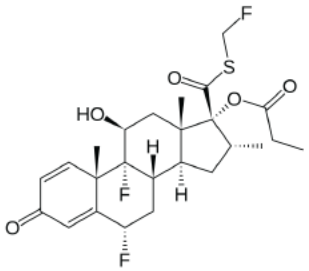
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205434Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	205434 (Related NDA 20121)
Submissions Date:	09/23/2013
Submission Type:	505(b)(1) Rx to OTC switch
Proposed Brand Name:	Flonase Allergy Relief
Generic Name:	Fluticasone propionate
Sponsor:	GlaxoSmithKline
Route of Administration:	Nasal spray
Dosage Form:	Aqueous solution
Dosage Strength:	50 µg fluticasone propionate in 100 µl aqueous solution per spray
Proposed Dosing Regimen:	Week1: 200 µg once daily (50 µg each spray, 2 sprays in each nostril) Week2 onwards: 100 or 200 µg once daily (1 or 2 sprays in each nostril)
Proposed Indication(s):	Nasal and ocular symptoms associated with allergic (b) (4) rhinitis
Proposed Population(s):	(b) (4) years and older
OND Divisions:	Nonprescription Clinical Evaluation, and Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Molecular Structure:	

Office of Clinical Pharmacology Recommendation

Office of Clinical Pharmacology/Division of Clinical Pharmacology II, has reviewed NDA 205434 submitted by GlaxoSmithKline, requesting partial prescription to over-the-counter (OTC) switch of Flonase, fluticasone propionate aqueous nasal spray (FPANS), and found the proposed drug product acceptable from a clinical pharmacology perspective.

FDA Regulatory History of FPANS

- On October 19, 1994, Flonase®, FPANS, was first approved under NDA 20121 for allergic rhinitis in patients 12 years of age and older.
- On October 31, 1997, its supplemental NDA was approved for use in pediatric patients 4 years of age and older.
- On December 11, 1998, its supplemental NDA was approved for use in patients with perennial non-allergic rhinitis.
- On May 23, 2002, its supplemental NDA was approved for as needed (PRN) use.

Background of This Submission

Flonase is currently sold as a nonprescription treatment for allergies in 13 countries outside the U.S. Prior to this submission, the Agency approved the first-in-class prescription to OTC switch of Nasacort Allergy 24 hr® (triamcinolone actinide nasal spray) from Sanofi Aventis under supplemental NDA 20468 (October 11, 2013). As GlaxoSmithKline seeks prescription to OTC switch of Flonase (b) (4) years of age and older, this partial switch was submitted under a separate NDA. However, this partial OTC switch (b) (4) FPANS has been used in children for 20 years; (b) (4) . Moreover, Nasacort OTC switch was allowed in children 2 years and older, which also potentiates the off-label use of FPANS in children. Extrapolation of the OTC switch in pediatric population was reviewed by DPARP medical officer (Dr. Stacy Chin) and DNCE medical officer (Dr. Steven Osborne).

GlaxoSmithKline submitted data from 10 U.S. clinical trials to support broadening the list of symptoms to include the relief of ocular symptoms associated with allergic rhinitis to the FPANS OTC label (b) (4) years and above. This data was reviewed by medical officer (Dr. Stacy Chin) from DPARP. The actual use study (R180198) and safety reports from post-market experience were reviewed by medical officer (Dr. Steven Osborne) from DNCE. Two label comprehension studies (RH01305, RH01318), two human factor studies (RH01801, RH01929) and self-selection study (RH01442) were reviewed by Dr. Scott Komo from Office of Biostatistics.

General Pharmacokinetics information of FP

- Absorption: Fluticasone propionate (FP) delivered by the intranasal route has an absolute bioavailability averaging less than 2%. Based on a dedicated mass balance study, the oral bioavailability of FP is negligible and the majority of the circulating radioactivity is due to an inactive metabolite.
- Distribution: The volume of distribution of FP averaged 4.2 L/kg. The plasma protein binding averaged 91%.
- Metabolism: The total clearance of FP is high (mean, 1.1 L/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in humans is the 17β-carboxylic acid derivative of FP, which is formed through the CYP 3A4 pathway.

