSS for the FPANS treatment group at 2 weeks, which is the currently used treatment period for SAR trials. Results of the secondary efficacy endpoints (data not shown) generally tracked with the results of the primary efficacy endpoint. However, in Study FNM30034, the mean change from baseline for the individual symptom scores for ocular tearing, and the subject-rated overall evaluation of response to treatment in the FPANS group compared with placebo were not statistically significant at any time point (see Statistical Review by Dr. David Hoberman).

RH01619

Study RH01619 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. The study was conducted at 6 sites in Texas during the 2012-2013 Mountain Cedar pollen season. The study population included patients ≥ 12 years of age with a history of SAR for a minimum of 2 years, positive skin prick test to Mountain Cedar, and moderate to severe allergic rhinitis symptoms at study entry[2]. A total of 626 patients (314 treated with FPANS 200 mcg daily) were randomized to study treatment for 2 weeks. Subjects self-administered study treatment every morning and maintained a diary to record daily nasal and ocular symptoms. As in the pivotal trials, the primary endpoint was mean change from baseline in subject-rated rTOSS compared to placebo over the entire treatment period, which in this case was 2 weeks. One difference, however, was that this trial utilized a 4-point scale (0-3) for scoring individual ocular symptoms; thus the maximum TOSS score was 9 rather than 300 as in the pivotal trials. Secondary endpoints included mean change from baseline in morning rTOSS, in evening rTOSS, in reflective scores for individual ocular symptoms, in morning pre-dose iTOSS, and in daily rNCSS as well as overall response to therapy, rhinoconjunctivitis quality-of-life assessment, and physician assessment of conjunctival redness.

[2] Defined as an average reflective total ocular symptom score (rTOSS) ≥ 4 out of 9 and an average reflective nasal congestion symptom score (rNCSS) ≥ 2 out of 3 for three of the five days during placebo lead-in as well as an instantaneous TOSS ≥ 4 out of 9 and instantaneous NCSS ≥ 2 out of 3 on the morning of randomization

This trial met the primary endpoint (Table 3), and the secondary efficacy variables, with the exception of physician assessment of conjunctival redness, also favored FPANS 200 mcg daily over placebo.

Table 3. 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

3.4 Summary of Efficacy

In this full OTC switch NDA, the Applicant seeks to carry over (b) (4) indications from the prescription FPANS product (Flonase) to the proposed FPANS OTC product: those for allergic rhinitis, captured in the OTC label as "temporary relief of symptoms due to hay fever and other respiratory allergies" (b) (4) . Data were also submitted to support the inclusion of relief of ocular symptoms associated with allergic rhinitis, described in the OTC label as "itchy, watery eyes". The efficacy of FPANS for the treatment of nasal symptoms of allergic rhinitis (SAR and PAR) has previously been established for the Rx product for patients 4 years of age and older.

(b) (4)

(b) (4)

. For the new ocular claim, which is not currently approved for the Rx product, the Applicant submitted additional clinical trial data from three adequate and well-controlled studies. Overall, the clinical development program has demonstrated substantial evidence of efficacy for FPANS 200 mcg daily in the treatment of ocular symptoms associated with SAR in patients ≥ 12 years of age. Due to the similar pathophysiology between SAR and PAR across all age groups, it is reasonable to conclude that FPANS would have a similar treatment effect on ocular symptoms associated with both subtypes of allergic rhinitis in the full age range of patients, despite the fact that ocular studies were not specifically conducted in subjects with PAR or in subjects under 12 years of age. Furthermore, the OTC labeling language does not make a distinction between SAR and PAR, and the OTC labeling language is more akin with the SAR indication.

4. Review of Safety

The safety of FPANS is supported by the clinical development program for the prescription FPANS product in conjunction with the postmarketing experience obtained over the past 20 years. Similar to other intranasal corticosteroids, prescription labeling for FPANS contains Warnings and Precautions statements regarding the potential risks of corticosteroid use. These risks include the following:

- Local nasal effects
- Increased risk of glaucoma and/or cataracts
- Immunosuppression
- Hypercorticism and adrenal suppression
- Reduction in growth velocity

Common adverse events associated with FPANS and described in the current prescription label include headache, pharyngitis, epistaxis, nasal burning/irritation, nausea/vomiting, asthma symptoms, and cough. Of these risks, local nasal effects (epistaxis and nasal burning/irritation) are the most common adverse effect.

4.1 Adequacy of Safety Assessments

From the 28 controlled clinical trials conducted in the U.S. in support of the original NDA for the prescription product, a total of 4,999 patients over 4 years of age were treated with FPANS[3]. Of these, there were 25 short-term studies in which subjects received FPANS for at least 2 weeks, and there were 3 long-term studies in which subjects received FPANS for at least 26 weeks. In addition to the pooled safety data, the Applicant provided safety data from 15 non-

[3] Applicant's safety database differs from the current product label. For consistency, this review will use the database outlined in the Applicant's integrated summary of safety (ISS).

pooled studies to address specific safety issues such as HPA axis suppression, local nasal, oral, and ocular effects, and growth velocity.

4.2 Submission Specific Safety Concerns

This section of the review addresses each of the Warnings and Precautions statements carried by all intranasal corticosteroid products.

4.2.1 Local Nasal Effects

Current prescription labeling describes a risk of local nasal toxicity, such as epistaxis, nasal septum perforation, candidiasis, and impaired wound healing. Data from the pooled controlled clinical trials demonstrated a higher rate of epistaxis, nasal septum ulcers/ulcerations, and nasal septum perforations in patients treated with FPANS compared to those treated with placebo. Notably, the FPANS-treated subjects who experienced nasal septum perforations had underlying risk factors such as previous sinus/nasal surgery or cocaine abuse. No nasal septum perforations occurred in 6 non-pooled safety studies (FLIT08, FLIT11, FLIT22, FLN-230, FLTA3010E, FNS30003).

Table 4. 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

4.2.2 Ocular Effects

Current prescription product labeling reports that rare instances of cataracts and glaucoma have been reported following intranasal application of corticosteroids, including fluticasone propionate. There were no clinically significant imbalances in cataract or glaucoma adverse events between FPANS and placebo groups in the pooled clinical trials. Ophthalmic exams were not conducted in the non-pooled safety studies.

Table 5. Ocular effects: Pooled safety studies

	Placebo	FPANS
N	3160	4999[a]
Cataract	0	2 (<0.1)
Subcapsular cataract	1 (<0.1)	0
Lenticular opacities	1 (<0.1)	1 (<0.1)
Glaucoma	0	0

Source: ISS Table 14.5.4.1
[a] Includes doses less than 200 mcg/day

4.2.3 Immunosuppression

Current prescription labeling contains a general Warnings and Precaution statement regarding the risk of immunosuppression and worsened or reactivated serious infections. There were no clinically relevant imbalances in cases related to systemic immunosuppression between FPANS and placebo treatment groups. In addition, the frequency of oropharyngeal fungal infections was reported in 5 non-pooled safety studies (FLIT11, FLIT22, FLN-230, FLN-260, FLTA3010E). Overall, there were 5 FPANS-treated subjects and 1 beclomethasone dipropionate (BDP)-treated subject who had clinical evidence of oropharyngeal candidiasis.

Table 6. Immunosuppression: Pooled safety studies

	Placebo	FPANS
N	3160	4999[a]
Oral candidiasis	1 (<0.1)	0
Oropharyngeal candidiasis	0	3 (<0.1)
Fungal infection	3 (<0.1)	2 (<0.1)
Bacterial infection	0	1 (<0.1)
Herpes simplex	1 (<0.1)	0
Herpes zoster	2 (<0.1)	3 (<0.1)
Pneumonia	1 (<0.1)	2 (<0.1)
Nasal abscess	0	1 (<0.1)
Varicella	0	1 (<0.1)
Mycobacterium tuberculosis complex test positive	1 (<0.1)	0

	Placebo	FPANS
Source: ISS Table 14.5.4.1 and Table 14.5.5.1 [a] Includes doses less than 200 mcg/day		

4.2.4 HPA Axis

Intranasal corticosteroids contain a class-specific Warnings and Precautions statement regarding the potential for adrenal suppression when used at higher than recommended doses and in susceptible individuals.

The effect of FPANS on HPA axis was assessed by adrenal stimulation in 4 non-pooled safety studies (FLIT11, FLIT22, FLN-260, and FLTA3010E) and by morning plasma and/or urinary cortisol in 5 non-pooled safety studies (FLN-230, FLTB3053, FNM40017, FNM40183, and FNS30003). Results from the primary HPA axis studies are summarized below. In the pooled safety studies, there was a single report of increased blood cortisol in placebo-treated patients and no TEAEs related to HPA axis suppression in FPANS-treated patients. Study FLN-260 randomized adult subjects with allergic rhinitis to receive either placebo (n=21), FPANS 200 mcg qday (n=20), FPANS 400 mcg bid (n=23), oral prednisone 7.5 mg qday (n=21), or oral prednisone 15 mg qday (n=21). After 4 weeks of treatment, neither dose of FPANS affected the adrenal response to 6-hour cosyntropin stimulation while both doses of oral prednisone significantly reduced the response to cosyntropin. In pediatric studies, FNM40017 and FNM40183, there was no evidence of clinically relevant changes in HPA axis function as measured by 12-hour urinary cortisol excretion. Based on the collective data, the systemic exposure of FPANS 200 mcg daily is negligible (unless co-administered with other highly potent CYP450 3A4 inhibitors such as ritonavir) and appears to have no clinically significant effect on HPA axis function.

4.2.5 Effect on Growth

Intranasal corticosteroids carry a class-specific Warnings and Precautions statement regarding a potential reduction in growth velocity in pediatric patients. Previously, a concern regarding intranasal corticosteroids and a possible effect on growth was discussed in 1998 at a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Endocrine and Metabolic Drugs Advisory Committee (EMDAC)[4]. The 1998 meeting centered on the results of an early growth study conducted with a different intranasal corticosteroid, beclomethasone dipropionate. This trial indicated a difference in growth velocity between beclomethasone and placebo of -1.45 cm/year. The Advisory Committee panel recommended class labeling for all orally inhaled and intranasal corticosteroid products, identifying the possibility of a decrease in growth velocity.

[4] Joint Pulmonary-Allergy Drugs Advisory Committee and Endocrine and Metabolic Drugs Advisory Committee for Orally Inhaled/Intranasal Corticosteroids and Growth in Children, July 30, 1998. Website: http://www fda.gov/ohrms/dockets/ac/98/transcpt/3430t1.pdf accessed on June 13, 2013

Since that time, a number of growth studies for other corticosteroid products have been conducted. The Agency issued specific guidelines regarding the conduct of these controlled studies in 2007[5]. In general, these studies are conducted over the course of at least one year in prepubescent children who are on a stable, linear portion of their growth curves. The results from one-year growth studies for various intranasal corticosteroids have demonstrated a range of effects from +0.61 cm/year to -1.45 cm/year and are presented in Table 7 for reference. Of note, triamcinolone acetonide was approved for OTC use on October 11, 2013.

Table 7. 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] Flonase prescribing information accessed May 6, 2013
[6] Nasonex prescribing information accessed May 6, 2013
Source: NDA 20-468, primary medical officer review by Sofia Chaudhry, MD

For FPANS, a dedicated one year growth study (FNM40017) was conducted from 1999 through 2001 as a postmarketing commitment in 150 prepubescent children age 3.5 to 9.5 years with perennial allergic rhinitis. Treatment groups were FPANS 200 mcg once daily and placebo. Growth velocity was estimated for each patient using the slope of the linear regression of height over time as measured by stadiometry. The primary endpoint was growth velocity over one year of treatment for the primary population, the population of patients who completed at least three months of stadiometric measurements, had no protocol violations, and remained Tanner Stage 1 throughout. From the primary population of 56 patients receiving FPANS and 52 patients receiving placebo, the mean growth velocity was slightly lower, though not significantly different, in the FPANS group with a difference from placebo of -0.14 cm/year [95% CI (-0.54, 0.27)]. Mean height at the end of one year of treatment was 125.5 cm in the FPANS group

[5] Guidance for Industry: Orally inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007.

compared to 125.4 cm in the placebo group [LS mean difference -0.12; 95% CI (-0.600, 0.3520)]. In addition, mean bone mineral density increases after one year were comparable between treatment groups.

The growth study in FPANS was conducted prior to the issuance of the FDA guidance[6] and was therefore underpowered and lacked both a prospective baseline untreated growth phase and a follow-up growth phase. Despite the flaws in study design, the primary medical officer review of the study concluded that the data was reasonably robust based on a re-analysis of the primary population in the study that demonstrated a 95% confidence interval width of 0.80 (-0.54, 0.27) around a point estimate for a growth effect that was quite small. Moreover, the lower bound of the 95% confidence interval is consistent with observations in growth studies of the other intranasal steroids. While the Applicant initially pointed to the growth effects of fluticasone furoate to justify a partial OTC switch (b) (4), the Applicant had previously demonstrated fluticasone furoate to be a unique molecular entity that exhibits distinct functional characteristics from fluticasone propionate. Nonetheless, both FPANS and fluticasone furoate had less of an effect on growth than triamcinolone acetonide aqueous, which is approved for OTC use in adults and children 2 years of age and above. Ultimately, the Applicant amended this NDA submission to propose a full Rx-to-OTC switch for patients down to 4 years of age.

4.3 Common Adverse Events

Current prescription labeling notes that headache, pharyngitis, epistaxis, nasal burning/nasal irritation, nausea/vomiting, asthma symptoms, and cough occurred more frequently in the FPANS population. Other adverse events that occurred in ≤3% but ≥1% of patients and that were more common with FPANS included: blood in nasal mucus, runny nose, abdominal pain, diarrhea, fever, flu-like symptoms, aches and pains, dizziness, bronchitis.

5. Recommendations

5.1 Efficacy for Management of Nasal Symptoms of Allergic Rhinitis

Dose selection and efficacy of FPANS for adults and children ages 4 years and older in the treatment of nasal symptoms of perennial and seasonal allergic rhinitis were established during the prescription approval process, and efficacy for this indication is not expected to be different in the OTC setting. Thus, the benefit provided by FPANS for treatment of nasal symptoms of allergic rhinitis is well-established and prior precedent exists for consumer self-selection using an intranasal corticosteroid spray in the OTC setting.

[6] Guidance for Industry: Orally inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007.

5.3 Efficacy for Relief of Ocular Symptoms of Allergic Rhinitis

For the new ocular claim, which is not currently approved for the Rx product, the Applicant submitted additional clinical trial data from three adequate and well-controlled Phase 3 studies. Overall, the clinical development program has demonstrated substantial evidence of efficacy for FPANS 200 mcg daily in the treatment of ocular symptoms associated with SAR in patients ≥ 12 years of age. Due to the similar pathophysiology between SAR and PAR across all age groups, it is reasonable to conclude that FPANS would have a similar treatment effect on ocular symptoms associated with both subtypes of allergic rhinitis in the full age range of patients, despite the fact that ocular studies were not specifically conducted in subjects with PAR or in subjects under 12 years of age. Furthermore, there is no distinction between SAR and PAR in OTC labeling. With efficacy in ocular symptoms established, a determination must be made by DNCE as to whether or not an ocular claim of "temporary relief of itchy, watery eyes" (due to allergic rhinitis) is appropriate for the OTC setting and can be understood by consumers, so as not to lead to safety concerns such as the spraying of the product in the eyes rather than the nose. If DNCE is to conclude favorably, our understanding is that the relief of eye symptoms would be listed in "Uses" in the drug fact labeling under the broader indication limited to "hay fever and other respiratory allergies" and would not state or imply a claim for allergic conjunctivitis.

5.4 Safety of FPANS

The safety of FPANS is supported by the clinical development program for the prescription product, as well as by over 20 years of postmarketing experience. Clinical trial data in support of safety include pooled data from 28 placebo-controlled efficacy and safety trials, which include 3 long-term safety studies of ≥ 6 months duration, as well as specific trials evaluating the effect on the HPA axis and pediatric growth. The postmarketing experience encompasses data from the United States and in over 130 countries where FPANS is currently marketed, including data from 13 countries where FPANS is available without a prescription.

Overall, no new safety signals from the clinical trial database have been identified during this review, and there were no safety issues identified in the postmarketing database to change this assessment. The most common risk for the product is local nasal irritation, which is largely minor and self-limited. More serious local nasal events, including nasal septal perforation, have been reported, but occurrences are rare. In addition, FPANS was shown to have a small effect on growth velocity during a one year pediatric growth study (-0.14 cm/year, 95% CI -0.54, 0.27). Finally, the potential for additional class-specific safety concerns exists (e.g., ocular safety, HPA axis suppression), but overall, the data are reassuring and not suggestive of major safety concerns.

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/s/

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CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-434
Priority or Standard	Standard
Submit Date(s)	09/21/13
Received Date(s)	09/23/13
PDUFA Goal Date	07/23/14
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Steven Osborne, M.D.
Review Completion Date	June 4, 2014
Established Name	Fluticasone propionate
(Proposed) Trade Name	Flonase Allergy Relief
Therapeutic Class	Corticosteroid
Applicant	GlaxoSmithKline Consumer Healthcare (GSK)
Formulation(s)	Nasal Spray
Dosing Regimen	50 mcg/spray, 1 or 2 sprays each nostril daily
Indication(s)	Allergic rhinitis (seasonal and perennial) (b) (4)

Intended Population(s) Patients age (b) (4) and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the data reviewed, the risk-benefit analysis for fluticasone propionate aqueous nasal spray (FPANS) is favorable for consumers age (b) (4) and older with allergic rhinitis (AR) in the over-the-counter (OTC) environment. (b) (4) No special postmarket requirements or commitments are recommended except for routine pharmacovigilance.

1.2 Risk Benefit Assessment

The sponsor is proposing the prescription (Rx) to over-the-counter (OTC) switch of Flonase aqueous nasal spray (fluticasone propionate, FPANS, or Flonase in this review), for the treatment of the nasal and ocular symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and (b) (4) in (b) (4) years and older. In the USA, FPANS is approved for these indications for ages 4 years and older. Table 5 in section 2.6 shows that 28% of use occurred in the age range 0-17. These data suggest that OTC availability of FPANS would likely lead to use by the consumer in younger age ranges. Fluticasone propionate nasal spray would be a second in-class switch (Rx-to-OTC) for an intranasal corticosteroid to treat allergic rhinitis.

