BPCA CLINICAL SUMMARY OF NDA 20-121, SE8-028

APPLICATION:	20-121, SE8-028	**TRADE NAME:**	Flonase® Nasal Spray, 50 mcg
APPLICANT:	GlaxoSmithKline Research Triangle Park, North Carolina 27709	**USAN NAME:**	Fluticasone propionate nasal spray, 50 mcg
MEDICAL OFFICER:	Peter Starke, MD		
TEAM LEADER:	Eugene Sullivan, MD	**CATEGORY:**	Glucocorticoid
DUE DATE:	1 May 2003	**ROUTE:**	Intranasal
REVIEW DATE	26 March 2003	**FORMULATION:**	Aqueous suspension

1. SUMMARY OF CLINICAL FINDINGS

1.1. Brief Overview of Clinical Program

This NDA is an efficacy supplement for Flonase® Nasal Spray, 50 mcg (fluticasone propionate nasal spray or FPNS), providing the results of a long-term longitudinal growth study in children 3 to 9 years of age with perennial allergic rhinitis. As with other intranasal and orally inhaled corticosteroid containing drug products, the Flonase label contains a class-labeling warning of potential growth effects in the PRECAUTIONS: *Pediatric Use* section of the package insert. GlaxoSmithKline does not propose changing this warning, but proposes adding a paragraph describing the study and the results.

Flonase is currently approved for the management of the nasal symptoms of allergic and non-allergic rhinitis in patients 4 years of age and older. The recommended starting dose for adolescents and children is 100 mcg per day (one spray in each nostril once daily). The Application was not intended to support approval of FPNS in children younger than 4 years.

The clinical program consisted of one pivotal one-year growth study and two supporting studies. The studies are summarized in Table 1 and the sections below. The pivotal growth study (FNM40017) was conducted in response to FDA implementation of a class-labeling warning of potential growth effects for all intranasal and orally inhaled corticosteroid containing drug products following a July, 1998, Advisory Committee meeting which discussed the effects of orally inhaled and intranasal corticosteroids on growth. It is felt that growth suppression may be the most sensitive way to evaluate for potential systemic effects of corticosteroids in children, and that in this regard the evaluation of a potential growth effect may be more sensitive than evaluation of hypothalamic-pituitary-adrenocortical (HPA) axis function. One of the two supporting studies was an HPA axis study (FNM40183). This study was performed as a partial response to a pediatric Written Request issued by the Agency on June 25, 1999 (and amended May 21, 2001 and October 25, 2001) to study the fluticasone propionate moiety. The pediatric Written Request included seven dermatology and pulmonary studies, four for fluticasone propionate topical (Cutivate), two for fluticasone propionate inhalation aerosol (b)(4)----------and one for fluticasone propionate nasal spray (Flonase) (HPA axis study FNM40183). The second supporting study (FNM40181) was a knemometry study. This study was not performed in response to a request from the Agency.

Table 1. Summary of Clinical Program

Study	Conducted for Written Request?	Design	Dosage	Evaluations / Comments
Pivotal Study				
FNM40017 US	No	1-year, multi-center, randomized, double-blind, placebo-controlled, parallel group longitudinal growth safety study in 150 prepubescent children ages 3.5 to 9 (9.5 for boys) years with perennial allergic rhinitis	Flonase 200 ?g QD Placebo NS QD	Monthly stadiometric heights: growth velocity BMD* at 0 and 52 weeks 12-hour urinary cortisol at 0, 26, 52 weeks
Supporting Studies				
FNM40183 US	Yes	6-week multi-center, randomized, double-blind, placebo-controlled, parallel group HPA* axis study in 65 2-3 year old patients with allergic rhinitis	Flonase 200 ?g QD Placebo NS QD	12-hour creatinine-corrected urinary free cortisol at 0 and 6 weeks
FNM40181 Denmark	No	2-week, single-center, randomized, double-blind, 2-way crossover knemometry growth study in 28 prepubescent children ages 4-12 (Tanner stage 1) years with seasonal or perennial allergic rhinitis 14 day Rx, 14-day washout	Flonase 100 ?g QD Placebo NS QD	Knemometry Most patients were asthmatics who had been on inhaled CS up to 1 month prior to study
* BMD = bone mineral density. HPA axis = hypothalamic-pituitary-adrenocortical axis.				

1.2. Summary of Results

1.2.1. One-year growth study (FNM40017)

This study was **not** one of five studies requested by, and conducted in response to, a Written Request for pediatric information pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act.