- Elimination: Following intravenous dosing, FP had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.
- Special Populations: FPANS was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.
- Drug Interaction: Systemic exposure increases significantly when FP is co-administered with ritonavir. At steady state, Cmax increased from 12 pg/ml to 318 pg/ml (26.5-fold increase); $AUC_{(0-\tau)}$ increased from 8.4 pg•hr/ml to 3100 pg•hr/ml after concomitant administration of ritonavir (369-fold increase). This increase in FP exposure significantly decreased (86%) plasma cortisol, suggesting HPA axis suppression effects. A similar effect was observed when FP was co-administered with ketoconazole.

Summary of Available Clinical/Clinical Pharmacology Information for FPANS:

- Clinical pharmacology study FLTB-1009

In this NDA, the sponsor submitted one dedicated clinical pharmacology study that was conducted in 1997. It was a Phase I bioequivalence cross over study comparing the systemic exposure of fluticasone propionate (FP) after four 800 µg doses (one dose per 8 hours) to 12 healthy volunteers as either nasal drops or an nasal spray. FP nasal drops are available for treating nasal polyps in some foreign countries. The reason why the sponsor used 12-fold approved daily dose in this PK study is because the plasma concentrations of FP were below the limit of detection under approved doses. Even under the over-dosed condition, the FP plasma concentrations in plasma were undetectable in 2/12 of subjects on FPANS and 5/12 subjects on nasal drops. Because of these missing values, no formal statistical comparison was made between nasal spray and nasal drops (Table 1).

Both AUC_{last} and C_{max} are numerically higher in FPANS than the nasal drops.

Table 1 Systemic Exposure and Bioavailability of FP Administered as An Aqueous Nasal Spray or Nasal Drops 12 Healthy Volunteers

	Nasal Spray	Nasal Drops
AUC_{last} (pg/ml.h), mean (SD)	67.53 (71.84)	8.5 (15.41)
C_{max} (pg/mL), mean (SD)	31.40 (17.25)	14.50 (13.28)
t_{max} (h), median [range]	0.50 [0.17 – 4.00]	0.33 [0.08 – 0.75]

- Effects on Hypothalamic-Pituitary-Adrenal (HPA) axis
  The sponsor submitted one dedicated study and eight supportive studies investigating FP's effect on HPA axis. In general, the effect of FP on HPA axis is comparable to the effect of placebo in adults.

  - Study FLN-260

    This investigation was a 28-day randomized, double-blind, double-dummy, placebo-controlled study comparing HPA axis function in patients with allergic rhinitis. A total of 105 patients were randomly assigned to five groups:
    - Placebo
    - FP 200 µg, QD

- FP 400 µg, BID
- Prednisone 7.5 mg, QD
- Prednisone 15 mg, QD

At the end of the treatment period (Study Day 28-30), patients had HPA axis function evaluated by response to a 6-hour cosyntropin (synthetic derivative of ACTH) stimulation test. Oral prednisone at either dosage significantly reduced adrenal activity compared with both FP regimens and placebo (Fig.1). The overall p-value calculated from ANOVA F-test between prednisone and placebo/FP was < 0.001.

Among patients treated with FPANS for three weeks, FP plasma levels were detectable at a rate higher than the false positive rate only in the FP 400µg BID group (four times the recommended dosage in the proposed product labeling), and then only at levels <80pg/mL in approximately one-third of the samples.

