LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fluttasino
(fluticasone propionate)

SE/H/2497/01/DC

This module reflects the scientific discussion for the approval of Fluttasino. The procedure was finalised at 2025-04-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Fluttasino, 400 mikrogram, Nasal drops, suspension.

The active substance is fluticasone propionate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

The active ingredient in the product Fluttasino is fluticasone propionate, which is a corticosteroid with anti-inflammatory properties. The nasal drops are locally applied intranasally, and the claimed indication is *for the regular treatment of nasal polyps and associated symptoms of nasal obstruction.* The dose should be titrated to the lowest effective dose.

II.2 General comments on the submitted dossier

The application for Fluttasino, 400 mikrogram, Nasal drops, suspension, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Flutide Nasal, 400 µg, Nasal drops, suspension, authorised in Sweden since 1999 with GlaxoSmithKline as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate. However, it is noted that the toxicology part of the submitted non-clinical overview almost entirely relies on referencing the Product monograph of Flonase even though a non-clinical overview is expected to primarily be based on published scientific literature. Nevertheless, requesting new references are not expected to add value at this point.

Environmental Risk Assessment (ERA)
Since Fluttasino is intended to substitute products already on the market, 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 Fluttasino from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

Pharmacokinetic properties of the active substance
Absorption:
After recommended doses of intranasal fluticasone propionate plasma levels are low. Systemic bioavailability for the nasal drop formula is extremely low (mean value 0.06 %).
Following intravenous administration the pharmacokinetics of fluticasone propionate are proportional to the dose, and can be described by three exponentials.
Absolute oral bio-availability is negligible (<1 %) due to a combination of incomplete absorption from the gastro-intestinal tract and extensive first pass metabolism.

Biowaiver
No PK studies have been submitted as the applicant claims that therapeutic equivalence can be concluded based on *in vitro* data only.

Discussion and overall conclusion
There is currently no EU guideline specifying the requirements for demonstration of therapeutic equivalence between locally acting nasal drops, suspension formulations. There is however a concept paper for the development of a guideline on the demonstration of therapeutic equivalence for nasal products (EMA/CHMP/315603/2024). The aim of this new guideline would be to detail the data requirements for demonstrating therapeutic equivalence between nasal products containing the same active moiety(ies), as these are currently insufficiently covered in existing guidelines.

The applicant claims that in these conditions, according to the Guideline on the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00 Rev. 1) and the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr), no PK study is required. However, the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr) simply concludes that for generic nasal products claiming essential similarity to an originator/innovator product, studies required to demonstrate therapeutic equivalence may depend on the intended site of action of the active substance (local or systemic). This guideline is currently under revision. The draft first revision (EMA/CHMP/20607/2024) addresses some quality parameters to consider in the comparison between test and reference in order to conclude *in vitro* therapeutic equivalence. The Guideline on the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00 Rev. 1) does not include criteria for an *in vitro* data-based submission for nasal products. The ongoing revision of the OIP guideline (EMA/CHMP/101453/2024) presents a stepwise approach with *in vitro* criteria to be fulfilled and of additional PK studies to be conducted in case not all *in vitro* criteria are fulfilled. It is anticipated that a similar approach would be applicable for nasal products.

The Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) mentions that for locally acting products, a waiver of the need to provide equivalence data may be acceptable in case of solutions but provides no guidance regarding locally applied suspensions.

The principle of showing qualitative *in vitro* equivalence as a surrogate for clinical study/ies, has however been accepted in several mometasone nasal spray, suspension applications and azelastine hydrochloride/fluticasone nasal spray, suspension applications within the EU. In these procedures it

has been concluded that thorough *in vitro* comparisons of applied product versus reference product should be more sensitive indicators of therapeutic equivalence than *in vivo* systemic exposure data.

In conclusion, provided that *in vitro* equivalence has been adequately shown, no clinical PK studies or additional clinical studies to demonstrate therapeutic equivalence is considered necessary.

In vitro equivalence has been demonstrated. For quality assessment, see the Quality AR.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that equivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH : EQL Pharma AB

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
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 Fluttasino.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 14-August-2023, 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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.>

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Fluttasino, is found adequate. There are no objections to approval of Fluttasino, from a non-clinical and clinical point of view. *In vitro* equivalence has been demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 PL 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-