The pivotal study reviewed in this application was a randomized, double-blind, placebo-controlled study conducted at 25 centers across the US, evaluating the effects of FPNS 200 mcg daily and placebo on longitudinal growth over a one-year treatment period in 150 children (74 FPNS, 76 placebo) ages 3.5 to 9 (9.5 for males) years with perennial allergic rhinitis (PAR). The primary safety evaluation was monthly triplicate stadiometric measurement of height performed at the same time of day (within ? 1 hour) as the initial measurement. The primary endpoint was growth velocity (as measured by a regression analysis) over one year of treatment for the Primary population. The Primary population was defined as the population of patients who completed at least three months of stadiometric measurements, had no major protocol violations (inappropriate enrollment, withdrawal due to protocol violation, use of excluded medications, or violations of the per-protocol windows for stadiometry assessments), and remained Tanner stage 1 throughout. Compliance was assessed from parent diaries, and not from returned study drug. Efficacy was assessed by clinician-rated TNSS and global parent/guardian ratings. Bone mineral density (DEXA) scans, including whole body and an anteroposterior (AP) spine (L1-L4), were performed at baseline and at 52 weeks. Urine for 12-hour (8 PM to 8 AM) overnight

urinary free cortisol was collected at-home at baseline, 26 weeks, and 52 weeks. Urinary free cortisol levels were "corrected" with urinary creatinine results. Other safety measurements included vital signs and adverse events, but clinical laboratory evaluations were not performed.

A total of 150 patients were randomized 1:1 (FPNS:placebo), 74 in the FPNS arm and 76 in the placebo arm. Treatment groups were comparable at baseline. More males than females were enrolled to both groups, and Caucasians were in the majority.

In general, FPNS was well tolerated in this age group of children ages 3.5 to 9 (9.5 for males) years of age. Note that the dosage used in this study was the approved maximal adult, adolescent, and childhood dose of 200 mcg daily. Clinical adverse events were reported for 138 (92%) of the 150 patients. The high frequency of adverse events is likely attributable to the length of the study and the age of the study population. The frequency of adverse events considered by the investigator to be drug related was similar between treatment groups. There were no deaths. There were four serious adverse events (1 FPNS, 3 placebo), but none were judged by the investigator to be treatment related, and none appear to this reviewer to have been treatment related. Nine patients were discontinued (4 FPNS, 5 placebo) due to a clinical adverse event.

While the incidence of epistaxis was comparable between the two treatment groups, two patients in the FPNS group withdrew due to epistaxis. There was also a trend to more events of gastric pain in the FPNS group than in the placebo group. The incidence of gastric pain was more than was seen in the short-term pediatric studies for the original NDA, probably because of the length of exposure in this study. It is possible that the increased incidence of gastric pain represents the local effects of swallowed FPNS. While one might also expect adults to swallow excess medication, the original NDA review reported that gastrointestinal discomfort was rare in adults. The incidence of vomiting (9 FPNS, 10 placebo) and diarrhea (6 FPNS, 8 placebo) was almost equal between the two treatment groups.

There also appeared to be a higher incidence of upper and lower respiratory infections in the FPNS treatment group, including episodes of upper respiratory infections, sore throats, streptococcal pharyngitis, epistaxis, colds, serous otitis media, cough bronchitis, wheezing, and asthma. There was, however, no difference in the incidence of tonsillitis, sinusitis, or otitis media. The past medical history of the population enrolled in the two treatment groups were not reported, preventing an evaluation of the frequency of these events in light of the past medical histories of the patients.

The main results of this study are summarized in Table 2. The primary endpoint was growth velocity (as measured by a regression analysis) over one year of treatment for the Primary population, the population of patients who completed at least three months of stadiometric measurements, had no major protocol violations, and remained Tanner stage 1 throughout. The Primary population included 56 FPNS and 52 placebo patients. For this population, the mean reduction in growth velocity after one year of treatment with FPNS at a dose of 200 mcg QD compared to placebo was 0.137 cm/year (95% CI = -0.265, 0.538). Examination of interaction of treatment-by-age and treatment-by-gender showed no significant treatment-by-age ($p = 0.96$ for Primary pop) or treatment-by-gender ($p = 0.49$ for Primary pop) effects, although males (raw mean = -0.3 cm/year, n = 74) appeared more affected than females (raw

mean = +0.1 cm/year, n = 34). No difference in growth velocity was seen during the first three months of treatment compared to the growth velocity of the entire study.

The mean change from baseline in height throughout the study is represented graphically in Figure 1. For both the Primary and ITT populations, increase from baseline in total body and lumbar spine bone mineral density (BMD) was greater for the FPNS than for the placebo patients, suggesting that FPNS had no effect on BMD. HPA axis results showed no interpretable effects on urinary free cortisol. These results are consistent with the current scientific understanding that growth is a more sensitive an indicator of the systemic effects of corticosteroids in children than evaluation of HPA axis or BMD.

