LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fluticasone Elpen
(fluticasone propionate)

SE/H/1765/01-02/DC

This module reflects the scientific discussion for the approval of Fluticasone Elpen. The procedure was finalised on 2019-01-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AENORASIS S.A has applied for a marketing authorisation for Fluticasone Elpen, Inhalation powder, pre-dispensed 250 microgram/dose and 500 microgram/dose. The active substance is fluticasone propionate (a glucocorticoid with anti-inflammatory action).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of fluticasone propionate are well known. As fluticasone propionate is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Fluticasone Elpen is a hybrid product intended to replace marketed products containing the same active substance, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Fluticasone Elpen from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varies between approximately 5-11% of the nominal dose depending on the inhalation device used. In patients with asthma or COPD a lesser degree of systemic exposure to inhaled fluticasone propionate has been observed. Systemic absorption occurs mainly through the lungs and is initially rapid then prolonged. Due to pre-systemic metabolism, the oral availability is less than 1%. There is a linear increase in systemic exposure with increasing inhaled dose. The terminal half-life is approximately 8 hours. Plasma protein binding is 91%. The main pathway is metabolism to an inactive carboxylic acid metabolite, by the CYP3A4.

Pharmacokinetic studies aim at demonstrating similar pulmonary deposition and similar total systemic exposure between a hybrid inhalation product and the originator. According to the OIP guideline, bioequivalence studies with charcoal blockade could be used to compare pulmonary deposition as a surrogate for efficacy. In addition, bioequivalence studies without charcoal blockade could be used to compare systemic exposure as a surrogate for safety. For some inhaled medicinal products, the contribution of intestinal absorption to systemic exposure is negligible (<5%) and a single dose PK study without charcoal can be used for both efficacy and safety comparisons.

To support the application, the applicant has submitted 1 pivotal pharmacokinetic study, performed without activated charcoal blockade. For fluticasone, the contribution of intestinal absorption to systemic exposure is negligible, and thus a study without activated charcoal can be used for both efficacy and safety comparisons. Thus, a study without activated charcoal blockade is sufficient.

Therapeutic equivalence was evaluated in one single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Fluticasone, 500 microgram/dose, inhalation powder, pre-dispensed with Flixotide Diskus, 500 microgram/dose, inhalation powder, pre-dispensed, under fasting conditions and without administration of activated charcoal. It is considered sufficiently demonstrated that the flow rate dependency is similar for test and reference, and thus extrapolation of the results to the patient population is acceptable. The batches used in the study are representative for the intended product and the reference product on the market. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of fluticasone propionate were determined with

a validated LC/MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for fluticasone, n=60.

Treatment	**AUC_{0-t}** pg*h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	**1118.94±477.34**	**113.92±44.51**	**1.667 (0.750-3.000)**
Reference	**1111.34±452.73**	**107.68±42.90**	**1.667 (0.500-3.500)**
***Ratio (90% CI)**	**100.04 (91.27-109.64)**	**106.43 (96.77-117.05)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

The results of study FLU-BESD-03-ELP/05 with 500 microgram formulation CAN be extrapolated to the other strength 250 microgram.

Therapeutic equivalence between the applied product and the reference product has been shown based on PK data.

IV.1 Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. As therapeutic equivalence with the originator product is demonstrated, additional data is not necessary. The applicant has not provided any clinical data documenting handling of the device, nor any data on patients' capacity to empty the device (i.e. PIF-studies). However, such data are not needed as the Elpenhaler device is approved for use in EU with fluticasone in combination with salmeterol.

IV.2 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluticasone Elpen.

Safety specification

Summary of safety concerns as suggested by the applicant:

Summary of safety concerns	
Important identified risks	• Drug-interaction with CYP3A4 inhibitors • Pneumonia (in COPD patients)
Important potential risks	N/A
Missing information	N/A

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactorily responded to the issue raised and updated the RMP accordingly.
Issue is resolved.
The submitted Risk Management Plan, version 1.0 signed 2017-10-29 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Fluticasone Elpen, is found adequate. There are no objections to approval of Fluticasone Elpen, from a non-clinical and clinical point of view. Therapeutic equivalence between the applied product and the reference product has been adequately demonstrated based on PK data. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Fluticasone Elpen, Inhalation powder, pre-dispensed 250 microgram/dose and 500 microgram/dose. was positively finalised on 2019-01-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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