

Paediatric Public Assessment Report

EU Work sharing Procedure - Assessment of Paediatric data

FLIXONASE Aqueous Nasal Spray 50 mcg Fluticasone Propionate

Marketing Authorisation Holder: GlaxoSmithKline Pharma A/S

Rapporteur:	Denmark
Co-Rapporteur:	Sweden
Paediatric assessment Procedure start date:	4 October 2005
Deadline for (Co)-Rapporteur's preliminary report	13 October 2006 (Day 70)
Clockstop	13 January 2006
Deadline for Rapporteur's final report:	8 May 2006 (Day 90)
Deadline for member states final comments:	02 June 2006 (Day 115)
End of procedure	7 June 2006 (Day 120)
Date of this report:	26 July 2006

SCIENTIFIC DISCUSSION

I. INTRODUCTION

In recent years, both US and EU have taken initiatives to increase the number of studies in children. EU is still in the process of finalising a regulation. FDA, however, has already received data for many products on the use in children.

Most of the studies, conducted in the paediatric population, are a result of the new FDA approach and the study reports are submitted to the FDA for review.

The aim of the “EU worksharing project assessment of paediatric data” is to make the paediatric data, already submitted to FDA, available for the European health professionals. The aim is to achieve a harmonised decision between all MSs in the Work sharing procedure. The main principle is that two Member States assess the data and prepare an assessment report for the other Member States.

Regarding this application, data from three paediatric studies have been submitted by the MAH as a request within the “EU work sharing project assessment of paediatric data” The submitted data consists of one pivotal one-year growth study and two supporting studies. The result of those studies were previously evaluated by the FDA and resulted in a brief description of the pivotal study in the “precautions, paediatric use section in the US datasheet.

I.1 SCOPE OF THE ASSESSMENT

Allergic rhinitis is a common disease in the paediatric population. Several available intranasal steroids have been shown to be effective in the treatment of both seasonal and perennial rhinitis which has led to them being prescribed for more consistent and more prolonged use to younger patients in whom a mild degree of cortisol excess could have important systemic side effects e.g. on growth or bone metabolism. An estimate of the growth effect of a drug, while important *per se*, should also be considered an important sentinel of unmeasured systemic effects and can therefore provide additional safety information.

Flixonase is currently approved for treatment of 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 once daily.

In this application the MAH presents the results of 3 paediatric studies, one pivotal study (FNM40017) and two supporting studies (FNM40183, FNM40181), evaluating the potential growth effect of continuous treatment with intranasally inhaled corticosteroid in children with perennial allergic rhinitis.

A summary of the clinical program is shown in table 1.

Table 1. Summary of clinical program

Study	Design	Dosage	Evaluations
FNM40017 USA (Pivotal study)	1-year, multi-center, randomized, placebo-controlled, parallel group longitudinal growth safety study in 150 prepubescent children ages 3.5 to 9 years with perennial allergic rhinitis	Flixonase 200 mcg daily or placebo	Monthly stadiometric heights: Growth velocity BMD* at 0 and 52 weeks. 12-hours' urinary cortisol at 0, 26, 52 weeks
FNM40183 USA	6 week, multi-center, randomized, placebo controlled, parallel group HPA** axis study in 65 2-3 years old patients with allergic rhinitis	Flixonase 200 mcg daily or placebo	12-hour creatinine corrected urinary free cortisol at 0 and 6 weeks
FNM40181 Denmark	2-week, single-center randomized, double-blind, 2-way crossover knemometry growth study in 28 prepubescent children aged 4-12 years with seasonal or perennial allergic rhinitis (14 days treatment, 14 days washout)	Flixonase 100 mcg daily or placebo	Knemometry

*BMD = Bone Mineral Density

** HPA axis = Hypothalamic-pituitary-adrenocortical axis

II. SCIENTIFIC DISCUSSION

II.1 Quality aspects

Not applicable.

II.2 Non-clinical aspects

Not applicable.

II.3 Clinical aspects

II.3.1 Clinical pharmacology

Not applicable.