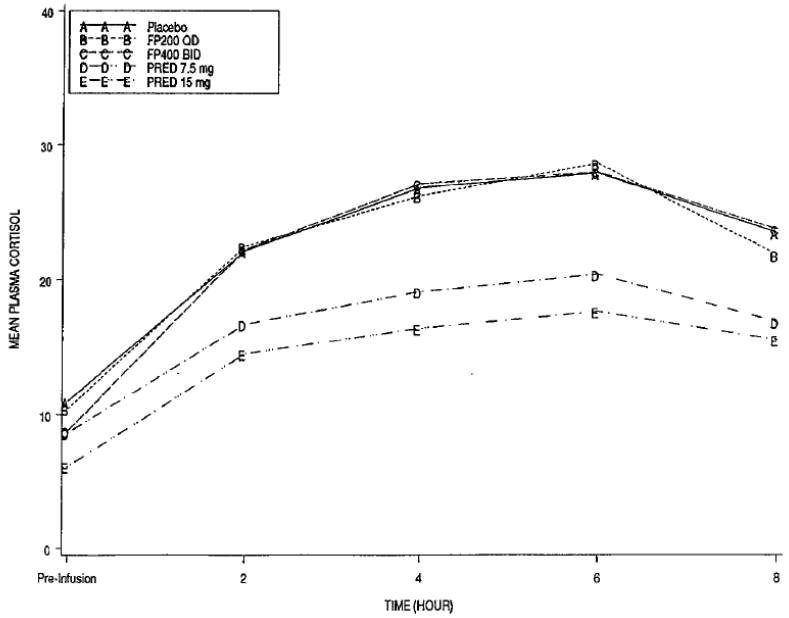


Figure 1. Concentration-time curves of plasma cortisol after cosyntropin stimulation in patients after 4 weeks treatment in five different groups.

Results indicate that intranasal FP at either dosage (200 µg QD, 400 µg BID) for 28 days did not affect the adrenal activity based on evaluation of plasma cortisol exposure (AUC) versus time and peak plasma cortisol concentrations following stimulation.

- Eight other studies (supportive)
  - Study FLN-261

    This investigation was a randomized, parallel-group, double-blind, placebo-controlled study conducted to assess the safety of long-term (one year) treatment of FPANS at a dosage of 200µg QD. A total of 81 male patients with perennial rhinitis were recruited in the study. HPA axis function was evaluated by cosyntropin stimulation test at 24 weeks and after one year of therapy.

Results indicate that no statistically significant differences were observed between the treatment groups in AM plasma cortisol, AUC and peak plasma cortisol concentrations.

- Study FLIT11

  This investigation was a double-blind, parallel-group study to assess the safety of one-year use of FPANS (200 µg BID) compared with beclomethasone dipropionate aqueous nasal spray (200 µg BID) in patients with perennial rhinitis. Plasma cortisol concentration following stimulation with synthetic ACTH was measured in some patients (47 out of 159 subjects in the FPANS arm and 23 out of 83 subjects in the beclomethasone arm) at visit 1 (start of the study), visit 2 (week 2), visit 4 (week 12), visit 7 (week52).

  None of the patients in either FPANS or active control treatment group exhibited a decrease in plasma cortisol levels considered to be clinically significant.

- Study FLIT22

  This investigation was a double-blind, placebo-controlled, randomized, parallel-group study to assess the efficacy and safety of one-year use of FPANS (100 µg BID) in patients with perennial non-seasonal allergic rhinitis. Plasma cortisol levels and ACTH stimulation tests were performed prior to the treatment, during the study and at the end of the treatment period.

  There was no evidence of clinically relevant suppression of the HPA axis related to FPANS.

- Study FLTA3010E

  This investigation was a double-blind, placebo-controlled, randomized study of the efficacy and safety of a 28-day course of three doses of FPANS (50 µg, BID, 100 µg BID, and 200 µg BID) with placebo for the treatment of perennial non-seasonal allergic rhinitis. A six-month open-label safety extension was followed in eligible patients. Cosyntropin stimulation testing for evaluation of HPA axis function was done at day 28 and day 183.

  At day 28, the percent of patients with any cosyntropin stimulation test abnormality was similar across the four treatment groups and there was no evidence of a treatment effect. There were some patients having negative cortisol changes upon cosyntropin stimulation at day 183. The Sponsor claimed that some blood samples might have been mislabeled.