The pivotal one-year growth study does support the safety of FPNS in children with PAR at a dose that is the maximum approved dose and twice the dose typically used in this age group. Equivalence with placebo is not assured, as the applicant seeks to state in the product label, since the results do not rule out a small effect on growth. While the results of the growth study point to a small and not statistically significant effect on growth, the clinical relevance of these results is not established, and must be placed in the context of the treatment of the individual patient. The study tried to address growth in children out to one year; longer-term effects on growth velocity beyond one year are unknown, as is any potential for rebound growth as patients either stay on drug for longer periods or are taken off as the course of the allergic rhinitis disease changes over time. Any differences in achievement of final adult height due to intranasal corticosteroid treatment may be difficult to determine for a given patient. The risk/benefit ratio should be weighed given the status of the patient's disease and the fact that intranasal corticosteroids are considered highly effective treatment for the symptoms of allergic rhinitis. The safety discussion between caregivers and the parents of children with allergic rhinitis should still include a discussion of the potential for systemic effects of intranasal corticosteroids, including potential effects on growth, and caregivers need to be reminded that growth and other signs of systemic effects should be monitored while patients are being treated. Despite the 'negative' results, the potential for Flonase to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Table 2. Study FNM40017, Growth velocity* (cm/year), Primary population†

Measurement / group	FPNS (200QD)		Placebo		Treatment Difference (Pla – FPNS) 95% CI
	n	LS mean (SE)	n	LS mean (SE)	
Growth velocity (cm/year)	56	6.16 (0.23)	52	6.30 (0.23)	**0.137 CI = –0.265, 0.538**

* Results for growth velocity are presented as least squares means and standard errors. Estimates come from the Division's analysis of covariance model with baseline height as covariate and main effects for treatment, investigator, and gender.

† The Primary population was defined as the population of patients who completed at least three months of stadiometric measurements, had no major protocol violations (inappropriate enrollment, withdrawal due to protocol violation, use of excluded medications, or violations of the per-protocol windows for stadiometry assessments), and remained Tanner stage 1 throughout.

Sources: Dr. Elashoff, Biometrics Consultant, Division of Pulmonary and Allergy Drug Products

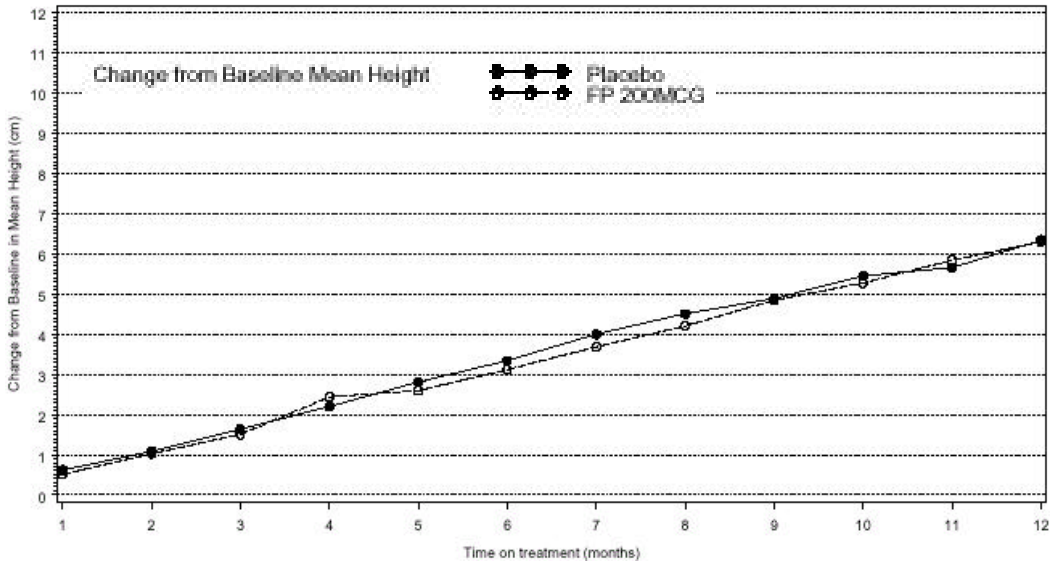

Figure 1. Study FNM40017, Change from baseline in mean height, Primary population
Source: Clinical, Study FNM40017, Figure 12.1, page 110; fnm40017.pdf

1.2.2. Six-week HPA Axis study (FNM40183)

This study was one of five studies requested by, and conducted in response to, a Written Request for pediatric information pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act.