Allergic rhinitis is an established OTC indication and is typically described on the Drug Facts Label (DFL) as "hay fever or other respiratory allergies". The sponsor's draft DFL reads: "for the temporary relief of symptoms of nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes due to hay fever, other upper respiratory allergies, (b) (4) ". The claims for relief of eye-allergy symptoms (b) (4) for a nasal spray would be new for an OTC drug. Including these claims, even if supporting data were available, could be confusing to consumers. Alignment with the label of the approved OTC intranasal corticosteroid, Nasacort Allergy 24 Hour, could help consumers use Flonase Allergy Relief properly.

Since 1994, Flonase has been available as a prescription drug in the USA for the treatment of SAR and PAR in adults and adolescents 12 years of age and older. Through supplements to the NDA, the indication was extended to children 4 years of age and older in 1997. In 1998, the indication was extended for perennial nonallergic rhinitis) and in 2002 for use on an as needed basis (prn).

Use in foreign countries

FPANS is registered in over 140 countries as a prescription drug, and in 13 countries as a nonprescription drug (not strictly "OTC" as pharmacist input usually required). In addition, nonprescription FPANS is approved for the relief both the nasal and ocular symptoms of allergic rhinitis in six of these 13 countries, including the UK, New Zealand, Ireland, Latvia, Slovenia and Estonia.

The sponsor conducted two label comprehension studies (RH01305 and RH01318), two Human Factors studies (RH01801 and RH01929 correct cleaning, priming, and use of product per the DFL and Consumer Package Insert), and a targeted self-selection study (RH01442). An Actual Use (AU) Study (R1810198) was completed in 2003, but not required for this application.

Comment:
Although the draft DFL has been updated with the current application, the changes from the label used in the 2003 AU study are minor and addressed by the Label Comprehension studies and the expected alignment with the label of the already approved OTC intranasal corticosteroid, Nasacort Allergy 24HR.

The sponsor conducted two studies (FNM30033 and FNM30034) to support a claim of relief of ocular symptoms associated with allergic rhinitis (SAR). These studies, and where to find discussion about them, are shown in Table 1 below.

Table 1. Studies pertinent for OTC switch (performed for switch or PMC/Written Request)

Study Type	Study Number	Purpose	Where Reviewed
Label Comprehension (LC) pilot	Rh01305	Can consumer understand DFL: Uses, Warnings and Directions	Social science review
LC pivotal	RH01318	Same as pilot LC, target key areas from pilot LC	Social science review
Self-selection	RH01442	Can consumer taking medications for HIV determine if the drug is right for them?	Social science review
Human Factors	RH01801	Can consumer properly use nasal spray: priming, cleaning, spray into nose correctly	Social science review
Human Factors	RH01929	Same as RH01801 except focus on low literacy population	Social science review
Legacy Actual Use (completed in 2003)	R1810198	Evaluate proper use in naturalistic OTC environment	Section 5 (design and results) and Section 7 (safety)
Ocular	FNM30033	Relief of symptoms such as itching	DPARP* review
Ocular	FNM30034	Relief of symptoms such as itching	DPARP review
HPA Axis suppression	FNM40183	Evaluate for adrenal	DPARP review

(FDA Written Request)		suppression (6-weeks)	
Growth Study	FNM40017	Growth effect from Flonase (200 mcg /day for 1 year)	DPARP review and Section 7.3.5
Growth Study	FFR101782	Growth effect from FF** 100 mcg /day	DPARP review and Section 7.3.5

* Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
** FF refers to fluticasone furoate

Application-specific and drug class considerations

The key consideration for use of FPANS in the OTC environment is whether the drug can be used safely, potentially for months or years without a learned intermediary. Topics to consider include local effects and potential systemic effects:

- Epistaxis or perforation of nasal septum
- Ocular adverse events such as cataracts or glaucoma
- Potential suppressive effect on the hypothalamic-pituitary-adrenal axis
- Slowing in growth velocity in children / impact on adult height
- Effect on glucose metabolism
- Immunosuppression or the development or worsening of infections such as tuberculosis (TB), ocular herpes, bacterial, fungal, or parasitic infections
- Potential drug-drug interactions (e.g. with CYP3A4 inhibitors)
- Effect on bone metabolism

Overview of Safety Data Submitted

The sponsor submitted an *Integrated Summary of Safety* (ISS) that included safety data from the following sources from 1994 through 2012:

- Clinical Trial Data
  --included Written Request (WR) and Postmarket Commitment (PMC) for HPA axis suppression and Growth delay studies
- Postmarket Data from Sponsor's Pharmacovigilance Database, FDA AERS, World Health Organization (WHO), Drug Abuse Warning Network (DAWN), and the National Poison Data System (NPDS)
- Literature Review
  --included 2 large epidemiological studies of FPANS
- Safety Update (120-day) for data received after the data lock for the NDA submission

Clinical Trial Data

DPARP will review the clinical trial, WR and PMC data. Clinical studies showed there was a slight, but insignificant, decrease in pediatric growth rate when FPANS was used for one year in children 3.5-9.5 years of age

Postmarket Safety Data

Postmarket safety data are reviewed in more detail in Section 8 of this review. The sponsor analyzed its pharmacovigilance database, FDA AERS and the WHO Vigibase system for safety

signals from product launch in 1994 until December 31, 2012, and recent data from DAWN (2004-11) and the NPDS (1999-2011).

Adverse events (AE) identified during postmarket use of Flonase include nasal discomfort and congestion, epistaxis, alterations of taste and smell, nasal septum perforation, decreased blood cortisol, headache, nausea, insomnia, dizziness, fatigue, dyspnea, ocular events (cataract, glaucoma, increased ocular pressure), and hypersensitivity.

Literature Review

The literature is discussed in Section 9 of this review. The sponsor submitted 118 references from 1985- 2012. Approximately half of these references discussed the safety and efficacy of nasal steroids, mostly FPANS, for the treatment of allergic rhinitis. Fluticasone propionate is noted to have minimal (<1%) systemic bioavailability[12]. Inhaled fluticasone propionate, but not intranasal fluticasone propionate led to adrenal suppression[13]. Approximately 85% of individuals with asthma have allergic rhinitis, and 21% of individuals with allergic rhinitis have asthma[8], which suggests that a significant minority of users of OTC Flonase could also be using an inhaled corticosteroid.

Comment:
The literature review identifies intranasal corticosteroid use as having the potential for adverse events, mostly local. However, the intranasal route of administration of 100-200 mcg of FPANS poses a low overall risk of systemic effects.

Safety Update (120-day, post data lock for NDA submission)

The sponsor provided a safety update of all spontaneous reports it received from their internal GSK Pharmacovigilance Database, the literature, and DAWN from January 1, 2013-October 31, 2013. There were no AEs associated with a fatal outcome. The significant elements of this update came primarily from the sponsor's safety database, which showed:

- 245 reports with 501 AEs, of which 37 were serious
- 30 reports of epistaxis (2 serious) and 1 nasal septum perforation
- 1 oral candidiasis in a patient taking ritonavir
- 2 glaucoma
- 3 HPA axis effects
- 0 growth AEs

Comment:
The 120-day safety update raises no new concerns, but highlights the need for effective labeling regarding concomitant use with medications involving ritonavir.

Consideration of Some Special Topics

Table 2 below shows AEs from the AERS database related to some of the special topics for consideration, followed by a discussion of the key areas.

Table 2. AEs of special interest from AERS database 1994-2012

Area of Interest	Preferred Term	Number of Events
Local Nasal Events	Nasal Septum Perforation	23
	Epistaxis	660
Ocular Events	Cataract	140
	Glaucoma or increased intraocular pressure	103
Effects on HPA Axis	Adrenal suppression or insufficiency	46
	Blood cortisol decreased	21
Effect on glucose metabolism	Diabetes (Type 2) or hyperglycemia	413
Bacterial rhinosinusitis	Staph, strep or other bacterial infection	81
Candidiasis	Oral	73
	Other fungal infection (nasal, esophageal, unspecified)	162

HPA Axis suppression

The sponsor also completed a 1-year growth study in 150 pediatric patients evaluating whether use of FPANS led to HPA axis suppression or affected their growth velocity. This study was reviewed by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). See Consideration of Special Topics below and in Section 7.3.5 of this review.

Reviewer's Sample Calculation for Prednisone-equivalent of FPANS 200 mcg per day

The sponsor notes that fluticasone propionate is approximately 4 times the potency of dexamethasone (which itself is approximately 4 times the potency of prednisone). A daily dose of 200 mcg of FPANS yields 3.2 mg prednisone equivalent if the drug were 100% absorbed (200 mcg x 16, using highest estimate of prednisone-equivalent potency). For 2% bioavailability (≤ 2% per Flonase Prescribing Information), the prednisone-equivalent is 0.064 mg (200 mcg x 16 x 0.02). This is a very low dose of steroid, although it is not zero (see Section 7.3.5 of this review).

Comment:

1. A suppressive effect on the HPA axis seems unlikely with labeled use of FPANS in adults. There may be a margin of safety in children, especially if dosed at the 100 mcg daily dose.

Growth Effects

The prescription label includes a Precaution about potential growth retardation in children and a recommendation to use the lowest dose at which effective control of symptoms is maintained. To assess growth effects, the sponsor performed a growth velocity study as a PMC, and evaluated treatment emergent adverse events (TEAEs) associated with growth effects by searching its integrated safety database. Based on these data, no evidence of TEAEs related to growth was observed in the adolescent subjects or the pediatric subjects. However, the growth velocity study showed a slowing of growth velocity of -0.23 cm over one year of use, compared with placebo, although the result was not statistically significant, possibly due to an underpowered study. The DPARP review team will discuss this topic.

Comments:

1. The sponsor requested an OTC age limit of (b) (4) *years and older* (b) (4) *. However, the effect of FF on growth rate cannot predict the effect of FP, which is a separate corticosteroid entity and showed no significant effect on growth rate in Study FNM40017.*

2. A caveat is that we do not have data on what happens with multi-year use during the growing stages, nor how various periods of non-use might help mitigate any slowing effects on growth.

3. If this product is approved for use in children, then we might consider limiting the dose to 100 mcg /day and aligning the terminology regarding growth effects with that of the OTC intranasal corticosteroid approved in 2013, Nasacort Allergy 24HR.

Ocular Safety

The sponsor searched its *clinical trials database* for ocular TEAEs and found reports of blurred vision, eye pain, ocular hyperemia and photophobia, but few reports of glaucoma or cataracts (<0.1%). In the postmarket setting, reports of glaucoma and cataracts are more common.

Comment:
Oral corticosteroids are associated with subcapsular cataracts, increased intraocular pressure and glaucoma. The draft Drug Facts Label warns consumers with glaucoma to ask a doctor before use of Flonase and to stop use and ask a doctor if: "you get new changes to your vision that develop after starting this product". The input of a healthcare intermediary will not likely affect the chance of developing either condition de novo.

Local Adverse Events: Perforated Nasal Septum and Epistaxis

In clinical trials, epistaxis was reported in 2.6% subjects in the total FPANS group, in 4.6% subjects in subjects exposed to other active comparators (e.g. intranasal beclomethasone dipropionate), and in 0.8% subjects exposed to placebo. One postmarket case of nasal septum perforation in a 38-year old female is discussed in section 8 of this review.

Comment:
Nasal septum perforation is not expected to be a hurdle for OTC use of FPANS because the occurrence and the treatment are likely to be similar with labeled use of Flonase in the Rx or OTC environment.

Summary

FPANS has a favorable risk-benefit profile for the treatment of SAR and PAR in the OTC environment. This reviewer's conclusions are:

- the product has an established safety profile in the prescription environment

- label comprehension testing and self-selection testing demonstrated that consumers generally understand the label
- the systemic effects of FPANS are minimized due to its low bioavailability (< 2%).
- the ocular claim would be new for an OTC drug used to treat allergic rhinitis; however, the potential for spraying in the eyes, is low with effective labeling
- a delay in the diagnosis of a serious medical condition (e.g. infection, diabetes) by use of Flonase is a potential concern, but was not seen in clinical trials
- the most common side effects are mild, reversible, local nasal events
- serious events, including glaucoma, nasal septum perforation, heavy epistaxis, or adrenal suppression have been reported infrequently in adults
- a review of the postmarket safety databases did not raise new signals, but use of this product with inhaled or topical corticosteroids could increase risks for HPA axis suppression
- fluticasone propionate (FP) has significant drug-drug interactions with CYP3A4 inhibitors that increase the blood level of FP (ritonavir; ketoconazole). These interactions will need effective labeling
- *if approved for children, there is a potential for slowing of growth with overuse or prolonged, unmonitored use. One option is to label with a limit for daily use of two months, after which a consumer should consult a doctor*

For any concerns about how the Drug Facts Label alone can communicate about adverse events or provide adequate information under the Warnings or Directions sections of the DFL, a Consumer Leaflet might help convey the information.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

No special postmarket requirements or commitments are recommended except for routine pharmacovigilance.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed OTC product, fluticasone propionate (aqueous nasal spray) is a second-generation, synthetic trifluorinated corticosteroid with approximately 4 times the potency of dexamethasone or twice as potent as triamcinolone and 16 times as potent as prednisone in animal models of inflammation.

FPANS is supplied as a white, opaque suspension of (b) (4) fluticasone propionate (FP) for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Each actuation of the nasal spray provides 50 mcg of FP. The recommended dose (b) (4) is 2 sprays into each nostril (200 mcg total) once daily in the first week and 1 or 2 sprays into each nostril in week 2 and thereafter.

The sponsor estimate bioavailability of FPANS at 2% or lower. Total bioavailability includes absorption from the nasal mucosa and from swallowing the drug. The Flonase prescribing information states, "The systemic corticosteroid effects of FPANS are mitigated due to its low bioavailability and route of administration. From pharmacokinetic studies, indirect calculations indicate that fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging <2% (Flonase® PI)".

The sponsor states that the OTC product will:

- Contain the same active pharmaceutical ingredient (API) as the Rx product
- Use the same excipients as the Rx product
- Be composed of the same formulation as the Rx product
- Be manufactured at the same facility as the Rx product
- (b) (4)
- Be dispensed using the same metered-dose spray pump as the Rx product

Since its approval in 1994 under NDA 20-121, Flonase Nasal Spray has been available as a prescription for the treatment of nasal symptoms of SAR and PAR in adults and children 12 years of age and older. Subsequent approvals were granted for Rx Flonase as follows:

- October 31, 1997 (S-005): approved in pediatric patients 4 years of age and older
- December 11, 1998 (S-009): approved in patients with perennial non-allergic rhinitis
- May 23, 2002 (S-0232): approved for as-needed (PRN) use

2.2 Tables of Currently Available Treatments for Proposed Indications

The indications the sponsor requests are for the treatment of nasal and ocular symptoms of SAR, PAR, and (b) (4) in (b) (4) years of age and older. The Uses section of the draft DFL states: temporarily relieves the symptoms of nasal congestion, runny nose, sneezing, itchy nose, itchy and watery eyes due to hay fever, other upper respiratory allergies, (b) (4)

There are many approved prescription and OTC products for relief of seasonal or perennial allergy symptoms (e.g. "hay fever"); and one approved OTC corticosteroid product (Nasacort Allergy 24HR) for these indications.

The most commonly used drug products used to treat allergic rhinitis are nonprescription antihistamines, both sedating and non-sedating, decongestants, prescription leukotriene inhibitors

such as montelukast and intranasal corticosteroids, including FPANS. All of these products have the same or similar allergy relief indications.

2.3 Availability of Proposed Active Ingredient in the United States

Fluticasone propionate is available by prescription in the USA as a nasal spray and drops and as an inhaled formulation. The first generic Rx fluticasone intranasal spray was approved in 2006. The regulatory status of Flonase nasal spray formulations is shown in Table 3 below.

Table 3. Regulatory status of fluticasone propionate formulations

Appl No	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
A077538	No	FLUTICASONE PROPIONATE	SPRAY, METERED; NASAL	0.05MG/SPRAY	FLUTICASONE PROPIONATE	APOTEX INC
N020121	Yes	FLUTICASONE PROPIONATE	SPRAY, METERED; NASAL	0.05MG/SPRAY	FLONASE	GLAXOSMITHKLINE
A077570	No	FLUTICASONE PROPIONATE	SPRAY, METERED; NASAL	0.05MG/SPRAY	FLUTICASONE PROPIONATE	HI TECH PHARMA
A076504	No	FLUTICASONE PROPIONATE	SPRAY, METERED; NASAL	0.05MG/SPRAY	FLUTICASONE PROPIONATE	ROXANE
A078492	No	FLUTICASONE PROPIONATE	SPRAY, METERED; NASAL	0.05MG/SPRAY	FLUTICASONE PROPIONATE	WOCKHARDT

Source: Orange Book March 2014
Applications beginning with an A refer to a generic product

2.4 Important Safety Issues With Consideration to Related Drugs

Corticosteroid drugs are widely used as oral, topical and inhaled (nasal and oral inhalation) formulations. High doses can exacerbate diabetes, and lead to immunosuppression and increased susceptibility to infections. Chronic use can be associated with potential suppression of the HPA axis or growth velocity delay in children. However, short-term use of a corticosteroid is generally well tolerated by any route of administration in most patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to this NDA switch application, the sponsor and FDA met in May 2001, February 2011, October 2012, and May 2013.

At the May 2001 meeting, FDA recommended careful attention in label comprehension to how long to use Flonase, any medical conditions that might contraindicate use of Flonase, and potential drug-drug interactions with CYP 450 inhibitors, such as protease inhibitors. FDA also recommended an actual use study.

Comment:
The sponsor then performed a label comprehension and actual use study (2003). In 2004, they made a business decision to place the switch application on hold. In 2011, they reactivated the development program.

At the February 2011 meeting, the sponsor and FDA discussed label comprehension (LC), self-selection (SS) and actual use (AU) studies. The sponsor proposed use of the product in (b) (4) (b) (4) years of age and older.

Comment:
The sponsor did not initiate, and FDA later dropped the requirement for, a second AU Study. FDA decided consumers understood the concept of a nasal spray drug and a competing corticosteroid nasal spray drug (triamcinolone acetonide) was not required to perform an AU study.