- Study FLN230

  This investigation was a double-blind, double-dummy, randomized, parallel group comparison of the efficacy of 14 days course of intranasal (200 µg QD) and oral FP (5 mg QD) treatment in patients with seasonal allergic rhinitis. Morning plasma cortisol concentrations were measured during the study as a means to monitor HPA axis function.

During the treatment period, no patients in any treatment group had morning plasma cortisol values <5ug/dl. There were no clinically important differences between treatment groups for laboratory tests or A.M. plasma cortisol concentrations.

- Study FLTB3053

  This investigation was a double-blind, placebo-controlled, parallel group study examining the effect of 14 days course of FPANS (200 µg QD) and cefuroxime axelil treatment in subjects with recurrent sinusitis. Morning serum cortisol was measured at every scheduled visit for subjects recruited in the UK or Canada.

  There were no statistically significant differences between the placebo and FP groups in post-treatment morning cortisol values, with no evidence of HPA axis suppression (p=0.78).

- Study FNM-40017

  This investigation was a double-blind, randomized, placebo-controlled trial assessing the growth effects of a one-year course of FPANS (200 µg QD) in prepubescent, pediatric subjects (aged 3.5 to 9.5 years) with perennial allergic rhinitis. HPA-axis function was assessed by measurement of creatinine and urinary free cortisol, using 12-hour (overnight) urine samples collected by the parent/guardian in the subject's home on an out-patient basis the evening immediately prior to Visits 2 (day 0), 8 (Week 26) and 14 (Week 52).

  Although there was a numeric reduction of the mean creatinine-corrected urinary free cortisol ratios changing from baseline, the FP200 QD group was comparable to the placebo group after six months and one year for the primary populations (Table 2).

Table 2 12-Hour Creatinine-corrected Urinary Free Cortisol in Primary Population

	Placebo (N=52)		FP200 QD (N=55)	
Interval	n	Mean conc. mcg/g (SD)	n	Mean conc. Mcg/g (SD)
Baseline	50	18.4 (16.4)	53	24.8 (26.9)
6 Months	47	13.5 (8.4)	49	24.1 (34.9)
12 Months	36	19.1 (17.8)	41	17.5 (14.0)

- Study FNM-40183

  This investigation was a randomized, double-blind, placebo-controlled study to assess the potential effects of a six-week course of FPANS (200 µg QD) on the HPA axis in ≥2 and <4 years of age children with allergic rhinitis. A total of 60 children completed the study.
  HPA axis effects were assessed by the change from baseline at the end of study in 12-hour creatinine-corrected urinary free cortisol excretion.
  The mean difference between FPANS and placebo in creatinine-corrected urinary free cortisol ratio changing from baseline was -0.96 (95% CI = -0.66, -1.39). The confidence interval lay entirely within the equivalence limit (-20, 20 µg/g) defined a priori (table 3).

Although there was a numeric reduction of the mean creatinine-corrected urinary free cortisol ratios changing from baseline, the FP200 QD group was statistically equivalent to the placebo group.

Table 3 Mean Change from Baseline in 12-Hour Creatinine-Corrected Urinary Free Cortisol (mcg/g)

	Placebo	FP200 QD
n	29	31
Baseline geometric mean (se)	14.73 (1.16)	16.24 (1.15)
Week 6 Adjusted geometric mean (se)	14.19 (1.15)	14.79 (1.14)
Adjusted geometric mean change (se)	0.94 (1.15)	0.98 (1.14)
Placebo - FP200 QD		
Difference (se)	0.96 (1.20)	
p-value[1]	0.825	
95% CI	0.66, 1.39	

- 120 day safety report
  The report includes a total of 245 cases describing 501 adverse events received between the time period January 01, 2013 and October 31, 2013.
  Three reports describing effects on the HPA axis were received (Cushing's syndrome/secondary adrenocortical insufficiency, adrenal insufficiency and adrenal suppression) in association with use of FPANS. In two of the reports, drugs known to increase the systemic availability of FPANS (ritonavir and nefazodone) were also documented and in the third report, the patient was taking an intranasal steroid concurrently.