This was a randomized, double-blind, placebo-controlled study conducted at 11 centers across the US, evaluating the effects of 6-weeks of FPNS 200 mcg daily on the hypothalamic-pituitary-adrenocortical (HPA) axis in 65 children (33 FPNS, 32 placebo) ?2 to <4 years (24 to 47 months) of age with allergic rhinitis. Randomization was stratified by age group in a 1:1 fashion ?2 to <3y : ?3 to <4y. The primary safety measure was the 12-hour creatinine-corrected urinary free cortisol. Urinary free cortisol uncorrected for creatinine results were also submitted on February 14, 2003, to (b)(4)----------(b)(4)----------as part of a request for information in the evaluation of the studies submitted for a determination of Pediatric Exclusivity. Overnight (8PM to 8AM) timed 12-hour urine samples were collected as an outpatient during the screening period and after 42 days of treatment. Patients also had one blood sample for fluticasone level drawn on the last day of the study one hour after dosing (Tmax, based on adult pharmacokinetic data). Other safety measures included physical examinations, clinical laboratory tests (chemistry, hematology, electrolytes, and urinalysis), assessment of exposure, and adverse events. No efficacy assessments were performed.

In general, FPNS was well tolerated in this age group of children ages 24 to 47 months. Note that the dosage used in this study was the maximal approved dose of 200 mcg daily instead of the recommended starting dose for children of 100 mcg daily. Except for a higher incidence of vomiting in the FPNS treatment group, the frequency of adverse events was roughly similar between treatment groups. As in the one-year growth study, there appeared to be minor trends toward cough, nosebleeds, and gastric pain in patients on FPNS. FP was detected in the blood in 7 of the 18 patients in the FPNS group who had adequate samples.

Two of these patients had creatinine-corrected urinary free cortisol levels decrease to below one standard deviation from the mean at the end of treatment, but none of these patients experienced adverse events suggestive of a systemic effect of FPNS.

There were no efficacy measures. The primary safety measure was the change in outpatient overnight 12-hour creatinine-corrected urinary free cortisol as measured prior to randomization and at the completion of the 6-week treatment period. The results of the 12-hour creatinine-corrected urinary free cortisol excretion for each treatment group were fairly similar (adjusted GM change of 0.98 (SE = 1.14) mcg/g for FP200, and 0.94 (SE = 1.15) mcg/g for placebo), with the 95% confidence interval of 0.66 to 1.39 within the prespecified bounds of equivalence (–20 to + 20 mcg/g) defined in the protocol.

The major difficulty with this study was the difficulty in collecting 12-hour timed overnight outpatient urine collections in a very young population. Just as for the urinary cortisol results from within the one-year growth study in a slightly older population of children, the urinary cortisol results from this study were inconclusive. The variation in uncorrected and creatinine-corrected urinary free cortisol at baseline between treatment groups was larger than the change from baseline within each treatment group. However, despite the limitations presented by difficulties in urine collection, the results tend to support a conclusion that there are no significant effects of six weeks of FPNS treatment on HPA axis in this age group.

1.2.3. Knemometry study (FNM40181)

This study was **not** one of five studies requested by, and conducted in response to, a Written Request for pediatric information pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act.

This was a randomized, double-blind, placebo-controlled, outpatient, 2-period crossover study conducted at 1 center in Denmark evaluating the effects of 2-weeks of FPNS at a dose of 100 mcg daily or placebo on a surrogate marker for longitudinal growth (knemometry) in 28 prepubescent (Tanner stage 1) children 4 to 12 years of age with allergic rhinitis. There was a 2-week washout between treatment periods. The primary endpoint was lower leg growth, as measured by knemometry, and calculated for each patient and for each treatment period in mm/week. The same observer measured knemometry at the same time of day (?1 hour) at the beginning and end of each study period. Other safety measures included physical examinations (including pulse, BP, weight, height, and nasal examinations), clinical laboratory tests (chemistry, hematology, electrolytes, and urinalysis), and assessment of exposure and adverse events.

The growth velocity of patients while on placebo was 0.61 mm/week, whereas the growth velocity of the same patients while on Flonase 100 mcg/day was 0.49 mm/week, a difference between treatments (reduction in growth velocity with FPNS treatment) of 0.123 mm/week. The upper limit of the one-sided 95% CI for the difference between treatments was 0.225 mm/week, which was very close to the Applicant's pre-specified non-inferiority margin of 0.230 mm/week. Whether the pre-specified inferiority margin carries clinical relevance, as the Applicant claims, is open to interpretation. The Division made no attempt to evaluate whether this was an appropriate threshold, nor did the Division's Biometrics Reviewer attempt to confirm the statistical findings. The p-value for the difference in

knemometry-measured growth between treatment groups was p = 0.051, implying that the results may be of significance despite the fact that the confidence intervals for the results were within the prespecified bound. The ANOVA analysis showed that there were no patient (p = 0.11), period (p = 0.58) or sequence (p = 0.52) effects.

2. RECOMMENDATIONS

2.1. Recommendation on Approvability

Approval. It is recommended that results of the one-year growth study be incorporated into the labeling, but that the class labeling otherwise not be changed. The PRECAUTIONS: *Pediatric Use* section of the label should include a brief description of the clinical study including a point estimate and 95% confidence intervals for the effect size.

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/s/

Badrul Chowdhury
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