FDA also requested targeted analyses for HPA axis suppression, effects on growth, bone metabolism, and glucose metabolism, potential drug-drug interactions, bacterial rhinosinusitis, and local adverse events such as perforation of nasal septum, and any other safety concerns the sponsor might have clinical relevance. FDA cited the safety synopsis included in the briefing material, which included 42 unexplained AERS reports of adrenal suppression associated with fluticasone propionate nasal spray.

At the October 2012 meeting, the sponsor and FDA agreed on the datasets for the Integrated Summary of Safety and the Consumer Studies. (b) (4) .

At the May 2013 meeting, FDA told the sponsor that since Flonase is currently approved as a prescription product down to 4 years of age, the Agency anticipates that consumers will use the OTC product in children, too. If the pediatric safety concerns are sufficient to warrant restricted labeling, the availability of Flonase as an OTC product may be an issue. The sponsor stated that it would provide trial data supporting a rationale for limiting use to consumer (b) (4) years of age and older. Of note, an actual use study was not discussed at the 2012 or 2013 meetings.

2.6 Other Relevant Background Information

Distribution of FPANS

Fluticasone propionate aqueous nasal spray (FPANS) was first authorized as a prescription in the UK in March 1990, and is now marketed in 143 countries. The non-prescription (OTC) formulation of FPANS was first authorized in New Zealand in 1999 and has since been switched to non-prescription status in 13 markets. In most of these countries allowing nonprescription access, a pharmacist input is required, so the term OTC as we know it in the USA is not an exact equivalent. Table 4 shows overseas age restrictions and Table 5 shows USA Rx use by various age groups

.

Table 4. Age restrictions for nonprescription use of FPANS in foreign countries

Country	mcg/spray	Age Restriction	Age or Duration of Use Comments (examples)
UK	50	18+	Do not use for more than 3 months continuously without consulting your doctor
Finland	50	18+	
Estonia	50	12+	"take special care with Flixonase in children under 12 years of age"
Latvia	50	12+	
Sweden	50	12+	1-2 sprays for up to 3 months
Ireland	50	12+	
Australia	50	12+	Seek medical advice if you intend to use the product more than 6 consecutive months
New Zealand	50	12+	For the short term (3-6 months) prevention and treatment….of hay fever
Denmark	50	12+	Contact the doctor if symptoms are getting worse, or if you don`t feel better within 7 days.
South Africa	50	12+	Short-term (less than 6 months) prophylaxis and treatment of symptoms of allergic rhinitis (hay fever)

China	50	12+	
Singapore	50	12+	Do not use the spray for more than 3 months without the advice of your doctor or pharmacist
Slovenia	50	12+	

Source: sponsor's submission, module 1: 1.14.15 Foreign Labeling
China's OTC label says epistaxis is a very common adverse event
Flixonase is the trade name for the sponsor's fluticasone propionate in some foreign countries

Table 5. Prescription FPANS Exposure by Age January 2012 to December 2012

Age	Prescriptions Written (000s)	% of total Prescription FPANS use	Estimated Patient Years Exposure
PAT AGE 0 - 11	(b) (4)	19.38%	11046600
PAT AGE 12 - 17		8.99%	5124300
PAT AGE 18-65		57.04%	32512800
PAT AGE >65		12.99%	7404300
Unspecified AGE		1.59%	906300

Source: sponsor's Postmarketing data, page 5

Comments:
1. Table 5 above shows that 19% and 9% of use occurred in the age range 0-11 and, 12-17, respectively. These data suggest that OTC availability of FPANS would likely lead to use by the consumer in the pediatric age range, possibly down to 4 years of age as with Flonase Rx.

2. The column in Table 5 showing Estimated Patient Years Exposure is likely an estimate over more than the one year (2012) since the values are multiples higher than possible even if the prescriptions were written for a full year. For example, (b) (4) prescriptions for patients 0-11 years of age could at most yiela (b) (4) patient-years of exposure, not the 11,046,600 listed.

Exposure of FPANS
As of December 2011, the cumulative exposure to FPANS is approximately 31.2 million patient years. The sponsor estimates that during the 5-year period from January 2008 to December 2012 there have been approximately 0.6 million patient years of exposure to non-prescription FPANS. The sponsor estimates that (b) (4) canisters of nasal spray were distributed from February 2012-2013.

Determination of optimum dose of FPANS for OTC switch
The dosing recommendations for the use of FPANS for the management of the nasal symptoms of AR were established as part of the original prescription NDA 20-121. GSK conducted two trials of FPANS 100 mcg per day for the treatment of PAR (R1810220) and

SAR (R1810221). The 100 mcg per day dose provided efficacy for both conditions, but the time-to-onset of effect was slower (3 days vs. 12 hours) and the treatment effect less than previously observed for 200 mcg per day. The sponsor proposed the OTC starting dose for (b) (4) to be the same 200 mcg per day as for the prescription product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was adequate. This was an electronic submission of all data used to support the application. The data provided was well organized and complete. The integrity of the submission was good.

3.2 Compliance with Good Clinical Practices

The sponsor states that the AU study (R1810198) completed in 2003 was conducted in accordance with Good Clinical Practices (GCP), including the archiving of essential documents.

A data audit was not performed for this prescription to OTC switch. The sponsor submitted some portions of the Actual Use study (a clinical study) that it performed, but this study was completed in 2003 and not required by FDA in this NDA submission. No inspections were conducted for this submission.

The sponsor submitted a Debarment Certification, stating:
"GlaxoSmithKline Consumer Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in connection with the New Drug Application for *Flonase Allergy Relief (NDA* 205-434)."

3.3 Financial Disclosures

The sponsor provided Financial Certification/Disclosure information for 13 studies and provided a Form 3454 for certification along with 3 FDA Form 3455 for investigators who owned equity during the conduct of the covered clinical studies:(30033, R1810220 and R1810221 (source: section 1.3.4 of Module 1).

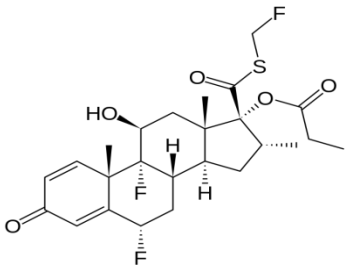
Comment:
The sponsor submitted appropriate and adequate financial disclosure documents. The financial information submitted by the sponsor did not raise any questions regarding the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See the CMC review for further information. The chemical structure of fluticasone propionate, a fluorinated corticosteroid, is shown in Figure 1 below. FP is approximately 16 times as potent as prednisone and 4 times as potent as dexamethasone in animal models of inflammation.

Figure 1. Chemical structure of fluticasone propionate ($C_{25}H_{31}F_3O_5S$)



The unit must be primed with 6 actuations before initial use. Each actuation is intended to deliver 50 mcg of FP. CMC drug product information is provided in prior submissions to NDA 20-121 except for the following changes:

- Change in target fill weight to support additional OTC spray counts: (b) (4), 60, (b) (4) spray configurations
- Qualification of Type III glass as an alternative bottle type
- Change in (b) (4) the dust-cover (b) (4)

4.2 Clinical Microbiology

This section does not apply.

4.3 Preclinical Pharmacology/Toxicology

Flonase was approved in the United States for prescription use in 1994. FDA agreed in meetings with the sponsor that no additional preclinical work was needed to support the Flonase Rx-to-OTC switch.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were conducted in support of this submission. The clinical pharmacology team will review how the drug's bioavailability and drug-drug interactions will influence approval or labeling for the OTC switch. A brief discussion of the topic is shown below.

4.4.1 Mechanism of Action

The precise mechanism of the corticosteroid anti-allergic action is unknown; however, corticosteroids have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils,

neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.

4.4.2 Pharmacodynamics

The sponsor evaluated oral versus intranasal FP and demonstrated that the efficacy of intranasal FPANS could be attributed to its topical effect. See Section 7 for a discussion about the HPA axis suppression study: The sponsor compared FPANS 200 mcg once daily or 400 mcg twice daily compared with placebo or oral prednisone 7.5 or 15 mg given in the morning. FPANS at either dosage for 4 weeks did not affect the adrenal response to 6-hour cosyntropin stimulation, while both dosages of oral prednisone significantly reduced the response to cosyntropin.

4.4.3 Pharmacokinetics

The sponsor notes that following administration of 200 mcg to (b) (4) patients, systemic exposure to FPANS is limited, with an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic rhinitis for 3 weeks, fluticasone propionate plasma concentrations were above the level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The data consists of clinical trials, postmarket commitment studies, consumer behavior studies, and a legacy actual use study. Safety studies are listed in Section 7.1.1

Clinical Trials to support NDA and Supplements
The sponsor pooled 28 clinical studies and added 15 non-pooled clinical studies that supported the approval of NDA 20-121 and the supplements, including the sNDA that extended usage to children 4 to 17 years of age. The 28 pooled studies had a minimum 2-week treatment and used FPANS at doses of 100 mcg/day and 200 mcg/day for children and adults. These studies included safety data on subjects 4 to 17 years of age. Three of the 28 studies were long-term studies in which subjects received drug for at least 26 weeks. These 43 (28 pooled, 15 non-pooled) studies are considered in the DPARP review.

Postmarket Commitments (b) (4)
The sponsor performed a 6-week HPA axis suppression study (FNM40183) and a 1-year Growth Effects study (FNM40017). These studies used FPANS 200 mcg per day. These studies assessed the likelihood of adrenal axis suppression and any change in growth velocity, respectively.

The long-term growth study that was in response to corticosteroid class labeling (b) (4) went down to children 3.5 years, but the number of children under 4 years of age was few. Flonase was approved in ages 4 years and older based on the Sponsor's request, with very limited data in patients under 4years, and the lack of evidence that significant use occurs in patients under four.

Table 6 below lists studies key to the OTC switch:

Table 6. Studies pertinent for OTC switch (performed for switch or PMC (b) (4))

Study Type	Study Number	Purpose	Where Reviewed
Label Comprehension (LC) pilot	Rh01305	Can consumer understand DFL: Uses, Warnings and Directions	Social science review
LC pivotal	RH01318	Same as pilot LC, target key areas from pilot LC	Social science review
Self-selection	RH01442	Can consumer taking medications for HIV determine if the drug is right for them?	Social science review
Human Factors	RH01801	Can consumer properly use nasal spray: priming, cleaning, spray into nose correctly	Social science review
Human Factors	RH01929	Same as RH01801 except focus on low literacy population	Social science review
Legacy Actual Use (completed in 2003)	R1810198	Evaluate proper use in naturalistic OTC environment	Section 5 (design and results) and Section 7 (safety) of this review
Ocular	FNM30033	Relief of symptoms such as itching	DPARP* review
Ocular	FNM30034	Relief of symptoms such as itching	DPARP review
HPA Axis suppression	FNM40183	Evaluate for adrenal suppression (6-weeks)	DPARP review and Section 7.3.5
Growth Study	FNM40017	Growth effect from Flonase (200 mcg /day for1 year)	DPARP review and Section 7.3.5
Growth Study	FFR101782	Growth effect from FF** 100 mcg /day	DPARP review

* Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
** FF refers to fluticasone furoate

The LC studies evaluate the consumer's understanding of the DFL, the SS study evaluates whether consumers can interpret the label and select whether the drug would be appropriate for them. The HF studies evaluate the consumer's understanding of the Consumer Package Insert (CPI), which describes proper priming, use, and cleaning of the pump, to support appropriate use of the product in the consumer environment.

Ocular Studies

Studies FNM30033 and FNM30034 were clinical trials designed to assess the efficacy of FPANS on ocular symptoms in subjects with allergic rhinitis. Both studies evaluated the efficacy of FPANS 200 mcg QD compared with placebo and loratadine 10 mg tablets in the relief of ocular symptoms associated with in subjects aged 12 years and older. Both studies were multicenter, randomized, double blind, placebo-controlled, parallel-group trials. These studies will be reviewed by DPARP.

Comment:
Studies FNM30033 and FNM30034 examined subjects with SAR but not with PAR or non-allergic rhinitis.

5.2 Review Strategy

The DPARP team will discuss the clinical trials supporting the original approval and the supplements. The results of the Actual Use study are reviewed in Section 5.3 below. In addition:

- The safety data from clinical trials is briefly reviewed in Section 7, as is the safety data from the Actual Use study
- The safety from postmarket data about FPANS is reviewed in Section 8 of this review
- The safety from the literature is discussed in Section 9 of this review
- The PMC studies regarding HPA axis suppression and potential growth delay in children are discussed briefly regarding safety in Section 7.3.5 of this review. They are reviewed in detail by DPARP in their clinical review
- Special topics of bone metabolism, glucose metabolism, and sinus infection are reviewed in Section 7.3.5 of this review
- The label comprehension and human factors studies are reviewed by the social scientist

5.3 Discussion of Individual Studies/Clinical Trials

Actual Use Study R1810198
Title: An Actual-Use Study in Support of the Over-the-Counter Switch of Flonase Allergy

Design/Methodology:
The study was a pharmacy-based, open-label, all-comers, naturalistic trial conducted at 63 pharmacy sites in 10 communities within the US. The sponsor conducted the study from March 4, 2003-November 29, 2003 enrolling 2017 subjects (1572 evaluable).

The first stage of the study involved the recruitment of subjects to test self-selection and purchase of the study drug. Following self-selection, participants who agreed to purchase the medicine and satisfied the inclusion/exclusion criteria, could purchase as much Flonase as they wished and enter the 6-month actual use period of the study. Subjects were contacted by telephone seven times during the actual use period.

Two variations of the study package were used to differentiate between adult and adolescent use. The adult package directed adults 18 years of age or older to start with a dose of 2 sprays into

each nostril (200mcg), which could be reduced to 1 spray into each nostril (100mcg) after 4-7 days if nasal allergy symptoms improved. The teen package directed adolescents aged 12-17 years to use a dose of one spray into each nostril (100mcg).

Comments:
1. FDA did not review the specific DFL or protocol for this 2003 AU study prior to initiation.

2. The sponsor states that the self-selection and use portion of the AU study is not relevant, because it incorporated an early version of the DFL (2003), which it modified for the current submission (2013). On the other hand, the sponsor states that the safety results support an OTC approval.

3. The sponsor made a business decision not to complete the study report for the AU study in 2003 and chose not to pursue the OTC switch of fluticasone propionate until now.

Treatment Duration
Up to 6 months

Main Criteria for Inclusion
- Healthy, ambulatory male and female subjects
- at least 12 years of age
- chose to purchase Flonase Allergy at the initial pharmacy visit for personal use during the actual use portion of the study

Exclusion criteria
- History of hypersensitivity to the study drug or its excipients
- Participation in any previous FP study within 12 months whether or not the study required the use of study medication
- Participation in any clinical trial requiring the use of study medication within 30 days prior to the initial pharmacy visit
- Subject was unable or unwilling to be contacted by phone or unwilling to complete the Flonase Allergy Actual Use study
- Subject diagnosed with HIV or AIDS. This criterion was added as a Protocol Amendment once additional information from a drug interaction study (ritonavir) became available.

Primary Objective
The primary objective was to assess subjects' overall adherence with the Drug Facts label.

Secondary Objective(s)
The secondary objectives were to assess:
- self-selection/de-selection for appropriateness of use at the initial pharmacy visit.
- appropriateness of FPA use and adherence to all label instructions, including compliance with dosing instructions and correct product selection and purchase.

- safety based upon AE data for FPANS in a simulated, naturalistic OTC setting.
- patterns of use of FPANS as recorded on FPA use diaries.
- subject-perceived effectiveness and satisfaction and onset of relief of nasal allergy symptoms
- patterns of use, adverse events, selection/de-selection for appropriate use, and selection/de-selection to self-medicate in sub-groups of the total population

Table 7 below shows the schedule of events for subjects in the Actual Use study.

Table 7. Schedule of study events

PROCEDURES	Pharmacy Visit (Day 0)	Telephone Interview 1 (Day 7 ±2)	Telephone Interview 2 (Day 30 ±5)	Telephone Interview 3 (Day 60 ±5)	Telephone Interview 4 (Day 90 ±5)	Telephone Interview 5 (Day 120 ±5)	Telephone Interview 6 (Day 150 ±5)	Telephone Interview 7 (Day 180 ±5)
Label review	X							
Appropriate Use and Purchase decision questions:	X							
Baseline medical information and demographics form and REALM testing	X							
Informed consent	X							
Inclusion/exclusion review	X							
Initial medication purchase[1]	X							
Diaries and Worksheets dispensed[2]	X							
Interim telephone interview		X	X	X	X	X	X	
End-of-treatment period telephone interview[3]								X
All outstanding medication returned to pharmacy								

[1] All medication dispensation was at the discretion of the subject.
[2] A sufficient number of diaries, worksheets, and mailing materials were provided to allow subjects to return diaries and worksheets during a 6-month period.
[3] During this interview, subjects were reminded to return to the pharmacy with all used and unused medication bottles and to mail in all outstanding diaries/worksheets. This interview took place whenever the subject indicated he/she would discontinue product use, within the 6-month study period.
[4] This visit took place whenever the subject indicated he/she would discontinue product use.

The Draft Label (adult) for AU Study R1810198 is shown in Section 9.1 (Labeling)

Study Results

Criteria for evaluable subjects

- All subjects who participated in the initial pharmacy visit and supplied demographic and medical information were considered evaluable for initial self-selection or de-selection for appropriateness of use.
- All subjects who purchased FPA at the initial pharmacy visit were considered evaluable for assessing safety. All subjects who purchased FPA and who had post-

initial pharmacy visit data were considered evaluable for appropriate use and adherence to all label instructions during actual use.

- All subjects who returned at least one FPA Medication Use Diary were considered evaluable for assessing compliance with dosing directions and patterns of use.

Number of subjects

Investigators screened 2216 subjects and enrolled 2037 of them. The other 179 subjects did not enter the study for various reasons. Of the 2037 subjects entering the study, 2017 were in the ITT population (20 did not answer Question 1: "Do you think this medicine is appropriate for you to use?"). Of these 2017, 1616 made a purchase at the initial pharmacy visit, and 401 did not. There were 1572 evaluable subjects with subsequent data following purchase.

Initial Self-Selection Results

Self-selection

The self-selection analysis included 1892 subjects. Overall, 813 (43.0%) subjects made the correct initial self-selection decision. There were 1076 subjects who incorrectly self-selected and 3 who incorrectly de-selected. Most (914, 84.9%) of the 1076 incorrect self-selections were incorrect because the subject indicated sinus pain but did not indicate the need to speak to a doctor. Without the sinus pain warning as a reason for incorrect selection, 76.8% of subjects would have made a correct selection decision (post hoc analysis).