II.3.2 Clinical efficacy

No conclusions regarding efficacy were drawn

II.3.3 Clinical safety

3.3.1 One year growth study (FNM40017)

This pivotal study was a multi-centre, randomized, double-blind, parallel group study in 150 prepubescent males (aged 3.5-9.5 years) and females (aged 3.5 to 9.0 years) with perennial allergic rhinitis evaluating the effect of Flixonase 200 mcg daily (n=74) or placebo (n=76) on longitudinal growth over a one-year treatment period. The primary safety end-point parameter was growth velocity over one year of treatment performed as monthly triplicate stadiometric measurement of height. In addition bone mineral density (DEXA) scans including whole body and anteroposterior spine (LI-L4) were performed at baseline and at week 52. Urinary free cortisol levels, corrected with urinary creatinine, were measured baseline, week 26 and week 52.

The sample size estimation was based on a difference in height velocity of 0.8 cm/year or less. Later FDA has issued a recommendation in a draft Guidance for Industry on Evaluation of the effects of orally inhaled and intranasal corticosteroid on growth in children that the total width of the 95% confidence interval should be 0.5 cm.

The calculated growth velocity over one year of treatment in the ITT population was 6.20 cm/year in the placebo group and 5.99 cm/year in the Flixonase group, with a mean difference between treatments in growth velocity after one year of 0.20 cm/year (SE=0.28, 95%CI – 0.351, 0.757). For the primary population (n=56 in the Flixonase group, and n=52 in the placebo group) defined as the population of children who completed at least 3 months of stadiometric measurements and no major protocol violations, the mean reduction in growth velocity after one year of treatment with Flixonase compared to placebo was 0.137 cm/year (95%CI = - 0.265, 0.538).

The mean bone mineral density increases for the Flixonase group and the placebo group were comparable after one year in both the ITT and primary populations. Also mean creatinine corrected urinary free cortisol excretions were comparable after 6 months and one year for both the ITT and primary population.

Upper respiratory tract infection were reported in 24 (32%) and 17 (22%) of the Flixonase and placebo recipients, respectively. Similarly gastric pain was noticed in 15 (20%) children in the Flixonase group compared to 8 (11%) children in the placebo group.

Rapporteur's comments to the pivotal study FNM40017

This study failed to demonstrate a significant decrease in growth velocity over one year in children receiving continuous Flixonase aqueous nasal spray 200 mcg daily when compared to placebo treated children. However equivalence with placebo has not been fully documented.

The clinical relevance of the small and non significant effect on growth during prolonged treatment with Flixonase has not been established. It is recommended that the data presented in the one year growth study be incorporated into the current SPC. Also countries not having a class-effect statement relating to HPH axis effects, including adrenal and growth suppression, should consider adding this in SPC section 4.4.

The MAH is requested to comment further on the increased risk of gastric pain (a local effect of swallowed corticosteroid?) seen among children treated with Flixonase.

Co-rapporteur's comments to the pivotal study FNM40017:

The fluticasone propionate dose chosen seems adequate. In US and in some European countries the recommended starting dose for paediatric patients is 100 mcg once daily, which can be increased to 200 mcg once daily if symptoms are not adequately controlled. Thus the dose of 200mcg daily is representing the highest recommended dose in the paediatric population. In the nationally approved SPC in Sweden, the highest recommended dose for children aged of 8-12 years, is 100mcg once daily.

The primary endpoint is relevant. Growth velocity with a minimum duration of one year (to avoid the effect of seasonal variation), is a sensitive way to evaluate for potential systemic effects of corticosteroids in children and stadiometry is acknowledge as being a reliable way of measuring height. The number of included study participants, a total of 150 subjects, is though rather limited for a non-inferiority study.

The clinical relevance of the a priori defined equivalence limits of -0.8 cm /year is difficult to evaluate. There are no safe predictions of the relation between intermediate term growth velocity (as estimated by 1-year trial) and final adult height. In the design of this clinical trial it was considered by the applicant that a difference in growth velocity of more than 0.8cm/year between fluticasone propionate and placebo would be clinically relevant. After completion of the pivotal study the FDA has issued further recommendations in its draft "Guidance for Industry on Evaluation of the effects of orally inhaled and intranasal corticosteroid on growth in children" The current guidance recommends that the total width of the 95% confidence interval should be 0.5 cm and that studies with a 95 percent confidence interval considerably wider than 0.5 cm might not be interpretable due to lack of precision in the estimate of treatment effect.