  Reviewer's comments:
  1) *It seems that FPANS generally do not suppress HPA axis or the effect is comparable to placebo in adults.*
  2) *Although there were no statistically significant differences between FPANS and placebo on HPA axis suppression in children, the FPANS group showed a numerically higher reduction of creatinine-corrected urine free cortisol concentrations after long term treatment. If the OTC switch of FPANS is extrapolated to pediatric population, long term use in children should be avoided.*
  3) *Co-administration of FPANS and ritonavir is not recommended in the current FPANS label. Also in the label, "Caution should be exercised when FPANS is co-administered with ketoconazole and other known potent CYP3A4 inhibitors." It says in the warning section "The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis." This information should be reflected in the OTC drug facts. The prescription of antidepressant nefazodone was presumed rare in the U.S. as its major brand Serzone® was discontinued in the U.S. due to high incidence of causing hepatic injuries. Therefore, it is not necessary to mention nefazodone in the drug facts.*

- Effects on growth rate in children
  - Study FNM-40017

    This investigation was a double-blind, randomized, placebo-controlled trial assessing the growth effects of a one-year course of FPANS (200 µg QD) in prepubescent, pediatric

subjects with perennial allergic rhinitis. The study was conducted from 1999 to 2001. The growth velocity was measured by stadiometry. The mean difference between FPANS and placebo in growth velocity after one year was -0.20 cm/year (95% CI=-0.351, 0.757).

Although there was a numeric reduction of mean growth velocity from baseline in FPANS group (-0.4 cm/year) than the placebo group (-0.1 cm/year), FPANS (200 µg QD) was statistically equivalent to the placebo on growth velocity in prepubescent children (Table 4).

Table 4 Growth Velocity (cm/year) in Primary Population

	Placebo (N=52)		FP200 QD (N=56)
n (Baseline)	52		56
Baseline growth velocity (cm/yr) (se)	6.30 (0.14)		6.39 (0.14)
n (1 year)	52		56
1-year growth velocity (cm/yr) (se)	6.20 (0.23)		5.99 (0.23)
Difference (se)		0.20 (0.28)	
95% confidence interval		-0.351, 0.757	

NOTE: Results are presented as least-squares means and standard errors. Estimates come from an analysis of covariance model with baseline growth velocity as covariate and main effects for treatment.

- Study FNM-40181

This investigation was a randomized, double-blind, placebo-controlled, cross-over study to investigate two week-lower leg growth in children with FPANS (100 µg QD) and placebo as measured by knemometry. 28 children (aged 4 to 12 years) with seasonal and perennial rhinitis completed study. Two patients were excluded during analysis due to records of negative growth. The estimated lower leg growth rate from FPAN treatment was 0.123 mm/week slower than placebo control (Table 5). The non-inferior boundary of the one-sided 95% CI for treatment difference in lower leg growth was set priori at -0.225mm per week. Therefore FPANS was still considered to be non-inferior compared to placebo on lower let growth rate in children.

FPANS treatment was non-inferior to placebo in terms of longitudinal lower leg growth (Table 5).

Table 5 Mean Lower Leg Growth of 28 Children in Two-period Treatment

	FPANS			Placebo		
Knemometry-measurement *	n	Mean	SD	n	Mean	SD
Pre-treatment (mm) **	28	186.48	34.00	28	186.32	33.39
Post-treatment (mm) ***	28	187.47	33.99	28	187.55	33.46
Difference (mm) ****	28	0.99	0.43	28	1.23	0.57
Weekly difference (mm/week)	28	0.49	0.21	28	0.61	0.29

Reviewer's comments:
In a recent study (FFR101782) conducted from 2007 to 2011, GSK evaluated the one-year effect on growth rate in children for another product, fluticasone furoate (FF) nasal spray. The sponsor observed significant reduction of growth velocity (-0.27 cm, CI=-0.48, -0.06) by FF (Table 6) as compared to placebo. This observation could be contributed by multiple factors:

1) *The sample size, as suggested in 2007 FDA guidance, was much greater in study FFR10782 (total 435 subjects) than in study FNM-40017 (total 108 subjects), therefore the former had much more power than the latter to detect statistical significance.*
2) *From pharmacology perspective, FF is more potent than FP as*
    a. *FF has a higher binding affinity with glucocorticoid receptors than FP (K_d 0.3 nM vs. 0.51 nM).*
    b. *FF showed greater inhibition effect in inhibiting lung eosinophilia in rat model (75% vs. 50%).*

Table 6 Analysis of Growth Velocity (cm/year) in FFR101782

	Placebo N=218	FFNS 110 mcg N=217
n	218	217
LS mean (SE)	5.46 (0.10)	5.19 (0.10)
LS mean difference		-0.270
95% CI		(-0.48, -0.06)

Detailed Labeling Recommendations

Flonase is proposed as an OTC product and therefore, no clinical pharmacology information is included in the proposed "Drug Facts" label.

In the FPANS Drug Facts, the recommendation for patients taking medicine for HIV infection is (b) (4) . This is reasonable as it is known that ritonavir dramatically increases the systemic exposure of FP (C_{max} increases 27-fold and $AUC_{0-\tau}$ increases 368-fold). Under the current label of prescribing FPANS, "Coadministration of ritonavir is not recommended". Using "HIV infection" to replace "ritonavir" is reasonable as most HIV multi-drug therapies include ritonavir which patients may not be aware of.

In the FPANS Drug Facts, it is recommended that patients taking ketoconazole "Ask a doctor or pharmacist before use". This is reasonable as it is known that ketoconazole increases FP AUC by 1.9-fold (from FLOVENT HFA label). Under the current label for prescribing FPANS, "Caution should be exercised" for coadministration of FPANS and ketoconazole.

In the pilot label comprehensive study 1305, the comprehension rate point estimates for question "Ask a doctor or pharmacist before you are taking ritonavir" is 99.1% in general population and 96.8% in low-literate population. The comprehension rate point estimates for question "Ask a doctor or pharmacist before use if you are taking ketoconazole pills" is 100% in general population and 90.3% in low-literate population. The results indicate that the drug-drug interaction-related labeling in the proposed "Drug Facts" is acceptable.

It states in the warning section of the current label of prescribing FPANS "The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis." Also in the Drug Facts of approved Nasacort Allergy 24 hr®, it says "Ask a doctor before use if you are using a steroid medicine for asthma, allergies or skin rash". Therefore, it's reasonable to include the same label language in the FPANS Drug Facts.

If the clinical division considers it is appropriate to fully switch the OTC in the entire population, including children of 4 years age and older described in the current Rx label, the same pediatric Rx dosing regimen should be applied in the Drug Facts. In addition, the similar label language as "Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients" should be displayed on the Drug Facts. The long-term use in children should be avoided.

Recommended label changes:

Ask a doctor before use if you

- Have glaucoma
- (b) (4)

~~Ask a doctor or pharmacist before use if you are taking~~

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

When using this product

- Remember to tell your doctor about all the medicines you take, including this one.

Attached is the proposed drug label

Drug Facts

Active ingredient *(in each spray)* — **Purpose**

Fluticasone propionate 50 mcg[1] _____ Allergy symptom relief[2]

Uses[3]

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

Warnings

Only for use in the nose. Do not spray into your eyes or mouth.[4]

Do not use

- to treat asthma[5] (b) (4)
- if you have an injury or surgery to your nose that is not fully healed[7]
- if you have ever had an allergic reaction to this product or any of its ingredients[8]

Ask a doctor before use if you have

- glaucoma[9]

Ask a doctor or pharmacist before use if you are taking

- (b) (4) ketoconazole pills (medicine for fungal infection)[10]

When using this product

- stinging or sneezing may occur for a few seconds right after use[11] (b) (4)