Comment:

The sponsor's request to ignore results of the AU study may be an effort to mitigate the resulting low rate of correct self-selection (43%) and the low proper use rate (32.4%, see below) in this study due to the subjects not heeding label directions about sinus pain or other factors.

About half of the subjects (50.8%) who selected the product stated that they had allergies or general allergy symptoms, 20% mentioned specific allergy symptoms and 19.3% stated that they had used Flonase before. For those subjects who stated the product was not appropriate for them to use, 33.3% said they had used the product before, 12.5% did not like or could not tolerate nasal sprays and 6.3% did not currently have allergies or allergy symptoms.

Actual Use of the Product

Among the 1572 evaluable subjects, 509 (32.4%) used the study drug appropriately and 1,063 (67.6%) used the product inappropriately. For those subjects who used the product inappropriately, the most common reason was the presence of sinus pain and not speaking with a doctor (n=693, 65.2%). The number of subjects stating that Flonase was being used specifically to treat a sinus infection was 0.5% (n=5). In the sponsor's post hoc analysis in which the sinus pain warning was removed as a reason for inappropriate use, 53.3% of subjects would have appropriately used the drug.

The majority of subjects (810 subjects, 62.6%) reported regular use (defined as daily for at least 75% of the days) and 61.3% (776 of 1265 adults) used the recommended dose of no more than 4

sprays per day for more than 80% of the days they used the product. The overall incidence of overuse was 2.5% (40 out of 1572).

Subject-perceived efficacy and satisfaction were both favorable. Of the 1572 evaluable subjects, 737 (46.9%) reported the onset of relief of symptoms within 12 hours and 885 (56.3%) within 24 hours. This finding is consistent with the proposed labeling that states, "you should start to feel relief after the first use and full effect after several days of regular, once-a-day use".

Most subjects used the number of sprays indicated on the label. Twenty-one (21) of the 29 teenagers (72.4%) used 1 to 2 sprays per day for more than 80% of the days they used FPA. Seven (7) of the 29 teenagers (24.1%) used 3 to 4 sprays per day for more than 80% of the days they used FPA. Seven hundred seventy-six (776) of the adults (61.3%) used the recommended dose of no more than 4 sprays per day for more than 80% of the days they used FPA. Eleven (11) adults (0.9%) exceeded the recommended dose for more than 80% of the days they used FPA. These data are shown in Table 8 below.

Table 8. Percent of days of FPA use by frequency for teen and adult subgroups

Percent[a] of days of FPA use	Unknown sprays n (%)		1-2 sprays n (%)		3-4 sprays n (%)		5-6 sprays n (%)		7-8 sprays n (%)		9-10 sprays n (%)		11+ sprays n (%)	
Teen (12-17 years) (N=29)														
>0-10%	1	(3.4)	2	(6.9)	5	(17.2)	1	(3.4)	1	(3.4)	0		0	
>10-20%	1	(3.4)	1	(3.4)	1	(3.4)	0		0		0		0	
>20-30%	0		0		1	(3.4)	0		0		0		0	
>30-40%	0		0		0		0		0		0		0	
>40-50%	0		0		0		0		0		0		0	
>50-60 %	0		0		0		0		0		0		0	
>60-70%	0		0		0		0		0		0		0	
>70-80%	0		1	(3.4)	0		0		0		0		0	
>80-90%	0		1	(3.4)	3	(10.3)	0		0		0		0	
>90-100%	0		20	(69.0)	4	(13.8)	0		0		0		0	
Adults (≥18 years) (N=1,265)														
>0-10%	79	(6.2)	90	(7.1)	266	(21.0)	100	(7.9)	91	(7.2)	13	(1.0)	13	(1.0
>10-20%	24	(1.9)	44	(3.5)	145	(11.5)	15	(1.2)	12	(0.9)	2	(0.2)	2	(0.2
>20-30%	6	(0.5)	64	(5.1)	110	(8.7)	3	(0.2)	5	(0.4)	0		1	(<0.1
>30-40%	2	(0.2)	45	(3.6)	103	(8.1)	1	(<0.1)	5	(0.4)	0		1	(<0.1
>40-50%	3	(0.2)	70	(5.5)	81	(6.4)	3	(0.2)	4	(0.3)	1	(<0.1)	0	
>50- 60%	2	(0.2)	55	(4.3)	47	(3.7)	0		2	(0.2)			0	
>60- 70%	0		92	(7.3)	52	(4.1)	0		0		0		0	
>70-80%	1	(<0.1)	107	(8.5)	65	(5.1)	1	(<0.1)	1	(<0.1)	0		0	
>80-90%	0		144	(11.4)	53	(4.2)	0		2	(0.2)	0		0	
>90-100%	0		289	(22.8)	290	(22.9)	1	(<0.1)	6	(0.5)	0		0	

One spray contains 50 mcg of FPA.

[a]calculated for each subject based on: number days at frequency divided by total number of days FPA used, according to the diary cards

Comments:
1. Table 8 above shows that most subjects used the proper amount of Flonase. About 11 adults who used the drug on 70% or more days of the study used 5-6 sprays per day. No teenagers who used the drug more than 30% of the days of the study used more than 4 sprays per day.

2. The sponsor states that the safety consequences of incorrect initial self-selection or inappropriate use were not clinically significant. Although correct self-selection and adherence to the label during actual use were low, this was due primarily to the label direction for patients to ask their doctor before use if they have sinus pain. Sinus pain, sinus pressure, and sinus headache are commonly reported in conjunction with allergic rhinitis. Additionally, references to sinus pain and sinus pressure were common to many OTC allergy and cough/cold products. Therefore, subjects may not have felt it was necessary to contact their doctor before using FPANS since sinus pain, or a symptom perceived as similar to sinus pain, was a normal feature of their nasal allergies.

Adverse events from the AU study are discussed in Section 7 of this review.

6 Review of Efficacy

Efficacy Summary
Efficacy of FPANS has been established through clinical studies conducted for the original approval and supplements encompassing about 5000 adults and children. There do not appear to be any efficacy issues for the allergic rhinitis claim or use in children down to the age of 4, although the sponsor requests age (b) (4)

6.1 Indication
The sponsor is seeking the same indications (and dosing regimen) for SAR, PAR and an ocular claim as in the approved prescription product. However, the sponsor asks for age (b) (4) and older, whereas the Rx product is approved down to age 4. The ocular claim may be a new indication for an OTC medication for allergic rhinitis (see comment below.

For the ocular claim, the sponsor the sponsor submitted two controlled studies (FNM30033 and FNM30034) plus data from another eight studies to support the relief of ocular symptoms, such as itching, in subjects with allergic rhinitis. These studies are shown in Table 9 below.

Table 9. Studies submitted in NDA 205-434 in support of ocular efficacy

Studies with Ocular Symptoms as Primary Endpoints			
FNM30033	FNM30034	RH01619	
Studies with Ocular Symptoms as Secondary Endpoints			
FLN-401	FLN-402	FLN-411	FLN-412

FLTA4004	FLTA4006	FLTA4024	

Comments:

1.The DPARP reviewer noted that the seven studies with ocular symptoms as a secondary endpoint (Table 9) are older studies that evaluated symptom relief by a different mechanism than with the TOSS (total ocular symptom score). Thus, those seven older studies do not carry the same weight.

2. As the review of this application progressed, DNCE and DPARP came to view the claim for relief of eye itching as simply relief of a symptom often associated with allergic rhinitis. Thus, the sponsor's request to include relief of itchy, watery eyes is not considered a new indication.

(b) (4)

DPARP will review the efficacy data and provide input on whether the ocular claim is backed by sufficient data to be included in a consumer DFL, which does not lend itself to a discussion of data as in a prescription label.

7 Review of Safety

Safety Summary

Safety of FPANS has been established since the approval of NDA 21-121 in October 1994, and subsequent supplements. In addition to 19 years of use as a prescription drug, FPANS is a nonprescription drug in 13 foreign countries. The major consideration for use of FPANS in the OTC environment is whether the drug can be used safely without a learned intermediary.

In general, common adverse events in clinical trials and reports to postmarket databases include drug ineffective, headache, nasal discomfort, and minor nosebleeds. Serious adverse events (SAEs) such as nasal septum perforation, serious nosebleeds, or adrenal suppression are less common. In clinical trials, there was one death and in the Actual Use study, there were four deaths. None of the deaths could be attributed to FPANS. See Section 7.3.1 for further discussion.

The clinical trial safety data were obtained from 28 clinical studies that exposed subjects to doses of FPANS ranging between 100-200 mcg/day. For this application, the sponsor pooled the 28 studies, yielding 8,159 subjects: 4,999 received FPANS (3,452 at 200 mcg/day) and 3,160 who received placebo. More subjects exposed to FPANS 200 mcg daily (42.9%) reported treatment emergent adverse events (TEAE) compared to placebo subjects (38.0%). Most of the TEAEs were mild to moderate in intensity (>85%), see Table XYZ in Section 7.3.4. The incidence of TEAE leading to discontinuation was comparable across the treatment groups at approximately

2%. The incidence of SAEs was greater in the subjects treated with FPANS 200 mcg QD (2.1%) compared to placebo subjects (0.7%). These data are reviewed in the DPARP review.

Safety in the Actual Use Study (R181098) was acceptable despite the poor results in the self-selection phase. The four deaths seem to be high for a 6-month study involving 1572 evaluable subjects, but none of the deaths could be attributed to FPANS use. Other AEs were similar to those seen in clinical trials.

Specific safety concerns also discussed in the sponsor's ISS and in Section 7.3.5 of this review and the pertinent TEAEs are shown in Table XYZ in Section 7.3.5.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor submitted an Integrated Summary of Safety (ISS) that included safety data from the following sources:

- Clinical Trial Data: 28 pooled clinical studies and 15 non-pooled studies with FPANS doses ranging between 100-200 mcg/day in subjects age 4 and older.
- Postmarket Data from
  a) Sponsor's Pharmacovigilance Database: a summary of safety data reported to the sponsor, or that the sponsor became aware of
  b) FDA AERS: a summary of AE reports to the FDA AERS database
  c) World Health Organization (WHO): cumulative data in the WHO VigiBase
  d) DAWN
  e) NPDS
- Literature Review: including a summary of key safety findings
- Safety Update summarizing additional safety data received after the data lock for the NDA submission
- Legacy Actual Use study (2003)

Safety data from the Clinical Trial data are mentioned briefly in Section 7.1.1 below and are discussed in the DPARP review. Safety data of postmarket databases and the literature are discussed in Sections 8 and 9 of this review, respectively. The 120-day Safety Update is discussed in Section 7.7 (Additional Submissions). The targeted safety concerns are discussed in Section 7.3.5 (Submission Specific Primary Safety Concerns).

7.1.2 Categorization of Adverse Events

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 11.1, categorized by System Organ Class (SOC) and Preferred Term (PT), and summarized by seriousness, intensity and relationship to investigational product. The number and percentage of subjects who had a serious AE (SAE) was listed.

The severity of an AE was graded as follows:
• Mild: transient in nature and generally did not interfere with normal activities.
• Moderate: sufficiently discomforting to interfere with normal activities.
• Severe: prevented normal activities.

An SAE was any untoward medical occurrence that at any dose:
- Resulted in death.
- Was life-threatening
- Required in-patient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability or incapacity
- Was a congenital anomaly or birth defect.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For its safety evaluation, the sponsor pooled data from 28 controlled studies, organizing them into three groups: all studies (Group 1, all 28 studies), short-term studies (Group 2, 4 weeks or less, n=25 studies), and long-term studies (Group 3, 26 weeks or longer, n=3 studies), as shown in Table 10 below.

Table 10: Integrated summary of safety study groups

Group Number	Description of Group	Studies Included
1	All Studies	All 28 pooled studies
2	Short-term exposure studies (planned exposure ≤ 28 days)	FLN-202, FLN-203, FLN-204, FLN-270, FLN-306, FLN-320, FLN-321, FLN-350, FLN-351, FLN-401, FLN-402, FLN-411, FLN-412, FLTA3010, FLTA4004, FLTA4006, FLTA4024, FNM30030, FNM30031, FNM30033, FNM30034, FNM40184, FNM40185, R1810220, R1810221
3	Long-term exposure studies (planned exposure ≥ 26 weeks)	FLN-261 (1 year), FLN-310 (26 weeks), FLN-311 (26 weeks)

Source: Sponsor's ISS Section 14, Table 14.1.1.1

7.2 Adequacy of Safety Assessments

The sponsor's safety data is appropriate and the analysis is adequate to support the switch.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

From the clinical trial data of 28 pooled studies:

Exposure in short-term studies

Mean exposure for the FPANS 200 mcg daily group (n=2,250) was 21.0 days (median 17.0 days, range 1 to 50 days) and comparable to the placebo group (n=2,893) with a mean of 21.4 days (median 23.0 days, range 1 to 42 days).

Exposure in long-term studies

Median exposure to FPANS 200 mcg daily (n=288) was 169 days (or 5.6 months, mean 182 days) with most subjects (75%) exposed between 3 up to 6 months, and was comparable to the placebo group median exposure of 168 days (n=267, mean 169 days). There were 462 subjects exposed to FPANS 200 mcg/day for greater than 3 months and of these, 260 received a daily dose of FPANS 200 mcg QD for greater than 3 months.

Demographics

Distribution of subjects by demographic characteristics was comparable among the groups. There were 51% female subjects and mostly white (> 90%) subjects. Over 80% of the subjects were 18-64 years of age, 14% were 4-17 years of age, and less than 3% were 65 years of age or older. The mean age of the study participants was 34 years (range 4 to 86 years). In the long-term studies, all of the subjects were greater than 12 years of age and less than 2% were 65 years of age or older.

7.2.2 Explorations for Dose Response

GSK conducted two randomized trials of FPANS 100 mcg QD for the treatment of PAR (Study R1810220) and SAR (Study R1810221) in healthy adults. The 100 mcg daily dose provided evidence of efficacy for both conditions, but with a slower time-to-onset (3 days vs. 12 hours) and less treatment effect than with 200 mcg daily dose.

7.2.4 Routine Clinical Testing

The sponsor performed routine clinical testing in the clinical trials that supported the original approval and the supplements, but did not perform clinical testing for the switch application.

7.2.5 Metabolic, Clearance, and Interaction Workup

The sponsor performed pharmacokinetic studies to support the original NDA, but did not perform any new metabolic or clearance studies for the switch application but did conduct a review of potential drug-drug interactions; see Section 7.5.5 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Corticosteroids are used widely in clinical practice. Sufficient exposure to corticosteroids can lead to immunosuppression, muscle atrophy, glucose intolerance, and suppression of the HPA axis. At the maximum dose of Flonase 200 mcg daily (and the assumption of no concomitant steroid use), these types of AEs are expected to be rare with proper use.

7.3 Major Safety Results

7.3.1 Deaths

In clinical trials, there was one death reported in a 64-year-old white male who was treated with FPANS 100 mcg BID for 33 days (study FLTA3010). The death was diagnosed as caused from arteriosclerosis and the investigator considered it not related to study drug.

In the 6-month Actual Use Study (R1810198), four deaths were reported. These are listed below:

Cause of Death	Related to Study Drug (per investigator)?
• high blood pressure (subject 53034)	Unknown (no autopsy)
• cardiac arrest (subject 34001)	No
• loss of consciousness (subject 49008)	No
• head injury (subject 58003)	No

Three (3) cases were unrelated to study medication, according to the Actual Use study investigator. The relationship to study medication was unknown (autopsy not performed) in one case (subject number 53034) where the cause was listed as “high blood pressure,” according to the actual use trial physician..

7.3.2 Nonfatal Serious Adverse Events

In clinical trials involving about 5800 subjects (28 pooled studies), one subject had a nasal septum perforation. Another 21 subjects had SAEs; five (0.2%) subjects in the placebo group and 17 (0.5%) in the FPANS group. There were eight subjects (0.5%) in the FPANS 200 mcg QD group reported SAEs. Among all of the SAEs, 3 subjects (0.1%) in the FPANS 200 mcg QD group had asthma. The remaining SAEs, occurred in one or two subjects each within a different SOC and no clear safety signal. See Postmarket Safety in Section 8 of this review for other nonfatal SAEs.

7.3.3 Dropouts and Discontinuations

Over 90% of the randomized subjects completed the studies in the clinical trials. A greater proportion of placebo subjects withdrew prematurely from the study for any reason (7.9%) compared to the FPANS 200 mcg QD group (6.0%). There were more subjects who withdrew due to lack of efficacy in the placebo group (2.1%) compared to the FPANS 200 mcg QD (0.9%).

7.3.4 Significant Adverse Events

The most frequently reported TEAEs (≥ 2%) included headache, epistaxis, upper respiratory tract infections, oropharyngeal pain, sinus headache, nasal discomfort, cough, and sinusitis. Headache, the most commonly reported event, had an incidence comparable among the placebo and FPANS 200 mcg QD groups, including the All FPANS group (10.0% to 10.6%). There was a higher incidence of epistaxis in the FPANS 200 mcg QD treatment group (6.7% for FPANS 200 mcg/day) compared to placebo (3.9%). The remaining frequently reported TEAEs were reported with approximately the same frequency (2-5%) among the placebo and the FPANS groups. These data are shown in Table 11 below.

Table 11: Most frequent (≥2% in FPANS 200 mcg QD) treatment emergent AEs in clinical trials from 28 pooled studies

	Placebo (N=3,160) n (%)	**All FPANS (N=4,999) n (%)**	**FPANS 200 mcg/day1 (N=3,452) n (%)**	**FPANS 200 mcg QD (N=2,538) n (%)**
Subjects with at least one TEAE	11,228 (38.9%)	2,188 (43.8%)	1,582 (45.8%)	1,089 (42.9%)
Headache	317 (10.0%)	515 (10.3%)	360 (10.4%)	270 (10.6%)
Epistaxis	122 (3.9%)	321 (6.4%)	233 (6.7%)	134 (5.3%)
Upper respiratory tract infection	139 (4.4%)	238 (4.8%)	184 (5.3%)	121 (4.8%)
Oropharyngeal pain	128 (4.1%)	258 (5.2%)	180 (5.2%)	117 (4.6%)
Sinus headache	75 (2.4%)	129 (2.6%)	98 (2.8%)	63 (2.5%)
Nasal discomfort	57 (1.8%)	114 (2.3%)	89 (2.6%)	54 (2.1%)
Cough	73 (2.3%)	130 (2.6%)	83 (2.4%)	50 (2.0%)

[1] Includes FPANS 200 mcg QD and 100 mcg BID
At least 2% in FPANS 200 mcg QD group
Source: ISS Section 14, page 54, Table 14.5.2.1

AEs seen in long-term studies in adults are shown in Table 12 below.