The pivotal study was however designed four years before the publication of the draft guidance and it is acknowledge that the study provides information on the magnitude of effect on growth of intranasal fluticasone propionate. If there is an effect on growth, this is probably small. Furthermore the confidence interval included zero suggesting no difference between treatments.

The result of the pivotal study presented in the dossier is though somewhat unclear, as there are two different results presented for the primary population:

In study FNM40017 an analysis of covariance model was used for analyses of the primary endpoint which included terms for treatment, gender, baseline age, investigator and baseline growth velocity. The primary analysis showed that the mean difference between treatments in growth velocity after one year was 0.20 cm/year (95% CI: -0.351, 0.757).

Another result of the study has also been presented stating that the mean reduction in growth velocity after one year of treatment with FPNS compared to placebo was 0.137 cm/year (95% CI: -0.265, 0.538). This is also the result included in the US datasheet following FDA assessment and the result proposed by the MAH to be included in the European SPCs.

The latter analysis is, as we understand it, based on an analysis performed by the Division of Pulmonary and Allergy Drug Products at the FDA. In this analysis an analysis model was used which differs from the one stated in the original study protocol.

One can probably argue about what model is the most appropriate, from our point of view however without a rationale for the choice of another analysis model, the presentation of the results from the study FNM40017 should comprise the result actually obtained in the primary analysis of the study (i.e. 0.20 cm/year, 95% CI: -0.351, 0.757).

Regarding Adverse Events:

As described by the MAH, 138 subjects (92%) reported at least one adverse event during the study which is a rather high rate of adverse events. The frequency of adverse events considered by the investigator to be drug-related was rather similar between active and placebo groups. None of the serious AE were considered to be drug related. There were no deaths.

The incidence of epistaxis was comparable between the two treatment-groups. In the FPNS group two patients withdrew due to epistaxis maybe suggesting a more pronounced severity of epistaxis in the active group.

There were more events of gastric pain in the FPNS group than in the placebo group. It is possible that the incidence of gastric pain represents the local effects of swallowed FPNS. The incidence of vomiting (9 FPNS, 10 placebo) and diarrhea (6FPNS, 8 placebo) was however almost similar 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,

Neither the higher incidence of gastric pain nor the higher incidence of upper and lower respiratory infection in children, correspond to the described undesirable effects included in section 4.8 in the Swedish national approved SPC for Flutide nasal (Flixonase).

3.3.2 Six week HPA axis study (FNM40183)

This was a multi-centre, double-blind, placebo-controlled study evaluating the effect of Flixonase 200 mcg daily on the hypothalamic-pituitary-adrenocortical (HPA) axis in 65 children 24-37 months of age with allergic rhinitis. The primary safety end-point was the change from baseline in 12-hour creatinine corrected urinary free cortisol excretion. The sample size (24 subjects per treatment group) was based on an FDA written recommendation providing at least 85% power to demonstrate equivalence between fluticasone propionate and placebo within 20 mcg/g in mean change from baseline in 12-hour creatinine corrected urinary free cortisol.

The results of the 12-hour creatinine corrected urinary free cortisol excretion showed a change of 0.98 (SE=1.14) mcg/g for Flixonase and 0.94(SE=1.15) mcg/g for placebo (95% confidence interval of 0.66 to 1.39 well within the predefined equivalence limit (-20, 20 mcg/g)).

The adverse event profile in the two treatment groups was not significantly different, however with a trend towards more gastric pain and vomiting in the Flixonase recipients.

Rapporteur's comments to the HPA axis study FNM40183:

The study demonstrates that short-term 6 week treatment with Flixonase aqueous nasal spray does not significantly affect the HPA axis in children aged between 2 and 4 years based on 12-hour creatinine corrected urinary free cortisol excretion.

Co-rapporteur's comments to the HPA axis study FNM40183:

This study has several deficiencies which make the clinical relevance of the study results questionable. This is a rather small study with a total number of 65 participants (33 subjects in the fluticasone propionate group), performed during a short time period of only 6 weeks, which unable any conclusion regarding long-term effects after long term treatment.

