17 December 2012
EMA/813493/2012
Committee for Medicinal Products for Human Use (CHMP)

Avamys

(fluticasone furoate)

Procedure No. EMEA/H/C/000770/A46/0024

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Rapporteur's Final Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Avamys (fluticasone furoate)

EMEA/H/C/000770

Marketing Authorisation Holder: GlaxoSmithKline Research & Development Limited

Rapporteur:	Poland
Start of the procedure:	16.02.2012
Date of this report:	19.03.2012
Preliminary Assessment Report:	20.03.2012
Deadline for CPMP's comments:	04.04.2012
Final Assessment Report	17.04.2012
CHMP Adoption	19.04.2012

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Avamys
INN (or common name) of the active substance(s):	Fluticasone furoate
MAH:	GlaxoSmithKline Group
Currently approved Indication(s)	Avamys is indicated for the treatment of the symptoms of allergic rhinitis in adults and adolescents (12 years and over) and children (6-11 years).
Pharmaco-therapeutic group (ATC Code):	R01AD12
Pharmaceutical form(s) and strength(s):	Nasal spray suspension; 27.5 mcg/spray

I. EXECUTIVE SUMMARY

Changes in SmPC and PL are proposed.

II. RECOMMENDATION[1]

The study FFR101782 has shown that a one-year course of fluticasone furoate nasal spray 110 mcg QD influences growth in pre-pubescent, paediatric subjects 5-8.5 years of age with periannial allergic rhinitis. This information should be placed in section 4.4 - Warnings and Precautions, and section 4.8 - Adverse reactions of the FFNS label, and section 5.1 - Clinical Trial Section.
The changes in SmPC concerning ocular safety will be proposed after supplementary information presented by MAH (see section VI of this Report).

III. INTRODUCTION

On 30 January 2012, the MAH submitted a completed paediatric studies for Avamys, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided, dated 23 January 2012, written by safety development leader Simon Ashworth.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Avamys, nasal spray. However, MAH reviewed the results of clinical studies and considers that it is appropriate to include data from these paediatric studies in the Prescribing Information.

The MAH proposed the following regulatory action:
As a Type II variation:
"The inclusion of 'growth retardation' to the Warnings and Precautions and Adverse reactions of the FFNS label in association with the pre-existing wording relating to potential systemic effects of corticosteroids, is warranted. Additional wording relating to the study is also recommended for the "Clinical Trials" section. Furthermore, additional wording relating to maintaining the lowest possible efficacious dose for children is recommended and should be included in Warnings and Precautions."

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

Avamys, fluticasone furoate, nasal spray, suspension 27.5 mcg/spray.

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final reports for:

[1] *The recommendation from section V can be copied in this section*

- **FFR110537**; A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter, Two-Year Study to Evaluate the Ocular Safety of Once-Daily, Fluticasone Furoate Nasal Spray 110mcg in Adults and Adolescents 12 Years of Age and Older with Periannial Rhinitis.;

- **FFR101782**; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Effects of a One-Year Course of Fluticasone Furoate Nasal Spray 110 mcg QD on Growth in Pre-Pubescent, Pediatric Subjects with Periannial Allergic Rhinitis;

2. Clinical studies

STUDY - FFR110537; A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter, Two-Year Study to Evaluate the **Ocular Safety** of Once-Daily, Fluticasone Furoate Nasal Spray 110mcg in Adults and Adolescents 12 Years of Age and Older with Periannial Rhinitis

Methods

This study is to assess ocular safety in subjects with Periannial Allergic Rhinitis (currently approved indication).

• Objective: The objective of this study was to assess ocular safety in adult and adolescent Perennial Allergic Rhinitis (PAR) subjects (12 years of age and older) after two years of continuous treatment with FFNS 110mcg QD.

• Study design: This was a two-year, randomized (2:1,stratified by age (12 to <18 years, 18 to <40 years, 40 to <50 years, 50 to <60 years, and ≥60 years), double-blind, placebo-controlled, parallel-group, multicentre (53) study conducted in the United States (US).