Table 12. TEAEs by System Organ Class in long-term studies

Group 3 Long-term Studies

System Organ Class (disorders)	Placebo (N=267) n (%)	FPANS 200 mcg/day[1] (N=528) n (%)	FPANS 200 mcg QD (N=288) n (%)
Subjects with at least 1 TEAE	205 (76.8%)	426 (80.7%)	238 (82.6%)
Blood and Lymphatic System	1 (0.4%)	5 (0.9%)	1 (0.3%)
Cardiac	3 (1.1%)	5 (0.9%)	4 (1.4%)
Congenital, Familial and Genetic	0	1 (0.2%)	1 (0.3%)
Ear and Labyrinth	13 (4.9%)	15 (2.8%)	6 (2.1%)
Endocrine	1 (0.4%)	0	0
Eye	25 (9.4%)	35 (6.6%)	19 (6.6%)
Gastrointestinal	43 (16.1%)	69 (13.1%)	42 (14.6%)
General Disorders and Administration Site Conditions	17 (6.4%)	45 (8.5%)	29 (10.1%)
Immune	3 (1.1%)	6 (1.1%)	5 (1.7%)
Infections and Infestations	118 (44.2%)	239 (45.3%)	148 (51.4%)
Injury, Poisoning and Procedural Complications	21 (7.9%)	58 (11.0%)	37 (12.8%)
Investigations	9 (3.4%)	12 (2.3%)	8 (2.8%)
Metabolism and Nutrition	4 (1.5%)	1 (0.2%)	0
Musculoskeletal and Connective Tissue	29 (10.9%)	71 (13.4%)	41 (14.2%)
Neoplasms	3 (1.1%)	3 (0.6%)	0
Nervous System	62 (23.2%)	125 (23.7%)	81 (28.1%)
Psychiatric	3 (1.1%)	6 (1.1%)	2 (0.7%)
Renal and Urinary	1 (0.4%)	3 (0.6%)	2 (0.7%)
Reproductive System and Breast	5 (1.9%)	7 (1.3%)	5 (1.7%)
Respiratory, Thoracic and Mediastinal	101 (37.8%)	217 (41.1%)	114 (39.6%)
Skin and Subcutaneous Tissue	21 (7.9%)	36 (6.8%)	22 (7.6%)
Surgical and Medical Procedures	4 (1.5%)	0	0
Vascular	3 (1.1%)	9 (1.7%)	5 (1.7%)

[1] Includes FPANS 200 mcg QD and 100 mcg BID
Source: sponsor's ISS, page 52
Data based on 3 studies: FLN-261 (1 year), FLN-310 (26 weeks), FLN-311 (26 weeks)

Comment:
The AEs in long-term studies are revealing in that they are common and scattered across many body systems and disorders, highlighting that possibly none are related directly to FPANS and that subjects experience various maladies over the course of 26-52 weeks. Approximately 80% of subjects experience at least one TEAE, with infection, respiratory, nervous system, and

gastrointestinal being the most common. There were a few (1%) of subjects with cardiac AEs, but there is no evidence to suggest these are drug-related.

7.3.5 Submission Specific Primary Safety Concerns

Consideration of Special Topics

The sponsor provided targeted analyses for the following submission specific safety concerns:

- HPA axis suppression
- Growth effects
- Ocular effects
- Local adverse events such as perforation of nasal septum
- Effect on glucose metabolism
- Bacterial rhinosinusitis
- Potential drug-drug interactions

Comment

See Section 8, Postmarketing, for additional discussion of these topics. Although there may be limited reports of AEs in the clinical trials, postmarket use of the drug can lead to AEs under conditions of use that may be closer to OTC use.

Table 13 below shows TEAEs of special interest (excluding growth and DDIs) from 28 pooled clinical trials, followed by discussion of key topics.

Table 13. TEAEs of special interest: 28 pooled studies

	Placebo (N=3,160) n (%)	**All FPANS (N=4,999) n (%)**	**FPANS 200 mcg/day[1] (N=3,452) n (%)**	**FPANS 200 mcg/day (N=2,538) n (%)**
TEAE	82 (2.6%)	119 (2.4%)	99 (2.9%)	60 (2.4%)
HPA Axis Suppression				
Blood cortisol increased	1(<0.1%)	0	0	0
Glucose Metabolism				
Hyperglycaemia	0	1(<0.1%)	1(<0.1%)	0
Fungal Infection (overall)	10 (0.3%)	18 (0.4%)	14 (0.4%)	11 (0.4%)
Nasal candidiasis	0	1 (<0.1%)	1 (<0.1%)	0
Oral candidiasis	1 (<0.1%)	0	0	0
Oropharyngealcandidiasis	0	3(<0.1%)	2(<0.1%)	1(<0.1%)
Eye Disease (all)[2]	2 (<0.1%)	3 (<0.1%)	3 (<0.1%)	2 (<0.1%)
Cataract	0	2 (<0.1%)	2 (<0.1%)	1 (<0.1%)
Cataract subcapsular	1 (<0.1%)	0	0	0
Lenticularopacities	1(<0.1%)	1(<0.1%)	1(<0.1%)	1(<0.1%)
Bacterial Rhinosinusitis (all)	72 (2.3%)	95 (1.9%)	79 (2.3%)	48 (1.9%)

Acute sinusitis	7 (0.2%)	5 (0.1%)	5 (0.1%)	3 (0.1%)
Chronic sinusitis	1 (<0.1%)	0	0	0
Sinusitis	64(2.0%)	91(1.8%)	75(2.2%)	46(1.8%)
Nasal septum perforation	0	4 (<0.1%)	4 (0.1%)	1 (<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: Sponsor's submission ISS Section 14, Table 14.5.4.1

- **HPA axis suppression**: The potential of HPA axis suppression as assessed by adrenal stimulation was measured in four non-pooled safety studies (FLIT11, FLIT22, FLN-260, and FLTA3010E). In another 5 non-pooled safety studies, morning plasma and/or urinary cortisol were measured (FLN-230, FLTB3053, FNM40017, FNM40183, and FNS30003) to assess the same potential risk. The findings from two of these 9 studies are described below.

  FNM40017: In this double-blind, parallel-group study conducted in the U.S., subjects 3.5 to 9.5 years of age (males, females 9 years of age) were randomized to receive either placebo (n=76) or FPANS 200 mcg QD (n=74) in the treatment of perennial allergic rhinitis for 1 year. Mean creatinine-corrected urinary free cortisol ratios for the FPANS 200 mcg QD group and the placebo group were comparable after 6 months and 1 year. FPANS 200 mcg QD was comparable to placebo in prepubescent children with perennial allergic rhinitis in HPA-axis function

  FNM40183 ((b) (4)): In this double-blind, parallel-group study conducted in the U.S., subjects 2 to 3 years of age received a six-week course of FPANS 200 mcg QD (n=33) or placebo (n=32) in the treatment of allergic rhinitis and to assess the effects of FPANS on the HPA axis in pediatric subjects. There was no effect on the HPA axis as measured by 12-hour urinary free cortisol levels. Because the data failed to meet the criterion of being normally distributed, the 12-hour creatinine-corrected urinary free cortisol values were transformed to a natural log scale prior to analysis. Treatment with FPANS was comparable to placebo with respect to the change from baseline in 12-hour creatinine-corrected urinary free cortisol excretion. There was no evidence of a differential effect on 12-hour urinary free cortisol as a result of the age strata (≥2 and <3 years; ≥3 and <4 years) when examined separately. The adjusted geometric mean change from baseline value was 0.98 for FPANS 200 mcg QD (SE = 1.14) and 0.94 for placebo (SE = 1.15); a value of 1.0 reflects no change from baseline

  Reviewer's Sample Calculation
  FPANS is approximately 4 times the potency of dexamethasone (sponsor's estimate), which itself is about 4 times the potency of prednisone in animal models of inflammation. Then, 200 mcg of FPANS (2 sprays each nostril daily) yields an equivalent of approximately 3.20 mg of prednisone (200 mcg x 4 x 4 =3.2 mg), and one

spray in each nostril yields an equivalent of 1.60 mg of prednisone. These are low doses of prednisone for daily use, but are not zero. Using the (approximate) ≤ 2% bioavailability of FPANS (Flonase Prescribing Information), yields a daily dose of 0.064 mg prednisone-equivalent (200 mcg x 16 x 0.02). This is a very low dose of steroid, although it is not zero.

Comment:
1. FNM40017 and FNM40183 are discussed because they involve children, who may be at greater risk for HPA axis suppression due to a higher relative dose (mcg/kg basis). The results of these 2 studies appear reassuring for up to one year of labeled use; however see Section 8 Postmarketing for relevant case reports.

2. A suppressive effect on the HPA axis seems unlikely with labeled use of FPANS in adults. There is a margin of safety in children, especially with one spray in each nostril daily (total 100 mcg FPANS).

- **Growth Effects**:
  As background, corticosteroids are known to affect linear growth in children. For a previous consideration of OTC steroid availability in 1998, FDA held a Joint Pulmonary Allergy, Endocrinology and Metabolic Drugs Advisory Committee Meeting (July 1998) at which the AC discussed orally inhaled/intranasal corticosteroids and growth in children. FDA recommended the addition of class labeling for orally inhaled and intranasal corticosteroids to the Precautions/General, Precautions/Pediatric Use, and Adverse Reactions sections.

  The current prescription label for Flonase states:

  "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 reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height are unknown. The potential for "catchup" 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)."

  Subsequently, FDA published the draft Guidance for Industry "Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children" in March 2007, which provided recommendations for sponsors of orally inhaled and intranasal corticosteroids regarding the design, conduct, and evaluation of clinical studies to assess the effects of these drug products on growth. The recommendations comprise study

design and efficacy and safety issues for: 1) approved drug products whose treatment effect on prepubescent growth has not been adequately characterized, and 2) potential new drug products that could be used in the treatment of AR and/or asthma in children.

Growth measurements in pediatric subjects were collected in two safety studies (FNM40017, FNM40181). An additional study (FFR101782) evaluated growth in pediatric patients administered fluticasone furoate, (b) (4)

FNM40017 (also discussed in HPA axis suppression above): In this double blind, parallel-group study conducted in the U.S., subjects 3.5 to 9.5 years of age were randomized to receive either placebo (n=76) or FPANS 200 mcg QD (n=74) in the treatment of perennial allergic rhinitis for 1 year. No growth suppression was evident, measured by stadiometry. The mean baseline growth velocity was 6.30 cm/year (SE=0.14) in the placebo group and 6.39 cm/year (SE=0.14) in the FPANS 200 mcg QD group. The estimated growth velocity over one year of treatment was 6.20 cm/year (SE=0.23) in the placebo group and 5.99 cm/year (SE= 0.23) in the FPANS 200 mcg QD group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% confidence interval [CI] -0.351, 0.757). Baseline height was 119.1 cm (SE=0.72) in the FPANS group (n=56) and 119.0 cm (SE=0.71) in the vehicle placebo group (n=52). Mean height at the end of one year of treatment was 125.5 cm (SE=0.18) in the FPANS group (n=44) and 125.4 cm (SE=0.19) in the vehicle placebo group (n=39) (least-squares mean difference -0.12; 95% CI -0.600, 0.352). The results of this one-year, double-blind study demonstrate that FPANS at the maximum recommended dose (200 mcg) QD was equivalent to vehicle placebo with no effects on growth rate in prepubescent children, as well as no effects on standing height and bone mineral density.

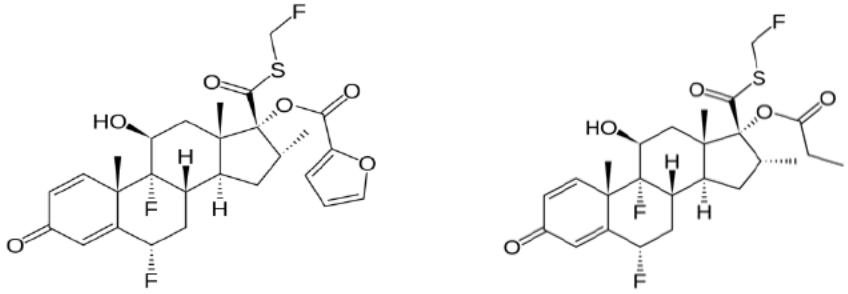
- FNM40181: In this double-blind study conducted in 1 center in Europe, 28 subjects 4 to 12 years of age were randomized to receive either placebo or FPANS 200 mcg daily in a crossover fashion for 14 days each for the treatment of rhinitis. No growth suppression was evident, measured by stadiometry and there was no difference in lower leg growth velocity measured by knemometry after 14 days treatment. For the ITT population, the mean difference in growth rate of FPANS and placebo was -0.123 mm/week. The lower limit of the one-sided 95% CI for treatment difference in lower leg growth was -0.225 mm per week; therefore, non-inferior per *a priori* statistical analysis plan (p=0.051). A reduced population ITT analysis (excluding outlying data from 2 patients with apparent negative growth) showed that FPANS was still considered non-inferior compared to placebo. The mean difference in growth rate of FPANS and placebo was -0.067 mm/week. The lower limit of the one-sided 95% CI for treatment difference in lower leg growth was -0.153 mm per week; therefore, non-inferior per *a priori* statistical analysis plan (p=0.20). From stadiometry, there were no clinically relevant changes in height from pre- treatment

to post-treatment in either treatment group. The mean height at pre- treatment was 142.0 cm and at post-treatment was 142.3 cm in both treatment groups. The mean change in height was 0.3 cm (SD 0.2) in both the FPANS and the placebo groups. This provides reassurance that both groups grew approximately 3 mm over the course of the study.

- FFR101782: This study, in which height was measured by stadiometry, was conducted using fluticasone furoate (FF) 100 mcg daily in 474 pediatric patients (5 to 8.5 years). This study using FF showed a decrease in growth velocity with FF compared to placebo of -0.27 cm per year, which is similar to the growth velocity of the 1-year study (FNM40017) conducted with FPANS (200 mcg QD) in 150 pediatric subjects 3.5 to 9.5 years (-0.23 cm/year). The study with FF was sufficiently powered so although a similar decrease in growth velocity was seen with FF as was seen with FPANS, the FF decrease in growth velocity was statistically significant. GSKCH is proposing OTC use in consumers (b) (4)

Comments:
1. The pediatric population may be at risk for growth delay from steroid use; however, the results from the study with FPANS are reassuring and the results from FF cannot be extrapolated to FPANS because these two drugs are distinct. The structure of fluticasone furoate (FF) compared with fluticasone propionate (FP) is illustrated in Figure 2 below. FF differs from fluticasone propionate at the position of the furan ring (FP has a methyl group). These two drugs have different structures, different metabolic pathways and no common intermediate, such as fluticasone (e.g. they are not salts of the same moiety).

Figure 2. Chemical structures of FF ($C_{27}H_{29}F_3O_6S$) and FP ($C_{25}H_{31}F_3O_5S$)



2. FDA discussed FP and FF at a Regulatory Briefing in 2008 and noted the following:
- *FF has a greater potency than fluticasone propionate in certain assays, but similar potency in others*
- *Toxicology profiles are generally comparable*

- *the furoate moiety of fluticasone furoate and the propionate moiety of fluticasone propionate are each covalently bonded to the same C-atom….they are both esters, but neither is a salt*
- *the ester moiety of each compound is maintained during metabolism and is not hydrolyzed; these 2 chemicals maintain their difference throughout metabolism*
- *fluticasone furoate bonds more tightly at the cell glucocorticoid receptor relative to fluticasone propionate (and has a greater action)*
- *these are two different molecules and share no common metabolites*

- **Ocular**: Ophthalmic examinations were not conducted in the non-pooled safety studies. The sponsor searched its clinical trials safety database for ocular TEAEs and found reports of blurred vision, eye pain, ocular hyperemia and photophobia, but no reports of glaucoma or cataracts. In the long-term studies, the percentage of subjects with cataracts or elevation in intraocular pressure in either eye was low (≤ 1%) and comparable between the placebo and the FPANS 200 mcg daily dose group.

- **Nasal septum perforation**: The incidence of nasal adverse events was collected in six non- pooled safety studies (FLIT08, FLIT11, FLIT22, FLN-230, FLTA3010E, and FNS30003). There were no reports of nasal septum perforation in these studies.

- **Glucose metabolism**: The adverse effect on glucose metabolism (e.g. hyperglycemia or diabetes) was studied in three non-pooled safety studies (FLN-260, FLTA3010E, FLTA4025). There was no clear effect on glucose metabolism from FPANS use.

- **Bacterial rhinosinusitis**: The incidence of acute bacterial rhinosinusitis was collected in 5 non-pooled safety studies (FLTA4025, FLTA4033, FLTB3052, FLTB3053, and FNS30003). FPANS use did not have a clear effect on bacterial rhinosinusitis.

For bone metabolism and fungal infections, no signals, beyond what is already mentioned in the prescription label, were detected in clinical trials. DDIs, discussed in Section 7.5.5

Comments:
1. An effect on glucose or bone metabolism seems unlikely with labeled use of FPANS. However, if the drug is used concomitantly with other corticosteroid drugs, except perhaps for 1% hydrocortisone OTC, it could contribute to hyperglycemia, osteopenia or other serious AEs related to glucose or bone metabolism.

2. Fungal growth, such as growth of Candida, may be stimulated by a corticosteroid, but an affected patient will experience local symptoms and will probably discontinue the drug or consult a doctor, so labeling should suffice for this potential adverse event.

Growth-related findings from the Postmarket Safety Database and Published Literature are discussed in Sections 8 and 9 of this review, respectively.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events include drug ineffective, local nasal effects of stinging, irritation, or epistaxis, headache, cough, upper respiratory infection.

7.4.2 Laboratory Findings

There were no laboratory evaluations for the label comprehension or human factors studies. No laboratory abnormalities are noted in the drug label with the use of FPANS..

7.4.3 Vital Signs

There were no vital signs measured for the label comprehension or human factors studies.

