European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR
FLUTICASONE FUROATE GSK

International Nonproprietary Name:
FLUTICASONE FUROATE

Procedure No. EMEA/H/C/1019

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

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TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Glaxo Group Limited submitted on 9 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Fluticasone furoate GSK, through the centralised procedure falling within the Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 28 April 2008.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The applicant applied for the following indication:

Adults, adolescents (12 years and over) and children (6 - 11 years)

Fluticasone furoate GSK is indicated for the treatment of:

- the symptoms of allergic rhinitis

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The initial product, AVAMYS, has been given a Community Marketing Authorisation on 11 January 2008.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Michal Pirozynski (PL) Co-Rapporteur: David Lyons (IRL)

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 9 May 2008.
- The procedure started on 28 May 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 30 June 2008.
- During the meeting on 21 – 24 July 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Fluticasone furoate GSK on 24 July 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 July 2008.
- The CHMP opinions were forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decisions on 6 October 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

Therefore the MAH of the reference product, AVAMYS, has provided consent to allow access to Module 2 to Module 5 of the initial dossier and any subsequent post-marketing procedures submitted, assessed and approved. AVAMYS had been submitted as a full application under Art 8(3) of Directive 2001/83/EC.
The dossier submitted for Fluticasone furoate GSK 27.5 micrograms/spray nasal spray suspension consists only of Module 1 information.

As a consequence, quality, safety and efficacy of Fluticasone furoate GSK are identical to the up-to-date quality, safety and efficacy profile of Avamys. Information on the scientific discussions can be found in the AVAMYS CHMP assessment report and in the European Public Assessment Report (EPAR).

The approved indication is:

"Adults, adolescents (12 years and over) and children (6 - 11 years)

Fluticasone furoate GSK is indicated for the treatment of:

- the symptoms of allergic rhinitis"

2.2 Quality aspects

Since this application is an informed consent dossier of the AVAMYS application, the quality data in support of the Fluticasone furoate GSK application are identical to the up-to-date quality data of the AVAMYS dossier which have been assessed and approved (including all post-marketing procedures).

2.3 Non-clinical aspects

Since this application is an informed consent of the AVAMYS application, the non-clinical data in support of the Fluticasone furoate GSK application are identical to the up-to-date non-clinical data of the AVAMYS dossier, which have been assessed and approved (including all post-marketing procedures).

The applicant has provided an update to the original environmental risk assessment. The regulatory and scientific strategy of ERA chosen by the applicant is reasonable and the scope of studies (Phase I and Phase II, Tier 1) acceptable. The calculated Predicted Environmental Concentration (PEC) for fluticasone furoate is significantly below the trigger value for a Phase II assessment according to Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00).

2.4 Clinical aspects

Since this application is an informed consent of the AVAMYS application, the clinical data in support of the Fluticasone furoate GSK application are identical to the up-to-date clinical data of the AVAMYS dossier, which have been assessed and approved (including all post-marketing procedures).

- User Consultation

Consultation with target patient groups has not been undertaken for Fluticasone furoate GSK. The applicant has included justification for this based on the fact that the Package Leaflet is the same as for the reference product and its User Testing was satisfactory.

2.5 Pharmacovigilance

PSUR

It is agreed by the CHMP that the PSUR cycle of Fluticasone furoate GSK will correspond to the cycle attributed to the cross-referred product, AVAMYS, until otherwise specified.

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Effects on nasal mucosa	Routine pharmacovigilance including targeted questionnaires 12-month biopsy study	SPC Section 4.8 (Undesirable effects) Very common: epistaxis Common: nasal ulceration
Concurrent use of CYP3A4 inhibitors	Routine pharmacovigilance	-SPC Section 4.4 "Ritonavir Concomitant administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate (see Section 4.5)." -SPC Section 4.5 "Based on data with another glucocorticoid (fluticasone propionate), that is metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the risk of increased systemic exposure of fluticasone furoate. Caution is recommended when co-administering fluticasone furoate with potent CYP3A4 inhibitors as an increase in systemic exposure cannot be ruled out.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		In a drug interaction study of intranasal fluticasone furoate with the potent CYP3A4 inhibitor ketoconazole there were more subjects with measurable fluticasone furoate concentrations in the ketoconazole group (6 of the 20 subjects) compared to placebo (1 out of 20 subjects). This small increase in exposure did not result in a statistically significant difference in 24 hour serum cortisol levels between the two groups (see Section 4.4).”
Use in patients with hepatic impairment	Routine pharmacovigilance	SPC Section 4.2: Hepatic Impaired Patients: No dose adjustment is required in mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see Section 4.4 and Section 5.2). SPC Section 4.4 Fluticasone furoate undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone furoate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events (see Section 4.2 and Section 5.2). Caution is advised when treating these patients.” SPC Section 5.2 Hepatic Impairment: There are no data with intranasal fluticasone furoate in patients with hepatic impairment. A study of a single 400 microgram dose of orally inhaled fluticasone furoate in patients with moderate hepatic impairment resulted in increased Cmax (42 %) and AUC(0-_) (172 %) and a modest (on average 23 %) decrease in cortisol levels in patients compared to healthy subjects. From this study the average predicted exposure of 110 micrograms of intranasal fluticasone furoate in patients with moderate hepatic impairment would not be expected to result in suppression of cortisol. Therefore moderate hepatic impairment is not predicted to result in a clinically relevant effect for the normal adult dose. There are no data in patients with severe hepatic impairment. The exposure of fluticasone furoate is likely to be further increased in such patients.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Systemic corticosteroid effects	Routine pharmacovigilance including targeted questionnaire	Warning in SPC Section 4.4 : "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. Fluticasone furoate 110 micrograms once daily was not associated with hypothalamic-pituitaryadrenal (HPA) axis suppression in adult, adolescent or paediatric subjects. However the dose of intranasal fluticasone furoate should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently."
Potential cataract development	Routine pharmacovigilance including targeted questionnaire 24 month ocular study	
Limited long term clinical experience in children including a potential effect on long-term growth in children	-12 month stadiometry study - Routine pharmacovigilance	
Pyrexia	Routine Pharmacovigilance including evaluation of events across age groups	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information

2.6 Overall conclusions, risk/benefit assessment and recommendation

Since this application is an informed consent of the AVAMYS application the CHMP was of the opinion that the risk-benefit balance of Fluticasone furoate GSK was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

Adults, adolescents (12 years and over) and children (6 - 11 years)

Fluticasone furoate GSK is indicated for the treatment of:

- the symptoms of allergic rhinitis