• Study population /Sample size: 548 subjects were included in the ITT Population (367 subjects in the FFNS 110 mcg QD group and 181 in the placebo group). A total of 245 subjects (168 in the FFNS 110mcg QD group and 77 in the placebo group) withdrew from the 104-week study treatment. The most common primary reason for premature withdrawal was protocol deviation (114 subjects in total).

• Treatments: Fluticasone Furoate Nasal Spray 110 µg once daily or placebo nasal spray for 104 weeks. Concomitant medication: Medications (prescription and non-prescription) and non-drug therapies were allowed during the study if they did not affect the subjects' perennial allergic rhinitis nasal symptoms. With the exception of topical hydrocortisone (1% or less, or equivalent), no corticosteroids were permitted. Subjects with intermittent asthma could be treated with short-acting inhaled beta2 agonists on an as needed basis only.
Use of anti-allergy or rhinitis medications, including oral or intranasal treatments, or nondrug therapies for rhinitis was not permitted during the study (except for loratadine 10 mg generic tablets to be taken on an as needed basis during the double-blind treatment period, not to exceed one tablet per day). In addition, oral decongestants (phenylephrine or pseudoephedrine) were permitted for use for no more than three consecutive days at any one time during the double-blind treatment period. However, use of these decongestants was not permitted within two days before an ophthalmic examination.

• Outcomes/endpoints: **Primary ocular safety** outcome measures:

- Time to first occurrence of an event for LOCS III posterior subcapsular opacity (P). An event for P was defined as an increase of 0.3 or greater from baseline in LOCS III grade for P, in either eye.
- Time to first occurrence of an event for IOP. An event for IOP was defined as an increase of 7mm Hg or greater from baseline in IOP, in either eye, using Goldmann Applanation Tonometry.

Secondary ocular safety outcome measures:

- Change from baseline in LogMAR (Logarithm of the Minimum Angle of Resolution) visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) charts;
- Change from baseline in LOCS III parameters (nuclear opalescence [NO], nuclear color [NC], cortical opacity [C], and posterior subcapsular opacity [P])
- Change from baseline in IOP
- Change from baseline in horizontal cup-to-disc ratio

Other safety measures:

• Frequency and type of adverse events (AEs)
• Clinical laboratory tests (hematology, chemistry, and urinalysis)
• Vital signs (heart rate and blood pressure)
• Nasal examinations (mucosal bleeding, ulcers, polyps, and nasal candidiasis) The primary efficacy endpoint was the mean change from baseline over the entire treatment period in daily, reflective, total nasal symptom scores (rTNSS). The mean change from baseline to the end of study in nasal finding score by rhinoscopy was the secondary efficacy endpoint.

• Statistical Methods: The sample size for this study was based on the study design (e.g., study duration, study population), the feasibility of conducting a post-marketing two-year long-term safety study, and consultations with the FDA.

Results

• Recruitment/ Number analysed: A total of 804 subjects were screened for this study. Eligible subjects were randomized in a 2:1 ratio (FFNS 110 mcg QD:Placebo) to FFNS 110 mcg QD and placebo nasal spray. A total of 525 randomized subjects (350 to FFNS 110 mcg and 175 to placebo) **including 66 subjects aged below 18 years** (21 in placebo group and 45 in FFNS group).

• Baseline data: The majority of subjects (79%) reported having PAR for ≥10 years and most PAR subjects (83%) had a positive allergen test for dust mites. The majority of subjects did not have a family history of glaucoma or a parent history of glaucoma (97%, respectively). No subjects had a sibling history of glaucoma. Additionally, the majority of subjects did not have a family history of cataract or a parent history of cataract (83%, respectively). At baseline, the mean daily rTNSS was similar between the two treatment groups as were the individual scores of nasal congestion, nasal itching, rhinorrhea and sneezing.