7.4.4 Electrocardiograms (ECGs)

There were no electrocardiograms performed for this application.

7.4.5 Special Safety Studies/Clinical Trials

For this application, the sponsor performed a retrospective, observational (epidemiological) study of steroid-related outcomes in users of FPANS or other intranasal steroids in the UK's General Practice Research Database (GPRD) from January 1990-January 2002. The sponsor considered the Warnings and Precautions in the drug label and evaluated the following outcomes in users of four or more prescriptions of fluticasone propionate or other intranasal steroid:

- Nasal septum perforation
- Hypercorticism
- Adrenal insufficiency
- Fractures (limited to hip, wrist and vertebral) as proxies for osteoporosis
- Acute otitis media
- Chronic otitis media
- Acute sinusitis
- Chronic sinusitis
- Cataracts
- Infectious complications of sinusitis

Of these outcomes, crude rate ratios comparing Flixonase (trade name of FPANS in UK) with other intranasal steroids suggested an increased risk of corticosteroid-related safety events associated with Flixonase; however, all adjusted hazard ratios were less than 1.5, suggesting weak associations. Table 14 below shows these associations. The remaining outcomes from the list above were no more likely with FPANS than with other INS.

Table 14. Associations (hazard ratios, HR) between Flixonase users (b) (4)) and other intranasal corticosteroids users ((b) (4)): 4 or more prescriptions from 1990-2002

	Crude HR (95%CI)	Adjusted HR (95%CI)
Chronic Sinusitis (N=984)		
Flixonase	1.80 (1.57, 2.07)	1.41 (1.23, 1.63)
Diabetes (N=353)		
Flixonase	1.19 (0.92, 1.53)	1.03 (0.80, 1.33)
Nasal Septum Perforation (N=841)		
Flixonase	1.39 (1.18, 1.63)	1.41 (1.21, 1.67)
Osteoporosis (N=221)		
Flixonase	1.66 (1.23, 2.23)	1.48 (1.09, 1.99)

Legacy Actual Use Study (R1810198)

GSK states that although draft labeling used in the AUT differed from the current draft OTC label in a number of ways, this study is still relevant as it provides safety data in an OTC environment for up to 6 months in a large number of subjects.

Safety

Safety was assessed by registered nurses during telephone interviews with subjects, based on information supplied by the subject during the interview and/or information provided by the Medical Problem Worksheet.

Most of the subjects (1352 of 1616 subjects, 83.7%) experienced at least one AE during the study. The most common AEs were allergic rhinitis (n=548, 33.9%), headache (n=474, 29.3%), and sinus headache (n=394, 24.4%). Treatment-related AEs were reported in 582 subjects (36%).

Deaths

Four (4) deaths were reported in this AU study, none apparently related to Flonase. See section 7.3.1 of this review.

SAEs (nonfatal)

Forty-six (46) subjects (2.8%) reported SAEs. One subject (subject number 24032) reported a hospitalization but refused to provide any additional information and withdrew from the study. No dosing history was provided. A possible cancer event reported in subject number 17011 was incorrectly reported as a SAE prior to confirmation that cancer was present. This event was downgraded by the actual use trial physician after the skin biopsy results returned benign.

The most frequently reported SAEs in the remaining 44 subjects were neoplasms (9 subjects, 0.6%) and nervous system disorders (5 subjects, 0.3%). Forty-three of these subjects experienced SAEs considered not related to study drug, and in the remaining subject, the relationship of the event to study medication was unknown, according to the investigator.

Discontinuations due to Adverse Events

Ninety-five (95) subjects (5.9%) discontinued from the study due to AEs. Of these, only 6 subjects discontinued due to an SAE. The most common AEs that led to study discontinuation were epistaxis (n=18, 1.1%), headache (n=16, 1.0%), and nasal passage irritation (n=9, 0.6%).

Pregnancy

Ten (10) pregnancies were reported during the study. Two ended in miscarriage and the other eight led to healthy children.

Table 15 below summarizes the common AEs.

Table 15. Actual use study: summary of adverse events with incidence >5%

All Purchasers (N=1,616)

Preferred Term	n	(%)	NAE
Subjects with at least 1 AE	1352	(83.7)	8589
Subjects with no AEs	264	(16.3)	---
Respiratory, Thoracic & Mediastinal Disorders	892	(55.2)	2513
Rhinitis allergic	548	(33.9)	1098
Cough	159	(9.8)	188
Epistaxis	153	(9.5)	284
Pharyngolaryngeal pain	129	(8.0)	161
Nervous System Disorders	843	(52.2)	2807
Headache	474	(29.3)	960
Sinus headache	394	(24.4)	997
Tension headache	185	(11.4)	483
Migraine	104	(6.4)	256
Infections & Infestations	489	(30.3)	747
Nasopharyngitis	193	(11.9)	232
Sinus infection[a]	120	(7.4)	144
Musculoskeletal & Connective Tissue Disorders	384	(23.8)	772
Back pain	151	(9.3)	220
Arthralgia	100	(6.2)	150

n (%) = number of subjects (percent of subjects)
NAE = number of adverse events
[a] this term is the literal adverse event and was not coded using MedDRA
Source: sponsor submission, Section 9, Table 9.6.2,

Comments:

1. The sponsor asks that FDA consider the safety aspects of this AU study as supportive for use

in the OTC environment, but to place no weight on the misuse data because the study was conducted using a drug facts label that was very different from the one being proposed currently.

2. The AEs observed in this study were similar to those identified with the prescription product. For example, 153 subjects (9.5%) experienced epistaxis and 474 subjects experienced headache.

3. The occurrence of 4 deaths in a 6-month study involving an OTC drug used by 1572 subjects seems unusual but none were assessed as drug-related by the investigator, and this reviewer concurs.

4. The results of this study provide some support the safety of FPANS for use without a prescription and provide evidence of subject-perceived efficacy in an OTC setting.

5. This AU study has a high misuse rate but the major reason cited for misuse, subjects who had sinus pain not asking a doctor before use, is not worrisome. The SAEs were mostly unrelated to study drug. In addition, FDA did not require an AU study for this NDA submission in 2013.

7.4.6 Immunogenicity

There were no immunogenicity studies for this submission. Corticosteroids are anti-inflammatory, immune-suppressive drugs and are not likely to promote immunogenicity.

7.5 Other Safety Explorations

There were no other safety explorations for this application.

7.5.1 Dose Dependency for Adverse Events

There were no dose-dependency studies for this submission; however, a slightly higher incidence of local AEs was seen with the 200-mcg daily dose of FPANS versus the 100 mcg daily dose. In clinical trials, there were slightly more subjects who reported SAEs in FPANS 200 mcg QD group (0.5%) compared to placebo group (0.2%).

7.5.2 Time Dependency for Adverse Events

There were no time-dependency studies for this submission; however, higher doses and longer durations of use with corticosteroid drugs tend to lead to more local and potential systemic effects (if absorbed) due to immune suppression or adrenal suppression (if absorbed).

7.5.3 Drug-Demographic Interactions

The sponsor notes that no meaningful gender, race, or region relationships have been reported for FPANS. Study in the geriatric age group is limited. In clinical trials, patients 65

years of age and older (n = 129) or 75 years of age and older (n = 11) treated with Flonase Nasal Spray in US and non-US clinical trials had adverse reactions similar to those reported by younger patients.

7.5.4 Drug-Disease Interactions

Use of a corticosteroid in consumers with infections or in patients who are immunosuppressed could lead to worsening of the condition. Systemic absorption of steroid administered through nasal inhalation is minimal and the draft label directs consumers to stop use and ask a doctor if they have or develop signs of an infection.

7.5.5 Drug-Drug Interactions

As noted in the Rx label, fluticasone propionate is a substrate of CYP 3A4 and may interact with potent CYP 3A4 inhibitors, such as ritonavir and ketoconazole. Coadministration of fluticasone propionate and ritonavir is not recommended based upon a multiple-dose, crossover, drug interaction study in 18 healthy subjects. FPANS (200 mcg once daily) was co-administered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when detectable, the AUC averaged 8.43 pg•hr/mL. Fluticasone propionate Cmax and AUC increased to 318 pg/mL and 3,102.6 pg•hr/mL, respectively, after administration of ritonavir with fluticasone propionate aqueous nasal spray.

The draft DFL says **Do not use**: if you are taking medicine for HIV infection Consumers who may be taking ketoconazole are directed to ask a doctor or pharmacist before using FPANS.

Comment:
The sponsor's DDI study showed a blood level about 300 times higher for fluticasone when combined with ritonavir versus fluticasone alone, which is a significant concern for HPA axis suppression with concomitant use of these 2 drugs, and possibly with other CYP 3A4 inhibitors.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no evidence that FPANS is a human carcinogen. The Rx label notes that fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses of 1,000 mcg/kg for 78 weeks or in rats at inhalation doses up to 57 mcg/kg for 104 weeks (2-20x multiples of human doses).

7.6.2 Human Reproduction and Pregnancy Data

Fluticasone propionate was teratogenic in mice and rats at subcutaneous doses 4 times the weight-adjusted human intranasal dose, but with no impairment in fertility. In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m2 basis). However, no teratogenic effects were reported at oral doses of 300 mcg/kg., which is approximately 25 times the maximum recommended daily intranasal dose in adults) of fluticasone propionate given to the rabbit.

There are no adequate and well-controlled studies in pregnant women. In addition, it is not known whether fluticasone propionate is excreted in human breast milk, but other corticosteroids have been detected in human milk. The prescription product is labeled as Pregnancy Category C for use in pregnancy: use only if the potential benefits justify the potential risk to the fetus.

Data from clinical trials are limited. Some information is available from an article by Carmichael et al who performed a population-based case-control (retrospective) analysis of live infant deliveries from October 1997-December 2002 as part of a National Birth Defects Prevention Study in 8 states.[3] The authors evaluated whether maternal corticosteroid use during pregnancy is associated with delivering an infant with an orofacial cleft. Mothers of 1141 infants with Cleft Lip +/-Palate (CLP), 628 with Cleft Palate (CP) and 4143 controls were interviewed. Mothers of 33 (2.9%) infants with CLP, 6 (1.0%) with CP and 72 controls (1.7%) reported any prior corticosteroid use (-4 through+12 weeks of conception). When analyzed by route of administration and medication components, odds ratios for CLP tended to be elevated, and odds ratios for CP tended to be close to 1. The authors concluded that maternal use of intranasal and inhaled steroids was associated with moderately increased risk of CLP but not CP.

Comments:

1. There were no reports of cleft lip or palate in the clinical trial data or postmarket data available for review.

2. The sponsor's proposed label:" ask a doctor before use if pregnant or breast-feeding" is consistent with labeling for other OTC drugs in Pregnancy Category C, and is acceptable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Flonase is approved as a prescription drug for seasonal and perennial allergic rhinitis in adults and children 4 years of age and older. In clinical trials, about 40% of 1479 pediatric subjects experienced at least one TEAE, but most were not serious. Table 16 shows the most frequent AEs in children.

Table 16: Most Frequent (≥2% in FPANS 200 mcg QD) Treatment Emergent Adverse Events by Age: 28 pooled Studies (Pediatric Subjects)

	Placebo n (%)	All FPANS n (%)	FPANS 200 mcg/day[1] n (%)	FPANS 200 mcg QD n (%)
Age: 4-11 years	**(N=168)**	**(N=331)**	**(N=164)**	**(N=164)**
Subjects with at least 1 TEAE	62 (36.9%)	138 (41.7%)	74 (45.1%)	74 (45.1%)
Asthma	6 (3.6%)	25 (7.6%)	14 (8.5%)	14 (8.5%)
Epistaxis	10 (6.0%)	21 (6.3%)	11 (6.7%)	11 (6.7%)
Cough	1 (0.6%)	15 (4.5%)	9 (5.5%)	9 (5.5%)
Upper respiratory tract infection	10 (6.0%)	12 (3.6%)	6 (3.7%)	6 (3.7%)
Abdominal pain upper	2 (1.2%)	8 (2.4%)	5 (3.0%)	5 (3.0%)
Headache	12 (7.1%)	14 (4.2%)	5 (3.0%)	5 (3.0%)
Nasal discomfort	3 (1.8%)	10 (3.0%)	5 (3.0%)	5 (3.0%)
Vomiting	3 (1.8%)	10 (3.0%)	5 (3.0%)	5 (3.0%)
Oropharyngeal pain	6 (3.6%)	11 (3.3%)	4 (2.4%)	4 (2.4%)
Age: 12-17 years	**(N=304)**	**(N=358)**	**(N=257)**	**(N=205)**
Subjects with at least 1 TEAE	119 (39.1%)	146 (40.8%)	107 (41.6%)	87 (42.2%)
Headache	31 (10.2%)	41 (11.5%)	32 (12.5%)	28 (13.7%)
Oropharyngeal pain	18 (5.9%)	33 (9.2%)	24 (9.3%)	20 (9.8%)
Abdominal pain upper	8 (2.6%)	10 (2.8%)	9 (3.5%)	7 (3.4%)
Upper respiratory tract infection	6 (2.0%)	11 (3.1%)	8 (3.1%)	6 (2.9%)
Epistaxis	15 (4.9%)	12 (3.4%)	6 (2.3%)	6 (2.9%)
Cough	7 (2.3%)	13 (3.6%)	7 (2.7%)	4 (2.0%)
Sinusitis	6 (2.0%)	6 (1.7%)	4 (1.6%)	4 (2.0%)
Pain inExtremity	6(2.0%)	6(1.7%)	4(1.6%)	4(2.0%)

[1] Includes FPANS 200 mcg QD and 100 mcg BID
Source: Sponsor's ISS, Section 14, Table 14.5.3.1

Comment
Table 16 above shows that the AEs that children experience are similar to those of adults. However, the total number of children exposed to active drug is low (331 ages 4-11, and 462 ages 12-17). Of not, it is not clear why the all FPANS group of 331 is not the sum of the subgroups, but it is still likely less than 500 subjects.

The HPA axis and Growth Effects studies were discussed in Section 7.3.5 of this review.

Sponsor's Request for a Pediatric Waiver
GSK requests use in (b) (4) and older. (b) (4)

(b) (4)

The question as to whether NDA 205-434 is subject to PREA was discussed briefly at the pre-NDA meeting on May 16, 2013. The sponsor was told in the May 2013 meeting, that expansion of the claims to relief of eye allergy symptoms would likely trigger the Pediatric Research and Equity Act (PREA) requirements for either a study in children or a deferral or waiver of pediatric studies. With this NDA submission, the sponsor initially requested a waiver from conducting pediatric studies to support the ocular claim.

In the 74-day letter sent to the sponsor, FDA requested a revised Pediatric Study Plan (PSP), stating that the application triggered the Pediatric Research Equity Act (PREA) because the sponsor proposed to add an ocular indication to labeling. The sponsor revised their PSP and presented two potential options to comply with the Pediatric Research Equity Act (PREA):

(b) (4)

Comments:

1. The sponsor's first choice (b) (4) *) is not optimal since the approved OTC intranasal corticosteroid is labeled down to age 2 and the Pediatric Review Committee (PeRC) would likely want studies in children and/or labeling for children. It would be confusing to consumers to have two similar products in the OTC market with one OK for use in children and the other having no labeling below age 18.*

2. Table 5 in section 2.6 of this review showed that in 2012, approximately 19.38% of prescriptions were written for ages 0-11, and 8.99% for ages 12-17. It seems likely that if OTC approval is only in ages (b) (4) *and older, then off-label use will occur in the pediatric age group.*

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An acute overdose of FPANS is unlikely to lead to a serious adverse event because therapeutic systemic dosing of corticosteroids equipotent to milligram quantities of triamcinolone (10-100 times the intranasal dose) or more occurs routinely in healthcare settings. There is no evidence of abuse, withdrawal or rebound phenomena with an inhaled corticosteroid.

7.7 Additional Submissions / Safety Issues

Sponsor's 120-Day Safety Update

On January 17, 2014, the sponsor provided a safety update of all spontaneous reports it received from January 1, 2013-October 31, 2013. There were no AEs associated with a fatal outcome. For this report, they queried FDA AERS, WHO, AAPCC, DAWN, the literature and their internal GSK Safety Database ("OCEANS").

The AERS review retrieved 14,199 reports, of which 7,580 were serious. This is 501 reports (289 serious) more than in the initial totals through December 31, 2012. No new safety concerns emerged from this report. The WHO Vigibase review retrieved an additional 453 reports but these reports did not highlight any new safety concerns. There were no additional reports to AAPCC or DAWN.

The literature did not reveal any new, pertinent findings, but a poster session described a patient who experienced adrenal insufficiency following a drug interaction between FPANS, and nefazodone, a CYP3A4 inhibitor (Lu J et al, 2013). Potential interactions of FPANS with CYP3A4 inhibitors are described under Drug Interactions in the Flonase Rx label, although nefazodone is not specifically mentioned.

Comment:
Nefazodone, an antidepressant with potential hepatotoxicity, was withdrawn from the market in the USA in 2007. There are approved generics still available, but their use is likely to be low due to the known risk of hepatotoxicity.

The other significant elements of this update came primarily from the sponsor's safety database, which showed 245 reports with 501 AEs. The sponsor analyzed these reports for the targeted areas of interest noted earlier. Of the 245 reports, there were:

- 30 reports of epistaxis (2 serious) and 1 nasal septum perforation
- 37 SAEs total
- 1 oral candidiasis in patient taking ritonavir
- 2 glaucoma and 2 intraocular pressure increased
- 0 growth AEs
- 38 of 245 reports in patients <17 years old

Comment:

The 120-day safety update data are consistent with the other safety data in the NDA submission and raise no new concerns. However, it is clear that effective labeling is needed to contraindicate FPANS with HIV medications, since some are potent CYP3A4 inhibitors that can increase systemic exposure to fluticasone propionate and lead to HPA axis suppression, effects from hypercortisolism, and other AEs.