Stop use and ask a doctor if

- your symptoms do not get better within 7 days of starting use. You may have something more than allergies, such as an infection.[13]
- you get new symptoms such as severe facial pain or thick nasal discharge. You may have something more than allergies, such as an infection.[14]
- you get a constant whistling sound from your nose. This may be a sign of damage inside your nose.[15]
- you get an allergic reaction to this product. Seek medical help right away.[16]
- you get new changes to your vision that develop after starting this product.[17]

If pregnant or breast-feeding, ask a health professional before use.[18]

Keep out of reach of children. In case of (b) (4), get medical help or contact a Poison Control Center right away.[19]

Directions [20]

- read the Quick Start Guide for how to (b) (4) [21]
- use this product only once a day [22]

(b) (4)	Week 1	Use 2 sprays in each nostril once daily
	Week 2 (b) (4)	Use 1 or 2 sprays in each nostril once daily, as needed to treat your symptoms
	After 6 months of daily use [23]	Ask your doctor if you can keep using

(b) (4)

Other information

- you (b) (4) start to feel relief (b) (4) the first (b) (4) and full effect after several days of regular, once-a-day use [25]
- store between 4° (b) (4) and 30°C (39°F and 86°F) [26]
- keep this label and the enclosed materials, they contain important additional information. [27]

Inactive ingredients benzalkonium chloride, dextrose, microcrystalline cellulose, phenylethylalcohol, polysorbate 80, purified water, sodium carboxymethylcellulose [28]

Questions or comments?

Call toll-free 1-xxx-xxx-xxxx (English/Spanish) weekdays 9:00am - 5:00pm EST [29]

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

/s/

YUNZHAO REN
06/12/2014

SATJIT S BRAR
06/12/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**205434**	**Brand Name**	**FLONASE**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Fluticasone Propionate**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Corticosteroid**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	**Temporarily relieves these symptoms due to hay fever, other upper respiratory allergies, and** (b) (4) • **nasal congestion** • **runny nose** • **sneezing** • **itchy nose** • **itchy** • **watery eyes**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Nasal Spray**
Other discipline reviewers	-	**Dosing Regimen**	**Once daily, 2 sprays into each nostril (200mcg total)**
Date of Submission	**9/23/2013**	**Route of Administration**	**Nasal**
Estimated Due Date of OCP Review	**6/18/2014**	**Sponsor**	**GSK**
PDUFA Due Date	**7/23/2014**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-	X	1	1	FLTB1009
single dose:				
multiple dose:	X	1	1	FLTB1009
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	FLTB1009
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- None

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

- None

GSK submitted NDA205434 under 505(b)(1) seeking approval for Rx-to-OTC switch. The original approved Rx NDA20121 fluticasone propionate aqueous nasal spray (FPANS) is indicated for management of the symptoms of allergic and non-allergic rhinitis in adults and pediatric patients 4 years of age and older.

There are three major changes proposed in this OTC NDA:

1) This submission contains new clinical efficacy and safety data from ten clinical studies in support of adding ocular symptoms associated with allergic rhinitis, i.e., itchy, watery eyes, to the OTC indication.
2) The sponsor is seeking approval (b) (4) years and older.
3) (b) (4) Therefore adults should only use 2 sprays in each nostril (total 200 mcg) once daily during the first week.

This NDA is fileable from the clinical pharmacology perspective because:

1) No new Clinical Pharmacology studies were conducted in this NDA submission.
   Of note, the applicant submitted one bioequivalent study during the development of prior approval Rx product. The cross-over study compared the systemic bioavailability of fluticasone propionate aqueous nasal spray (with 0.02% w/w benzalkonium chloride) and a nasal drops formulation (without 0.02% w/w benzalkonium chloride). Doses higher than approved (800 mcg every 8 hours, total 4 doses) were given in 12 health volunteers in an attempt to achieve measureable plasma concentration s for comparative purpose. Fluticasone propionate in plasma was undetectable in 2/12 of subjects on nasal spray and 5/12 of subjects on nasal drops. The systemic exposure (AUC_{last}) of nasal drops was approximately eight times lower than nasal spray.