• Efficacy results: The primary efficacy endpoint in this study was the mean change from baseline over the treatment period in daily rTNSS as evaluated on a 4-point categorical scale scores (sum of the scores for rhinorrhea, nasal congestion, nasal itching, and sneezing). Treatment compliance (rate of ≥80%) was confirmed by daily e-diaries and videophone observations, nasal device weights, and greater improvements in reflective total nasal symptom scores observed with FFNS 110mcg compared with placebo throughout the 2-year long study.
The LS mean difference between treatment groups for the change in daily rTNSS was -0.774 over Weeks 1 to 4, <-1.0 from Weeks 5 to 8 onwards for every 4-week increment during the treatment period, and was -1.153 over the entire 2-year treatment period; 95% confidence intervals were all below -0.44.

• Safety results: The treatment difference on time to event for LOCS III P was not statistically significant based on the survival analysis. Event rates for LOCS III P were low for both treatment groups: 14 (4%) for the FFNS 110mcg QD group and 4 (2%) for the placebo group. The treatment difference on time to event for IOP was not statistically significant based on the survival analysis. Event rates for IOP were low for both treatment groups: 7 (2%) for the FFNS 110mcg QD group and 1 (<1%) for the placebo group. The events of P and IOP were not accompanied by evidence of clinical disease; there were no cataract-or-glaucoma-related AEs during the study. There were no associated increases in funduscopic horizontal cup-to-disc ratio with these IOP events.
During the treatment period, the majority of subjects experienced an AE (82% in both groups). Epistaxis, upper respiratory tract infection, sinusitis, nasopharyngitis and influenza were the most common AEs that occurred during the treatment period (all occurred at an incidence of ≥7% incidence in either group). Epistaxis was reported by 34% and 19% of subjects in the FFNS 110mcg QD and placebo groups, respectively. It was also the most common drug-related AE reported in the study (28% of subjects in the FFNS 110mcg QD group and 14% in the placebo group). No fatal SAEs were reported during the study. Twelve subjects (3%) in the FFNS 110mcg QD group and seven (4%) in the placebo reported a non-fatal SAE.

STUDY-FFR101782; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Evaluate the Effects of a One-Year Course of Fluticasone Furoate Nasal Spray 110 mcg QD on Growth in Pre-Pubescent, Pediatric Subjects with Periannial Allergic Rhinitis;

Methods

In Europe the prevalence of allergic rhinoconjunctivitis ranges from about 3-13% in children 6-7 years of age and 5-20% in adolescents 13 to 14 years of age. Intranasal corticosteroids are considered a highly effective treatment for the symptoms of allergic rhinitis, both in children and in adults. This study is to assess the influence of 12 months treatment with intranasal corticosteroid on growth velocity in pre-pubescent children 5 to 8.5 years of age with allergic rhinitis.

• Objectives: **The primary** objective of this study was to characterize, as accurately as possible, the estimation of the difference in mean pre-pubescent growth velocities between subjects treated continuously for one year with FFNS 110 mcg once-daily (the highest dose approved for pediatric use in the US) and placebo nasal spray, as determined by stadiometry. **Secondary** objectives of the study included the evaluation of other safety measures including adverse events (AEs), routine laboratory assessments (chemistry, hematology, urinalysis), 24-h urinary free cortisol excretion, and nasal examinations.

• Study design: This was a Phase IV (Phase IIIb for Canada and Europe), multicentre (59), randomized, double-blind, placebo-controlled, parallel-group 76-week study evaluating the effects of once-daily treatment with FFNS 110 mcg on growth velocity in pre-pubescent children. The study design consists of 16-week baseline period, 52-week placebo/active treatment period, and 8-week follow-up period.

• Study population /Sample size: A total of 910 subjects (All Subjects Screened Population) were screened for this study.

• Treatments: once-daily, intranasal administration of fluticasone furoate nasal spray 110 mcg or placebo administered for 52 weeks.

• Outcomes/endpoints: see – “Objectives”

• Statistical Methods: A random coefficient analysis was performed to support the primary analysis findings using an ANCOVA model with height as the dependent variable, and baseline height, age, gender, treatment, time and treatment by time interaction as explanatory variables in the mixed effect model with random intercept and slope.