Safety Summary

FPANS has a favorable risk-benefit profile for the treatment of seasonal and perennial allergic rhinitis (SAR and PAR) in the OTC environment. This reviewer's conclusions are:

- the product has an established safety profile in the prescription environment and the potential for misuse, including spraying in the eyes, is low.
- the ocular claim would be new for an OTC drug used to treat allergic rhinitis, but the sponsor has done 2 new studies for the OTC application with acceptable results
- label comprehension testing and self-selection testing demonstrated that consumers generally understand the label
- a delay in the diagnosis of a serious medical condition (e.g. infection, diabetes) by use of Flonase is a potential concern, but was not seen in clinical trials
- the most common side effects are mild, reversible, local nasal events
- serious events, including cataracts, glaucoma, nasal septum perforation, hypersensitivity, and heavy epistaxis, have been reported infrequently
- the systemic effects of FPANS are minimized due to its low bioavailability (< 2%).
- a review of the postmarket safety databases did not raise new signals
- *fluticasone propionate (FP) has significant drug-drug interactions with CYP3A4 inhibitors that increase the blood level of FP (ritonavir; ketoconazole). These interactions will need effective labeling*

- *if approved for children, there could be potential slowing of growth and HPA axis suppression with overuse or prolonged, unmonitored use. One option is to label with a limit for daily use of two months, after which a consumer should consult a doctor*

For any concerns about how the Drug Facts Label alone can communicate about adverse events or provide adequate information under the Warnings or Directions sections of the DFPANS, a Consumer Leaflet might help convey the information.

8 Postmarket Experience

Overview

Adverse events identified during Postmarket use of Flonase from all sources of data include nasal discomfort and congestion, epistaxis, alterations of taste and smell, decreased blood cortisol, headache, nausea, insomnia, dizziness, fatigue, dyspnea, cataract, glaucoma, increased ocular pressure, and hypersensitivity. Nasal septum perforation was reported once in clinical trials but several dozen times postmarket (68 reports in the GSK database). It is considered a serious adverse event since it may require surgery to repair the septum.

Comment:
Postmarket reporting captures only a fraction of suspected adverse events. Many are unreported. Of those reported, multiple adverse events may be included in a single report and different databases may capture the same event, and thus overlap may occur.

The sponsor notes that July 1, 2012 was the cut-off date for the last IND safety report and December 31, 2012 is the cut-off date for safety data submitted with this NDA. A 120-day Safety Update submitted in January 2014 is discussed in Section 7.7 of this review.

The sponsor notes that fluticasone propionate nasal drops are indicated for nasal polyps. Some of the safety data in the postmarket setting does not distinguish between the nasal spray and nasal drops.

Comment:
The sponsor does not state what the distribution or sales are for FP nasal drops versus the nasal spray; however, allergic rhinitis is a common condition and nasal polyps are much less common.

Postmarket Exposure

The sponsor estimates cumulative exposure to FPANS to be 31.2 million patient-years through December 2012. In addition, during the 5-year period from January 2008 to December 2012, approximately (b) (4) % of the exposure to all intranasal FP formulations was OTC, based on overseas data.

Data Sources

The sponsor analyzed Postmarket safety 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

Comment

It is likely that some of the adverse events captured in the GSK, AERS, and WHO databases are duplicates.

GSK Pharmacovigilance Database (OCEANS)

GSK received 8041 spontaneous adverse event (AE) reports in association with intranasal formulations of FP since marketing in 1996 to December 31, 2012. These reports may include some use of the fluticasone propionate nasal drops, although the large majority should be from the nasal spray due to indication of use. Reports were from the US (64%), the UK (7.4%), Japan (6.4%), Canada (4.7%) and the Netherlands (4.5%). Most were medically unconfirmed reports (67.3 %, n=5408).

The majority of 8041 reports concerned primary events in the following SOCs:

- Respiratory, Thoracic and Mediastinal Disorders (28.4%, n=2282), including local nasal events (eg. epistaxis, nasal discomfort and nasal congestion), dyspnea and oropharyngeal pain.
- General Disorders and Administration Site Conditions (16.4%, n=1321), including drug ineffective, product quality issues and ill-defined disorder.
- Nervous System Disorders (15.6%, n=1251), including headache, dizziness and taste and smell disorders.

Of the 8041 reports, there were:

- 726 were serious reports
- 658 pediatric reports
- 203 related to OTC use (12 in children)
- 239 reports involved dosing errors (52 reports of use> 400 mcg/day), off-label use in children, or quality issues
- 44 reports of wrong route of administration (see below)

Of the 726 serious reports, 133 concerned Eye Disorders SOC (e.g. cataract, glaucoma, vision blurred), 133 involved Respiratory, Thoracic and Mediastinal disorders SOC (e.g. dyspnea, epistaxis, asthma, nasal septum perforation) and 120 involved Nervous System Disorders SOC (e.g. anosmia, ageusia). The remaining 386 SAEs were split, with no certain relationship to FPANS.

Of the 658 pediatric reports, 10.8% (n=71) were serious, including:

- 14 Nervous System Disorders SOC (e.g. convulsion, syncope)
- 13 Respiratory, Thoracic and Medistinal disorders SOC (e.g. dyspnea, asthma)
- 6 Endocrine Disorders SOC (e.g. adrenal insufficiency or Cushingoid) and Congenital, Familial and Genetic disorders SO
- The remaining 38 serious reports were scattered and of uncertain relation to FPANS.

Of the 8,041 intranasal FP reports, 203 are related to the use of OTC FPANS. Sixteen of the 203 reports were serious, including 3 reports of ocular events, and single reports of adrenal suppression in association with overdose, anaphylactic reaction, vocal cord paralysis, loss of consciousness, asthma and nasal septal perforation. Two reports indicated the patient was hospitalized (one report of malaise and one report of dyspnea), and two required medical intervention (one report of lymphadenitis and one of syncope).

Of the 52 reports involving use higher than 400 mcg/day, 24 did not describe an adverse effect, 27 described previously labeled AEs. One report involved adrenal suppression, but the dose and length of time were not specified ("may have been taking too much").

Of the 44 reports with the incorrect route of administration, 35 involved erroneous applications in the eye, of which 19 were accidental and 12 were of unclear intention, and four involved intentional eye application.

Comment:
The 35 reports of erroneous application in the eye highlight the importance of clear labeling regarding use of the product. In addition, the sponsor's request for an indication of relief of eye allergy symptoms should be carefully considered, as approving this indication could lead to additional erroneous applications in the eye.

GSK evaluated the 8041 AEs for events in 8 areas of interest:

- Local Nasal Events
- Bacterial rhinosinusitis
- Candidiasis

- Ocular events
- Effects on the HPA Axis
- Effects on Growth
- Effects on Bone Metabolism
- Effects on Glucose Metabolism

Adverse event reports for these categories are shown in Tables 17 and 18 below. Reports on bacterial rhinosinusitis (12) and bone metabolism (25) were few.

Table 17. 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: sponsor's Postmarketing data, p.18

Table 18. AEs of special interests from GSK database 1994-2012

Adverse Event (Preferred Term)	Number of AEs
Bacterial rhinosinusitis	12
Candidiasis	100
Ocular events	201
cataract	(83 of 201)
glaucoma	(118 of 201)
Effects on the HPA Axis	
Adrenal suppression	
Effects on Growth	22
Effects on Bone Metabolism	25
Effects on Glucose Metabolism	41
Blood glucose increased	30

Source: sponsor's Postmarketing data, p.18

HPA Axis Suppression

At the February 2011 sponsor meeting, FDA noted there were 42 unexplained postmarket (AERS) reports of adrenal suppression associated with FPANS. These are discussed in Section 8 of this review.

From its database covering 20 years of post-marketing, GSKCH identified 53 reports, received through December 31, 2012. Of these reports, 29 were confounded by use of use of concomitant steroids (22 cases with oral, inhaled, intranasal and/or topical use), 4 by use of a combination of concomitant inhaled/topical steroid and ritonavir and 3 by concomitant use of ritonavir, which increases fluticasone availability. Three (3) reports described medical history that was much more likely to have contributed to the event (primary adrenal crisis, adrenocortical carcinoma and possible Cushing's syndrome). Nine (9) reports described development of Cushing 's syndrome following treatment with FPANS. Three (3) of these were assessed as serious and are described below.

Case 1:

A physician reported the occurrence of weight gain, moon face and a "back hump on neck" in a 12-year-old male patient who had been taking FPANS (dose unspecified) over a period of 5 years for seasonal allergic rhinitis. FPANS was discontinued. A cortisol test was found to be "within range" (values not provided) and the patient's weight decreased. The reporter noted that the patient may have overused FPANS and that it was "highly possible" that the patient took oral prednisolone, however they considered the events to be related to FPANS.

Case 2:

A hospital physician reported that a 29-year-old female psychiatric patient who received FPANS developed Cushing symptoms. Dose was reported as "2 puffs daily" and duration of treatment was not specified. The patient was hospitalized and approximately 5 days later fluticasone was discontinued. The physician did not know whether the patient may have been receiving additional steroids from her general practitioner as the Cushing symptoms generally improved when the patient was hospitalized and reappeared when the patient returned home.

Case 3:

A consumer submitted the final serious report describing the occurrence of Cushing's syndrome in a 27-year-old female approximately 10 years after starting FPANS (unspecified dose) for sinus infection and allergies. The patient, who was taking no other steroid medications, reported that her physician believes her condition is due to long term use of FPANS, but was to confirm lack of other causes.

Growth Issue

From launch to 31 December 2012, GSK has received 22 reports of growth retardation in association with FPANS. Of these reports, over half (n=12) lacked significant information to be able to make an assessment. Four (4) of the remaining 10 reports indicated the patient had a medical history or had used concomitant medications that may have contributed to the event (e.g. severe asthma, use of oral and inhaled steroids).

One (1) non-serious report describes growth retardation in an 11-year old male who had been receiving FPANS for 1 month. Treatment was continued. This report was the only report of the

22 total reports to be associated with treatment with OTC FPANS. A further report involved a 15-year-old male who was reported not to have grown in the year since starting FPANS. No further information was available for these reports.

Two (2) separate reports describe a lowered increase in height compared to other children: 1 serious report (assessed as serious as intervention was required) in a 7 year old female who had been receiving FPANS for approximately 1 year and the other a non-serious report in a 5 year old male who received FPANS for 4 months. Treatment was discontinued in both cases and in the latter the event was reported to have resolved.

In over 20 years of post-marketing experience, GSK has received 22 reports of effects on growth in children. Only 1 of these reports described use of the OTC preparation. The majority of reports are too poorly documented to make an assessment or were confounded by medical history or concomitant use of oral/inhaled steroids. The other reports do not provide sufficient evidence alone to indicate a causal association of growth retardation with FPANS taken as recommended.

The sponsor concludes that, based on the results from pre-approval studies, its PMC studies, and a search for AEs in the integrated database, no evidence of clinically relevant HPA axis suppression was observed in the adult/adolescent subjects or the pediatric subjects. Serum cortisol over an integrated 24-hour period was not suppressed. The DPARP review team will review these data.

Local Adverse Events: Perforated Nasal Septum and Epistaxis

Of the 8041 reports received in association with FPANS use from launch to December 31, 2012, 1101 reports contain the PT “epistaxis” and in 636 of these reports, epistaxis is recorded as the primary event. From March 1990- December 31, 2012, GSK notes it has received 80 reports of AEs involving the nasal septum. Two cases are described below

Epistaxis

A regulatory authority submitted a report about a 38-year-old female patient with a history of epistaxis who used OTC FPANS (daily dose unspecified). No concurrent medication was reported. After approximately 34 months, the patient had developed nasal septum perforation and epistaxis. Treatment with FPANS was discontinued and at the time of report, the events were unresolved.

Nasal septum perforation:

A physician reported a patient (age? gender?) used FPANS (50mcg bid) for an unspecified time. Three months following discontinuation of FPANS, the patient underwent unspecified nasal surgery and had profuse nasal hemorrhage afterwards. The patient was hospitalized and the physician reported the events as being life threatening. The patient had a posterior nasal

tamponade and was treated with ethamsylate and aminocaproic acid. The physician thought the events were possibly related to treatment with FPANS.

Ocular Events

Of 8,041 AEs in the GSK database, 201 included ocular events consisting of 83 reports of cataract and 118 reports of glaucoma.

Comments:

1. In the OTC setting, the potential for glaucoma or cataract worsening in older patients should lead a consumer to ask a doctor before use of FPANS.

2. Oral corticosteroids are associated with subcapsular cataracts and can lead to increased intraocular pressure and glaucoma. However, a cause and effect relationship with use of FPANS cannot be definitively established in most cases, as these ocular conditions also occur naturally.

FDA AERS database

The search yielded 13,698 reports for FPANS from the FDA AERS database, of which 7,291 were serious reports. The majority of reported events involved General Disorders and Administration Site Conditions SOC (n=9,117, e.g. Drug ineffective, Pain, Product quality issue and Fatigue), Nervous System Disorders SOC (n=6,707, e.g. Headache, Dizziness, Paraesthesia, Hypoaesthesia), Respiratory, Thoracic and Mediastinal Disorders SOC (n=6,593, e.g. Dyspnea, Epistaxis, Cough, and Asthma) and the Gastrointestinal Disorders SOC (n=6,000, e.g. Nausea, Diarrhea, Vomiting, Abdominal Pain). The ten most reported AEs are shown in Table 19 and the AEs of special interest in Table 20 below.

Table 19. AERS Ten Most Reported PTs with Intranasal FP through 12/31/12

PT	SOC	Number of PTs
Drug ineffective	General Disorders and Administration Site Conditions	1336
Dyspnoea	Respiratory, Thoracic and Mediastinal Disorders	941
Headache	Nervous System Disorders	917
Nausea	Gastrointestinal Disorders	847
Dizziness	Nervous System Disorders	704
Pain	General Disorders and Administration Site Conditions	676
Epistaxis	Respiratory, Thoracic and Mediastinal Disorders	660
Product quality issue	General Disorders and Administration Site Conditions	611
Fatigue	General Disorders and Administration Site Conditions	610
Anxiety	Psychiatric Disorders	501

Source: sponsor's Postmarketing data, p.46

Note: the N corresponds to the PTs within the SOC Terms, so the totals are lower numbers than the broader SOCs (e.g. 1336 for drug ineffective vs. 9197 for the SOC that includes drug ineffective).

Table 20. AEs of special interest from AERS database 1994-2012

Area of Interest	Preferred Term	Number of Events
Local Nasal Events	Nasal Septum Perforation	23
	Epistaxis	660
Ocular Events	Cataract	140
	Glaucoma or increased intraocular pressure	103
Effects on HPA Axis	Adrenal suppression or insufficiency	46
	Blood cortisol decreased	21
Effect on glucose metabolism	Diabetes (Type 2) or hyperglycemia	413
Bacterial rhinosinusitis	Staph, strep or other bacterial infection	81
Candidiasis	Oral	73
	Other fungal infection (nasal, esophageal, unspecified)	162

Comments:

1. In Table 19, drug ineffective (1336) is the highest frequency adverse event reported for FPANS. This is often the highest report for a drug. Although the observed counts of dyspnea (941) and epistaxis (660, may appear to be high, dyspnea may be explained by concomitant asthma in patients with allergic rhinitis, and epistaxis is a labeled (and common) adverse events with a nasal spray for a nasal inflammatory condition. Review of the AERS post-marketing data does not highlight any new safety concerns for FPANS.

2. Table 20 shows that postmarket reports of nasal septum perforation, glaucoma, and diabetes-related AEs are to be expected with OTC marketing. However, the number of reports per year (divide by 18 for 18 years marketing) is not excessive. Effective labeling may help minimize the AEs.

WHO database

The search yielded 14,747 AE reports for FPANS, of which 5,459 were serious. The majority of AEs were in the General Disorders and Administration Site Conditions SOC (n=9,192, e.g.

Drug ineffective, Fatigue, Pain, Product quality issue), Nervous System Disorders SOC (n=6,668, e.g. Headache, Dizziness, Paraesthesia, Tremor), Respiratory, Thoracic and Mediastinal Disorders SOC (n=6,573, e.g. Dyspnea, Epistaxis, Cough, and Asthma) and the Gastrointestinal Disorders SOC (n=6,046, e.g. Nausea, Diarrhea, Vomiting, Abdominal Pain). Table 21 below shows the ten most common Preferred Terms with intranasal FP.

Table 21. WHO Ten Most Reported PTs with Intranasal FP through 12/31/12

PT	SOC	N
Drug ineffective	General Disorders and Administration Site Conditions	1356
Dyspnoea	Respiratory, Thoracic and Mediastinal Disorders	971
Headache	Nervous System Disorders	934
Nausea	Gastrointestinal Disorders	850
Dizziness	Nervous System Disorders	710
Epistaxis	Respiratory, Thoracic and Mediastinal Disorders	686
Fatigue	General Disorders and Administration Site Conditions	627
Pain	General Disorders and Administration Site Conditions	616
Product quality issue	General Disorders and Administration Site Conditions	595

Source: sponsor's Postmarketing data, p.50
Note: the N corresponds to the PTs within the SOC Terms, so the totals are lower numbers than the broader SOCs (e.g. 1356 for drug ineffective vs. 9192 for the SOC).

Comments:
1. Review of the WHO post-marketing data does not highlight any safety concerns for FPANS that have not been included in the product information.

2. As seen in the AERS data, drug ineffective is the most common AE, and dyspnea and epistaxis are common.

National Poison Data System

The sponsor's review of the annual reports indicates that no fatalities have been reported to US poison centers in association with FPANS use. Review of this data does not highlight any safety concerns for FPANS that have not been identified and included in the product information.

Drug Abuse Warning Network

The Drug Abuse Warning Network (DAWN) is a US-based, nationally representative public health surveillance system that continuously monitors drug-related visits, such as drug misuse, accidental ingestion and adverse reactions, to hospital emergency departments (EDs). Public-use datasets of the information collected from 2004 to 2011 were available to analyze online. Up to 22 drugs may be recorded as part of each case and the overall role that FPANS plays in each case is not clear. Table 22 illustrates the number of case types recorded from 2004-2011.

Table 22. DAWN: Numbers of Case Types Recorded for FPANS per Year

Case Type	Year							
	2004	2005	2006	2007	2008	2009	2010	2011
Adverse Reaction	3	3	5	0	2	7	16	62
Suicide Attempt	1	0	0	1	0	0	0	0
Overmedication	0	0	1	0	1	1	0	9
Accidental Ingestion	0	0	0	1	0	1	27	0
Other	0	0	0	0	1	0	0	2

Comment

There were 27 reports of accidental ingestion in 2010, but only zero or single reports in the other years. It is not clear why 2010 saw more reports of accidental ingestion in the USA. There is no reason to believe that availability OTC will lead to more accidental ingestion, and if it does, that any serious harm will occur from a single ingestion.