The clinical relevance of the primary endpoint could also be questioned as measures of basal HPA axis function have limited predictive value for clinically meaningful effects. In addition there are major difficulties in collection a representative urine sample in home settings, in this very young population. This is mirrored by the fact that the amount of urine collected during the 12 hour period was highly variable which in turn render difficulties in interpretation of the study results.

However, despite the limitations of this study, the result indicate that there are no significant differences of six weeks FPNS treatment compared to placebo on HPA axis function measured as

change from baseline in 12-hour urine creatinin corrected urinary free cortisol excretion in this age group. Stand alone, the result from this study does not contribute to any new understanding but as supportive to the results in the pivotal study it could be of some value.

There appear to be a minor trend toward cough, nosebleeds and gastric pain in the subjects treated with active substance but in total this study did not raise any new safety concerns in the paediatric population.

3.3.3 Knemometry study (FNM40181)

The objective of this randomized, double-blind, placebo-controlled 2-period crossover study was to evaluate the effect of Flixonase 100 mcg daily during a 2 week treatment period in 28 children (4 to 12 years of age) with allergic rhinitis on lower leg growth velocity as measured by knemometry. The growth velocity of patients treated with Flixonase was 0.49 mm/week, while on the placebo the growth velocity was 0.61 mm/week, a difference of 0.123 mm/week. The lower limit of the 95%CI was -0.225 mm/week, which was within the predefined non-inferiority margin ± 0.23 mm/week.

Rapporteur's comments on the knemometry study FNM 40181:

In this short-term study treatment with Flixonase aqueous nasal spray in a 2 week-period did not significantly influence the longitudinal growth using knemometry. However, an effect on the growth cannot be excluded.

Co-rapporteur's comments on the knemometry study FNM 40181:

This was also a small study with only 28 subjects included, performed over a short-time period of two weeks. The value of short-term studies, in predicting long-term, clinically relevant adverse effects, is poor. Short-term lower leg-growth rates cannot be extrapolated to intermediate- or long-term growth as childhood growth normally occurs in spurts, interspersed with periods during which essentially no growth occurs. There is no established clinical correlation between short-term growth velocity and final height. Establishing the clinical relevance of systemic INS effects requires that trials be performed using clinically relevant doses for clinically relevant time periods in patients with disease severity and age similar to those for which the drug would normally be prescribed. To ensure quality, only growth studies with a minimum duration of one year and involving measurement of height with a stadiometer is preferable. Whether the applicant's pre-specified non-inferiority margin of 0.230 mm/week has clinical relevance is not possible to interpret. 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.

Request for supplementary information

Rapporteur: The MAH should comment further on the observed increased prevalence of “gastric pain” in children receiving prolonged treatment with Flixonase aqueous nasal spray.

Other concerns as proposed by the CMS: The applicant is proposed to include gastric pain and upper respiratory tract infection to section 4.8 of the SPC.

Assessment of Requested supplementary information

Paediatric data generated in a one-year growth study in children with perennial rhinitis receiving Flixonase aqueous nasal spray.

There is a general agreement among the concerned member states that the data generated in the 1-year randomised, double-blind, placebo-controlled study in children aged 3 to 9 years should be included in SPC section 5.1 “Pharmacodynamics”.

The following wording has been proposed by the MAH taken into consideration the changes suggested by Sweden and Italy.

In a 1-year randomised, double-blind, placebo-controlled, parallel group growth study in pre-pubescent children aged 3 to 9 years (56 patients receiving intranasal fluticasone propionate and 52 receiving placebo) no statistically significant difference in growth velocity was observed in patients receiving intranasal fluticasone propionate (200 micrograms per day nasal spray) compared to placebo. 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 in the fluticasone propionate group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% CI= -0.35, 0.76). No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

Rapporteur's comments

It is recommended that the suggested wording is accepted and included in the SPC section 5.1 as it reflects the safety results of the 1-year controlled trial in children.

General class-effect warning concerning growth.

There is a general agreement among the concerned member states that a warning concerning growth be added to section 4.4 in the SPC in those countries not already having implemented a similar statement.

The following wording has been proposed by the MAH using the text already approved in UK SPC, but with cross-references to the text added to section 5.1 as suggested by Sweden.

Systemic effects of nasal corticosteroids may occur particularly at high doses prescribed for prolonged periods. These effects vary between patients and different corticosteroids (please refer to sections 5.1 and 5.2).