Results

• Recruitment/ Number analysed: Randomization failure occurred in 264 subjects (61%) and was most frequently due to not having a daily rTNSS of ≥5 on any four of the last seven days prior to Visit 2 (115 [26%]) or having a bone age which was not within ±1 year of the subjects' chronological age (82 [19%]) according to randomization criteria. **474** (52%) subjects were randomized and were included in the ITT Population of whom 435 (92%) were included in the Growth Population and 342 (72%) in the Urinary Cortisol Population. The majority of subjects (373 subjects, 79%) completed the study.

• Baseline data: At each clinic visit during the 16-week baseline period, the subject's height (assessed and recorded via the standardized Holtain Stadiometer) and Tanner stage were assessed. Physical examinations and clinical laboratory assessments (chemistry, hematology and urinalysis) were conducted at Visit 1 and Visit 5. Other baseline period assessments included a 24-h urine sample returned to the clinic at Visit 5, a hand/wrist X-ray. The baseline growth velocity in the current study was slightly lower than expected for the US and European populations.

• Results: This study demonstrates that FFNS, at the highest dose approved globally for both pediatric and adult use (110 mcg once-daily), has a small effect (-0.270 cm per year) on pre-pubescent growth velocity as compared to placebo over a 52-week treatment period. However, growth velocity over the 52-week treatment period is 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 is -0.270 cm per year [95% CI -0.48 to -0.06]. The 95% CI (-0.48, -0.06 cm/year) is below 0.5 cm indicating a precise estimation of the effect of FFNS 110mcg administered daily for 52 weeks on growth velocity. And, while the LS mean treatment difference in growth velocity of -0.270 cm per year is small, the clinical relevance of this difference is not known. Secondary analyses of growth velocity were performed for the Growth Population excluding subjects exhibiting Tanner stage characteristics of 2 and above, questionable height measurements, height measurements after receiving corticosteroids or oral CNS stimulants, or all of the above. Statistical analyses showed that the treatment differences on LS mean growth velocities for all of these subgroups ranged from -0.282 to -0.271 cm/year (Table 15) and the results were consistent with the primary analysis. During the treatment period, for each treatment group, the mean growth velocity was lower for each non-white race subgroup compared to White, the largest race subgroup (>75% of Growth Population), with the exception of the Asian placebo group, although these race subgroups were relatively small.

Table 15 **Subgroup Analyses of Growth Velocity (cm/year) (Growth Population)**

Population	Placebo N=218	FFNS 110 mcg N=217
Growth (primary analysis)		
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)
Excluding subjects with at least one post-baseline Tanner Stage assessment ≥2		
n	201	195
LS mean (SE)	5.47 (0.10)	5.18 (0.10)
LS mean difference		-0.282
95% CI		(-0.50, -0.06)
Excluding questionable height measurements		
n	218	217
LS mean (SE)	5.46 (0.10)	5.19 (0.10)
LS mean difference		-0.271
95% CI		(-0.48, -0.06)
Excluding height measurements taken after receiving any medication that may influence growth during the treatment period		
n	215	214
LS mean (SE)	5.47 (0.10)	5.20 (0.10)
LS mean difference		-0.272
95% CI		(-0.48, -0.06)
Excluding all of the above		
n	198	192
LS mean (SE)	5.47 (0.11)	5.19 (0.11)
LS mean difference		-0.281
95% CI		(-0.51, -0.06)

Source data: Table 6.2, Table 6.4, Table 6.6, Table 6.8and Table 6.10.

• Other safety results: Once-daily treatment with FFNS 110 mcg over 52 weeks was well tolerated without clinically relevant effects on clinical chemistry, electrolytes, hematology, 24-h urinary cortisol excretion or findings on nasal examinations. The incidence of AEs was similar between the placebo and FFNS groups (68% and 64%, respectively). The most common drug-related AE was epistaxis occurring at a similar rate in the placebo and FFNS groups (7% and 6%, respectively). SAEs were reported for 2 subjects in the FFNS group and 4 subjects in the placebo group, and withdrawals due to AEs occurred at the same rate for both groups (5[2%]).