Similarly to all FPANS reports, the majority (92.1%, n=187) of the OTC reports were non-serious. Of the 16 serious reports, the majority of primary events were in the Ear and Labyrinth Disorders SOC, the Eye Disorders SOC, Nervous System Disorders SOC and the Respiratory, Thoracic and Mediastinal Disorders SOC (3 reports per SOC). Three quarters (12) of the serious reports were assessed as medically serious by GSK, including 3 reports of deafness, 3 reports of ocular events, and single reports of adrenal suppression in association with overdose, anaphylactic reaction, vocal cord paralysis, loss of consciousness, asthma and nasal septal perforation. Two were serious as the patient was hospitalized (1 report of malaise and 1 report of dyspnea) and 2 required medical intervention (1 report of lymphadenitis and 1 of syncope).

Epidemiology / Observational Comparative Studies

GSK study: WWE113666/WE50001 (study report February 15, 2006)

Title: An Epidemiological Study of Overall Patterns of Use & Outcomes in Users of Fluticasone Propionate (Flonase) Nasal Spray

Purpose: To determine the rates of steroid-related AEs among patients using FPANS (n=52,870) compared to patients using other intranasal steroids (INS) (n=73,743) from a United States (US) insurance claims database.

Results and Conclusions

This study retrospectively examined a cohort in a large US population database, i3 Magnifi. GSK calculated rates and rate ratios with 95% confidence intervals for 13 separate events: adrenal insufficiency, cataracts, fractures, glaucoma, hypercorticism, nasal septum perforation, osteoporosis, sinusitis, and five sinusitis related complications. For the various outcomes, several

variables were assessed and incorporated into the multivariate statistical model to control for confounding factors. After adjusting for these factors, five outcomes were statistically associated with an FPANS dispensing. Of these five outcomes, three had rate ratios slightly above one (nasal septum perforation 1.10, sinusitis 1.10, and abscess 1.13), indicating marginal clinical impact, while risks of the rare events hypercorticism and empyema were two-fold higher among patients dispensed FPANS versus other INS. Of note, when patients taking concomitant steroids were excluded from the analyses, the rate of hypercorticism or empyema was no longer statistically elevated in FPANS versus INS users suggesting confounding by concomitant drug exposure. In contrast, FPANS patients were less likely to have received a diagnosis for cataracts than patients taking other INS. Rates of all other incident outcomes evaluated (adrenal insufficiency, fracture, glaucoma, osteoporosis, cellulitis, encephalitis, and meningitis) were not found to be statistically different between the FPANS and INS cohorts.

GSK study WWE111983/WE50002 (study report April 19, 2010)
Title: An Epidemiological Study of Steroid-Related Outcomes in Users of Fluticasone Propionate Nasal Spray in the General Practice Research Database (GPRD)

Purpose: To determine the rates of steroid-related adverse events in patients using Flixonase (fluticasone propionate) Nasal Spray (n=62,380), compared to patients using other INS (270,802).

Results and Conclusions
Flixonase users in the cohort appeared to have more severe allergic rhinitis and more co-morbidities than other INS users, according to prevalent conditions in the year prior to the index date. Crude rate ratios comparing Flixonase with other INS users suggested increased risk of a few corticosteroid-related outcomes associated with Flixonase (abscess, diabetes, nasal septum perforation, osteoporosis, and chronic sinusitis). Cox models for randomly selected intermittent Flixonase or other INS use episodes compared the time to the event of interest, adjusting for baseline markers of allergic rhinitis severity. Cox models reduced the risk ratio for most events elevated in the crude analysis. All adjusted hazard ratios were less than 1.5, suggesting weak associations. Few confounders for nasal septum perforation were identified in this GP database, and therefore, could not be included in the analysis. The chronic sinusitis association suggested FPANS prescribing more often after multiple acute events (confounding by disease severity). The sponsor notes that the US claims database allowed better identification of confounders for each event of interest.

Growth-related Findings from the Postmarket Safety Database
Effects on growth velocity are included in the Warnings and precautions sections for all corticosteroid products, including FPANS. The Sponsor's search of postmarket safety data revealed 22 reports of Growth Retardation.

The sponsor states that the results from a clinical study of intranasal fluticasone furoate (FFNS) led it to request labeling for ages (b) (4) and older. Study FFR101782 was the largest clinical trial

evaluating the effect of an intranasal corticosteroid on growth rate, which used the stadiometry methodology to measure the standing height of subjects. This was conducted in accordance with the FDA Guidance for Industry document: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children (March 2007) (FDA 2007).

This clinical trial was a placebo-controlled growth velocity study of FFNS in children aged 5.0 to 8.4 years treated for one year, continuously. There were 237 patients in each treatment group (total sample 474). The study demonstrated that growth velocity over the 52-week treatment period was lower in the FFNS group compared to placebo (LS means 5.46 cm/yr and 5.19cm/yr for placebo and FFNS, respectively), and the mean treatment difference was -0.270 cm per year [95% CI -0.48 to -0.06]. This study characterizes, within pre-specified precision, a small reduction in growth velocity compared to placebo when FFNS 110 mcg is administered daily for 52 weeks in pre-pubescent children. It was not designed to provide a determination of the longer term effect on growth.

Data from clinical studies and post-marketing use of FPANS have not shown a direct association between FPANS treatment and growth retardation to date. However, the magnitude of the suppression of growth was similar in both the FFNS and FPANS studies and it may be that the FPANS growth study was underpowered to demonstrate a significant effect on growth at one year.

Post-Marketing Adverse Events Summary

The most commonly reported adverse events with FPANS are local nasal events, mostly nonserious. Headache and disorders of taste and smell occur, and are present as background events in the AR population. Ocular events include cataract, glaucoma and raised intraocular pressure, but are uncommon. Serious adverse effects with FPANS are rare.

Eight areas of special interest were reviewed for FPANS; local adverse events (including nasal septum perforation), bacterial rhinosinusitis, candidiasis, ocular events (cataract and glaucoma), Review of the post- marketing data for these areas of interest does not highlight any safety concerns for FPANS that have not been identified and included in the product information. None of the reported events suggests that non-prescription use of FPANS leads to additional public health risk in adults. If the drug is approved in children, then effective labeling for duration of use (and consulting a doctor) could help to meet an important drug approval for the OTC consumer while minimizing risk.

9 Appendices

9.1 Literature Review/References

Literature

The sponsor searched the literature and supplied approximately 118 references to support its application. These references covered efficacy, safety, human factors, the condition of allergic rhinitis, topics for the class of corticosteroids and FPANS in particular. In addition, the sponsor searched the following databases in a targeted update for the most recent safety data about fluticasone propionate, covering the period from July 1, 2012-December 31, 2012:

- MEDLINE
- Biosis Previews(R)
- EMBASE
- Derwent Drug File
- ToxFile
- Medical Intelligence Solutions through Searchlight (for abstracts and posters)

Five clinical trials (RCTs), 2 reviews, 6 articles, 13 abstracts and 6 posters were published in the review period from these databases, discussing FPANS as a treatment either alone or as a co-treatment with azelastine (an antihistamine) or an inhaled steroid for asthma. In the five clinical trials, fluticasone propionate with or without azelastine was well tolerated[2, 3-6,87,10-12]. The most common adverse events seen in these trials were headache, dysgeusia and epistaxis. No new safety data about FPANS emerged from this targeted 6-month review.

An overview of some of the important topics is discussed below.

Astafieva et al[1] (2012) found fluticasone propionate safe and effective in patients with nonallergic rhinopathy.

Derby and Maier[6] (2000) performed a large retrospective observational cohort study using data from the GPRD in the UK investigated the relative risk of cataract in 286,078 patients classified as users of intranasal steroids, users of oral steroids and non-users of either drug form. The study showed that the use of intranasal corticosteroids, including FPANS, was not associated with an increased risk of cataract.

Griesner et al[9] (1998) discussed the co-existence of asthma and allergic rhinitis, noting that among 84 individuals with asthma, 85.7% had a history of AR. Among 388 patients with AR, 21.3% had asthma.

Sastre and Mosges[13] (2012) reviewed the literature discussing the side effect profile of intranasal corticosteroids. They noted most AEs are of mild severity and local, such as nasal irritation and epistaxis. They note that the second-generation nasal sprays (fluticasone propionate, fluticasone furoate, ciclesonide and mometasone furoate) have minimal systemic bioavailability (< 1%) compared with older agents, thereby limiting the risk for systemic AEs.

Wilson[14] (1998) conducted 3 separate crossover studies evaluating the effects of intranasal steroids (INS) on basal HPA axis function. Wilson evaluated the diurnal adrenocortical activity of patients with both asthma and rhinitis by means of 24 hour and fractionated serum cortisol

levels and urinary cortisol and creatinine excretion. Twelve subjects were evaluated in a placebo-controlled two-way crossover study to compare the effects of the highest labeled clinical doses of FPANS (inhaled and inhaled plus intranasal) and TAA (inhaled and inhaled plus intranasal). Both inhaled products produced significant adrenal suppression (e.g., asthma therapy) compared with placebo, although inhaled fluticasone propionate produced 2-fold greater suppression than TAA. The addition of intranasal formulations did not produce significant further suppression of mean values with the doses used in this study.

Wilson[14] (1998) also studied 16 healthy volunteers in a 4-way crossover study comparing the effects of 4 days each of FPANS (200 mcg/day), triamcinolone acetonide (220 mcg/day), and beclomethasone dipropionate (336 mcg/day) versus placebo, on HPA axis function. Suppression of overnight urinary cortisol occurred significantly with FPANS (43%) and nonsignificantly with TAA-AQ (23%) and beclomethasone dipropionate (21%). No intranasal steroid was associated with blunting of response to low-dose ACTH stimulation

Comments:

1. The Griesner et al publication clarifies that there may be a significant number of individuals with allergic rhinitis (a common condition in up to 40% of the population) who are taking medications for asthma, such as an inhaled steroid. There is likely to be a smaller number of individuals who have asthma, present in about 10% of the total population, but of these patients, with asthma as many as 85% may be candidates to use a nasal steroid for AR. The concomitant use of inhaled steroids and INS presents a higher risk of adverse events, especially related to HPA axis suppression, or growth velocity if the product is approved in children.

2. All corticosteroid use has the potential for adverse events; however, the intranasal administration of 100-200 mcg of FPANS, when used as the sole corticosteroid, poses a low overall risk of systemic effects.

References

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11. Price D et al. Intranasal azelastine/fluticasone propionate formulation: a novel therapy for the treatment of chronic rhinitis: safety data from a 12 month-trial. Poster 872. Allergy 2012; 67 (96) 336-37.

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14. Wilson AM. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenalaxis activity. J Allergy Clin Immunol. 1998;101:470-4.

9.2 Labeling Recommendations

Labeling

The Sponsor is proposing to market fluticasone propionate under the trade name of Flonase Allergy Relief. The draft label is shown at the end of this section. The label should inform consumers about proper self-selection and potential adverse events (e.g., growth delay, even if a small amount).

The proposed OTC labeling of FPANS recommends use in the (b) (4). The label directs adults to use 2 sprays into each nostril (200 mcg total) once daily in the first week and 1 or 2 sprays into each nostril in week 2 and subsequently. After 6 months of daily use, the consumer is directed to ask their doctor if they can keep using the product.

If this product is approved for use in children, then the labeling elements need to include information about potential growth delay. The Nonprescription Drugs Advisory Committee (NDAC) meeting on July 31, 2013 helped to clarify how some potential safety topics such as a potential slowing of growth and HPA axis suppression could be addressed in labeling.

Comment
The FDA social scientist notes that the low-literate respondents tested poorly (in the pilot LC study) on following the Direction to consult a physician about continued use after 3 months of daily use and on the Direction to use the product once a day. The sponsor adjusted the label to allow for 6 months of use before consulting a doctor, which is not a change that promotes safe use of the drug. Six months of continued daily use is too long for even adults to self-medicate with this drug

Reviewer's Summary of some key label considerations include:

- (b) (4)

- *Pregnancy*: the sponsor's FPANS is a Pregnancy Category C drug. On the prescription label the *Warning* about use in pregnancy says Pregnancy Category C, "…should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus". In the Drug Facts Label, this Warning is expressed as "**If pregnant or breast-feeding** ask a health professional before use", which is adequate.

- *Steroid activity*: Flonase contains an anti-inflammatory steroid and there is no anabolic steroid activity. (b) (4)

- *Chronic Use*: A recommendation for a period of non-use or "drug holiday" is neither in the prescription label nor in the sponsor's draft DFPANS. We do not have data about how various periods of non-use might help mitigate any slowing effects on growth (if the product is approved for use in children). A thought presented by the Advisory Committee (AC) was to label that a doctor should be consulted for use longer than a month. The AC was thinking of use in children, but the finding of poor adherence to the 3-month duration of use (before asking a doctor) in the Pilot LC study, suggests that 3 months may be too long even for adults.

- *Sniff Gently*: Use the spray, and then *sniff gently*. An AC panel member made this suggestion for the first OTC intranasal corticosteroid in order to optimize keeping the delivered drug in the nose and minimize both having the fluid drip out of the nose (by not sniffing) or to be swallowed (by forceful sniffing) .

- *Drug-drug interactions (DDIs):* Fluticasone propionate is a substrate of CYP 3A4 and may interact with inhibitors of potent CYP 3A4 inhibitors such as ritonavir and ketoconazole. The postmarket review case with nefazodone, an antidepressant and strong CYP3A4 inhibitor no longer on the market in the USA, is an alert that any CYP3A4 inhibitors used in chronic care conditions should be avoided. A safe approach is to direct consumers to avoid use of FPANS is they are taking medications for HIV. Consumers who may be taking ketoconazole are directed to ask a doctor or pharmacist before using FPANS. A question arises as to whether other DDIs related to CYP 3A4 inhibition may be important, too.

Comments:
1. If language about the relief of ocular symptoms (relief of itchy, watery eyes) is approved, then clear labeling regarding use of the product.is needed, as illustrated by the 35 reports of erroneous application in the eye in the GSK postmarket database.

2. If approved in children the final label language should reflect the potential for a slowing of the rate of growth (with prolonged use) and uncertainty about the effect on final adult height. The Nasacort Allergy 24HR label says:"the growth rate of some children may be slower while using this product. Talk to your child's doctor if your child needs to use the spray for longer than two months a year"

The sponsor plans to include a Question and Answer Book to help consumers understand how to use the product and what potential side effects to expect from use of the product.

Figure 3 below shows how to use the drug properly per the sponsor's package insert.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

STEVEN F OSBORNE

06/05/2014

Floanase Allergy Relief NDA. Recommend approval for as young as age 4 as in Rx label. Allow language regarding relief of itchy, watery eye, (b) (4)

NARAYAN NAIR

06/05/2014

DPARP CLINICAL FILING CHECKLIST FOR NDA 205-434

NDA Number: 205-434 **Applicant: GlaxoSmithKline Consumer Healthcare** **Stamp Date: 9/23/13**

Drug Name: Fluticasone proprionate aqueous nasal spray (Flonase Allergy Relief) **NDA/BLA Type: new NDA**

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5.6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1): NDA for partial Rx to OTC switch
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Approved product, proposed OTC doses unchanged
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: FNM30033 Indication: relief of eye symptoms associated with rhinitis			X	Approved product – efficacy established for rhinitis indication at proposed OTC doses and population

DPARP CLINICAL FILING CHECKLIST FOR NDA 205-434

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: FNM30034 Indication: relief of eye symptoms associated with rhinitis				in Rx NDA. Two pivotal and one supplementary study submitted to support new ocular indication.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			TOSS previously agreed to as an acceptable primary endpoint although acceptability of new ocular indication to be a review issue
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Efficacy trials to support ocular indication all conducted in the US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Approved product
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Approved product
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

DPARP CLINICAL FILING CHECKLIST FOR NDA 205-434

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			narratives for deaths and serious or significant AEs of special interest provided in individual study reports
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?	X			per DNCE
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Request drug specific waiver for ocular symptoms indication
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Reference to NDA 20-121 for CRFs previously submitted
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			per DNCE
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

DPARP CLINICAL FILING CHECKLIST FOR NDA 205-434

This is the DPARP filing checklist for GlaxoSmithKline Consumer Healthcare's NDA 205-434 proposing a partial OTC switch for Flonase nasal spray (fluticasone proprionate). While the Rx product is approved for adult and pediatric patients 4 years of age and older, the Applicant has proposed a partial OTC switch for patients (b) (4) years and above (b) (4). In addition, the Sponsor has proposed a new ocular claim for "itchy, watery eyes" and has provided new efficacy and safety data from three clinical trials as well as a pooled analysis of pre-existing data as support for the ocular indication. (b) (4) The contents of this submission are appropriately filed and indexed to allow for review. Per the DNCE clinical filing review dated 11/12/13, the application if fileable from a DNCE perspective. DPARP agrees with this assessment.

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

STACY J CHIN
11/20/2013

ANTHONY G DURMOWICZ
11/20/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205-434 **Applicant: GSK HealthCare** **Stamp Date: September 23, 2013**

Drug Name: Flonase Allergy Relief (fluticasone propionate) **NDA/BLA Type: Rx-to-OTC switch**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			Includes Clinical Trial Data for Efficacy and Safety, plus Postmarket Safety
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	Dose is same as Rx, 50 mcg / spray 1 spray (b)(4) or 2 sprays each nostril once daily = 200 mcg qd Of note: there may be no proven dose-response
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	x			Refer to DPARP

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				Filing Review for comments about studies supporting the ocular claim.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	Efficacy established for Rx approval in 1994
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	All studies for the new ocular indication were conducted in the United States.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			Yes, 19 years of use in USA
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	Sponsor re-coded AEs from 28 individual studies in pooled analysis using

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					MedDRA 15.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			HPA axis and Growth Issue are addressed (no apparent effect on either—bit surprising)
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Looks like yes DPARP reviewer input, too
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?	x			2 Label Comprehension, 1 Self-selection 2 Human Factors Studies. An Actual Use Study was performed in 2003.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Asked for waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	No abuse potential for corticosteroid
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	USA data adequate
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			CRFs also submitted for ocular claim study
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes_X (yes)_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Steven Osborne, M.D. November 7, 2013

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

STEVEN F OSBORNE
11/12/2013
Flonase NDA Rx to OTC switch Filing Review. No clinical issues for filing.

LESLEYANNE FURLONG
11/12/2013