2) Sponsor addressed several Agency's previous clinical pharmacology-related responses. The Agency's responses were to sponsor's question #7 and #10 raised in the pre-IND109805 meeting on Feb 22, 2011.

   Question 7. Does the Agency agree that ketoconazole is the only drug-drug interaction to be included in this section?

   FDA preliminary response:
   No, we do not agree. As stated in our previous meeting response dated May 2, 2001, we recommend that you add a bulleted statement advising consumers who are taking corticosteroid inhalers and oral corticosteroids to ask their doctor or pharmacist before using this product. This statement should also be included as one of the primary communication objectives and tested in the label comprehension study.

   We note that the prescription label advises caution and warning with concomitant use of known potent CYP3A4 inhibitors that is not limited to ketoconazole alone. In fact, the prescription label recommends not using Flonase with ritonavir unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. This cautionary language is also common for many inhalation and intranasal corticosteroids for prescription

use. We recommend that you assess the potential of this interaction with potent CYP3A4 inhibitor drugs and associated clinical implications for OTC use. We recommend that you address this issue in your application and/or label.

Sponsor's replies in the current NDA application:
The concurrent use of FPANS and inhaled or topical steroids results in a negligible incremental contribution to the systemic exposure from the intranasal route. The amount of FP delivered by FPANS would represent a small fraction of the overall steroid load and unlikely to add significantly to the steroid burden. For example, even under the condition of coadministration with steroids for treatment of asthma, FPANS was not shown to contribute to any clinically significant adrenal (or HPA axis) suppression. To mitigate this risk, the OTC DFL clearly states that consumers should not use the product to treat asthma. Further, the product insert instructs that consumers who may be taking medicines with corticosteroids - including some medicines for the treatment of eczema, asthma, inflammation, allergic reactions, or eye conditions - should check with a doctor before use.

Risk is mitigated by providing information about possible interactions within the proposed OTC labeling. Consumers who are treated with HIV medications are recommended not to use FPANS. Consumers who may be taking ketoconazole are directed to ask a doctor or pharmacist before using FPANS.

Question 10. Does the Agency agree with the format and language of dosage instructions for use in an OTC setting for our proposed indication and identified target population?

FDA preliminary response:
With respect to dosing regimen:
Provide justification for the (b) (4) *regimen. The proposed OTC dosing does not include all the dosing regimens recommended in the approved package insert for Flonase. The proposed OTC label recommends use of 2 sprays in each nostril once daily (50 mcg/spray; 200 mcg total daily dose) for the first week, followed by 1 or 2 sprays in each nostril daily (100 or 200 mcg total daily dose) "as needed to treat your symptoms"* (b) (4) *The approved Flonase dosing also allows for an alternative dosing regimen of 1 spray in each nostril twice daily (200 mcg total daily dose).*

With respect to target population:
As stated earlier in our response to question 2, you will need to provide justification for (b) (4) *from the OTC population. If the pediatric population is included, instructions for dosing will have to be revised accordingly.*

Sponsor's replies in the current NDA application:
While the 100 mcg QD dose provided evidence of efficacy for both conditions, the time-to-onset of effect appeared to be considerably slower (3 days vs. 12 hours) and the treatment effect less than that previously observed for the approved 200 mcg QD.

This recommendation is based on the observed effect of INS on pediatric growth rates. A one year study (FNM40017) was conducted with FPANS (200 mcg QD) in 150 pediatric subjects

(3.5 to 9.5 years). 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. A similar study (FFR101782) was also conducted using fluticasone furoate (FF) 100 mcg daily in 474 pediatric patients (5 to 8.5 years). The study using FF showed a statistically significant decrease in growth velocity with FF of -0.27 cm per year.

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/s/

YUNZHAO REN
11/15/2013

SATJIT S BRAR
11/15/2013