Table 21 Overview of Adverse Events (ITT Population)

	Placebo N=237	FFNS 110mcg N=237
Adverse events, n (%)		
Baseline period	92 (39)	108 (46)
On-treatment	160 (68)	152 (64)
During follow-up	39 (16)	40 (17)
Drug-Related AEs during the study period	26 (11)	32 (14)
On-Treatment, leading to withdrawal from study	5 (2)[a]	5 (2)[b]
Serious adverse events, n (%)		
During Study	4 (2)[c]	2 (<1)[d]
Drug-Related SAEs	0	0
On- treatment fatal SAEs	0	0

Source data: Table 6.20, Table 6.21, Table 6.24, Table 6.25, Table 6.26 and Table 6.27.

a. Of these, 3 subjects withdrew due to asthma events (of whom one also withdrew due to viral upper respiratory tract infection). One subject withdrew due to chicken pox; 1 subject withdrew to bronchospasm
b. Of these, 2 subjects withdrew to asthma events. Two subjects withdrew due to chickenpox (one also experienced respiratory tract infection, upper respiratory tract infection and bronchitis). One subject withdrew due to dysgraphia, insomnia and nervousness.
c. Of these, 1 subject had asthma and pneumonia atypical, 1 subject had osteomyelitis, 1 subject had myositis and viral respiratory tract infection, 1 subject had head injury.
d. Of these, 1 subject had gastroenteritis, 1 subject had appendicitis.

3. Discussion on clinical aspects

STUDY - FFR110537

Results of this study showed once-daily fluticasone furoate 110 mcg aqueous nasal spray produced greater reductions from baseline in subjects' self-assessed, allergy nasal symptom scores as compared with placebo nasal spray. These reductions were inferentially significant for the primary efficacy endpoint (rTNSS).
The safety data on the 66 paediatric patients is not clearly defined so it is requested to present this information separately . As ocular changes are seen in the population treated this information should be included in Warnings and precautions and adverse reactions in the FFNS label and Clinical Trial Section.

STUDY-FFR101782
This study has shown that a one-year course of fluticasone furoate nasal spray 110 mcg QD influences growth in pre-pubescent, paediatric subjects 5-8.5 years of age with periannial allergic rhinitis. This information should be placed in section 4.4 - Warnings and Precautions, and section 4.8 - Adverse reactions of the FFNS label, and section 5.1 - Clinical Trial.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

STUDY - FFR110537 – The study includes data from both children and adults and is presented without clear age distinction. It is difficult to assess relevant paediatric data from this study. Due to this the MAH is kindly requested to summarize results in paediatric population. MAH is also requested to present AE for the 66 children separately. This can be presented in tabular format.

STUDY-FFR101782 – The MAH is requested to present the proposed exact wording for changes in SmPC in sections: 4.4, 4.8 and 5.1.

VII. CHMP'S COMMENTS

SE Comments

STUDY- FFR101782 With regard to study FFR101782 Sweden considers that the study has shown that a one-year course of fluticasone furoate nasal spray 110 mcg QD has a small effect (-0.27 cm/year) on pre-pubescent growth velocity compared to placebo in paediatric subjects 5-8.5 years of age with periannial allergic rhinitis. The change is small -0.27 cm (-4.9%) in comparison to placebo. The noted change seems to be in line with data for other nasally administered glucocorticoidsteroids. Sweden agrees with the Rapporteur that data can be inlcuded in SPC section 5.1. However, does not support that data should be included in SPC sections 4.4 and 4.8 since relevant data already have been included in these sections.

VIII. FINAL RAPPORTEUR'S CONCLUSION

In spite of Sweden comments Rapporteur sustains raised requests for supplementary information as given below:

STUDY - FFR110537 – The study includes data from both children and adults and is presented without clear age distinction. It is difficult to assess relevant paediatric data from this study. Due to this the MAH is kindly requested to summarize results in paediatric population. MAH is also requested to present AE for the 66 children separately. This can be presented in tabular format.

STUDY-FFR101782 – The MAH is requested to present the proposed exact wording for changes in SmPC in sections: 4.4, 4.8 and 5.1.