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. In addition consideration should be given to referring the patient to a paediatric specialist.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery (see section 5.1 for data on intranasal fluticasone propionate).

Rapporteur's comments

It is recommended that the proposed text be adopted and included in section 4.4 in the SPC.

Other minor concerns

In the one-year controlled study it was noted that the frequency of “gastric pain” (15/74 (20%) vs 8/76(11%)) and “upper respiratory tract infection” (24/74(32%) vs 17/76(22%)) was higher in the Flixonase treated group than in the placebo group.

The following response was received by the MAH:

Upper respiratory tract infections (URTI) are not uncommon in the patient population with rhinitis. Five US intranasal fluticasone propionate (FP) studies in paediatrics were reviewed to compare the incidence rate of events associated with URTI between the treated and the placebo groups.

As seen from the analysis the incidence rates of URTI events are either comparable between the treated and the placebo group or the rates are higher in the placebo group indicating the prevalence of these events in this patient population.

The incidence rate of events of gastric pain and similar events was also analysed from the above studies (five intranasal FP paediatric studies). The results were inconsistent due to the very small number of reports of gastric pain in these studies, and therefore provide no strong evidence for a drug effect. Gastric pain is a commonly occurring event in children which is indicated by sporadic reporting in different studies.

Furthermore, there have been only a very few spontaneous reports of URTI or gastric pain with intranasal FP in children. These cases do not provide any evidence of a causal association between these events and treatment with intranasal FP.

In conclusion, GlaxoSmithKline considers that there is either no evidence or insufficient evidence of a causal relationship between the use of intranasal FP in children and URTI or gastric pain and considers that results of only one study do not justify addition of these events to the product label. This study is not powered to show a true difference in adverse events such as gastric pain and URTI between the treatment arm and the placebo arm. Intranasal FP has been on the market for over 15 years with extensive exposure (cumulative exposure = 25 million patient treatment years) and these events have not been identified as safety issues in children, either in clinical practice or several studies conducted with intranasal FP in children.

Therefore, we do not propose to add upper respiratory tract infection and gastric pain to section 4.8 “Undesirable Effects” of the national SmPCs.

Rapporteur’s comments

The concern raised by CMS regarding increased risk of “gastric pain” and “upper respiratory tract infection” has been addressed by the MAH in a satisfactory way. At the moment it is not considered appropriate to add these adverse events to section 4.8 in the SPC.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

In this application the MAH presents the results of 3 paediatric studies, one pivotal study (FNM40017) and two supporting studies (FNM40183, FNM40181), evaluating the potential growth effect of continuous treatment with intranasally inhaled corticosteroid in children with perennial allergic rhinitis.

Both the Rapporteur and the Co-rapporteur consider that, based on a review of the data generated in a pivotal placebo-controlled one-year safety study in paediatric patients with allergic rhinitis treated with Flixonase aqueous nasal spray, a statement of the key findings should be added to the approved SPC section 5.1.

Furthermore it is recommended that a general class-effect warning concerning growth be added to section 4.4 in the SPC in countries not already having implemented a similar statement.

IV. PROPOSED CHANGES IN THE SPC

Section 4.4

The following wording of class-effect warning concerning growth has been approved in the UK SPC and should be adopted by all concerned member states:

Systemic effects of nasal corticosteroids may occur particularly at high doses prescribed for prolonged periods. These effects vary between patients and different corticosteroids (please refer to sections 5.1 and 5.2).

Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. In addition consideration should be given to referring the patient to a paediatric specialist.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery (see section 5.1 for data on intranasal fluticasone propionate).

Section 5.1

The following statement on the key findings from the three studies should be included:

In a 1-year randomised, double-blind, placebo-controlled, parallel group growth study in pre-pubescent children aged 3 to 9 years (56 patients receiving intranasal fluticasone propionate and 52 receiving placebo) no statistically significant difference in growth velocity was observed in patients receiving intranasal fluticasone propionate (200 micrograms per day nasal spray) compared to placebo. 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 in the fluticasone propionate group; the mean difference between treatments in growth velocity after one year was 0.20 cm/year (SE=0.28, 95% CI= -0.35, 0.76). No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.