COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fluticasone furoate Basic Pharma, 27.5 microgram/actuation, nasal spray, suspension

(fluticasone furoate)

NL/H/5367/001/DC

Date: 9 September 2022

This module reflects the scientific discussion for the approval of Fluticasone furoate Basic Pharma, 27.5 microgram/actuation, nasal spray, suspension. The procedure was finalised on 23 May 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fluticasone furoate Basic Pharma, 27.5 microgram/actuation, nasal spray, suspension, from Basic Pharma Manufacturing B.V.

The product is indicated for the treatment of the symptoms of allergic rhinitis in adults, adolescents and children (6 years and over).

This medicinal product contains 8.25 microgram benzalkonium chloride in each actuation, which is equivalent to 150 microgram per gram. Long-term use may cause oedema of the nasal mucosa. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Avamys 27.5 microgram/spray, nasal spray suspension which has been registered in the EEA by GlaxoSmithKline (Ireland) Limited, Ireland since 11 January 2008 via the centralised procedure EMEA/H/C/000770.

The concerned member state (CMS) involved in this procedure was Luxembourg. However, the application was withdrawn on 23 December 2021 due to commercial reasons.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC (hybrid application). The medicinal product is a locally applied and local acting drug for which bioequivalence cannot be demonstrated through bioavailability studies. As required by article 10(3) a comparative clinical trial has been performed to demonstrate therapeutic equivalence as showing bioequivalence by pharmacokinetics is not possible.

II. QUALITY ASPECTS

II.1 Introduction

Fluticasone furoate Basic Pharma is a white nasal spray suspension. Each spray actuation delivers 27.5 micrograms of fluticasone furoate.

The suspension is packed in amber coloured glass bottles with a PE/PP/EVA spray pump. The product comes in pack sizes of 60 (5.3 g) and 120 (8.6 g) actuations.

The excipients are:
Glucose anhydrous, microcrystalline cellulose (E460), carmellose sodium (E466), polysorbate 80 (E433), benzalkonium chloride, disodium edetate and purified water.

II.2 Drug Substance

The active substance is fluticasone furoate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fluticasone furoate is a white to almost white crystalline powder and is practically insoluble in water. The molecule contains nine chiral centres with the configurations 6S, 8S, 9R, 10S, 11S, 13S, 14S, 16R, 17R, and shows three polymorphic forms (I, II and III). Polymorphic form I (thermodynamically stable at room temperature) is the chosen form for the innovator product and therefore, for this product. The manufacturer ensures consistently providing the same one single isomer, as no reaction occurs at chiral centres. This is controlled as part of the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of six chemical synthesis steps followed by five purification steps using various reagents and solvents. The active substance may sometimes be micronised. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. An additional test for residual solvents and particle size distribution has been included. The specification includes tests for description, identification, solubility, water, sulphated ash, related substances, assay, residual solvents, and particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Furthermore, the analytical methods have been adequately described and validated. Batch analytical data demonstrating compliance with the drug substance specification have been submitted for three batches.

Stability of drug substance

Stability data on the active substance has been provided for three full scaled batches in accordance with applicable European guidelines. The batches were stored at 30°C/65% RH (36 months) and 40°C/75% RH (6 months). The stability data show no clear trends or changes in any of the tested parameters at both storage conditions. All results were within the specification limits. Furthermore, results from a photostability study in line with ICH Q1B requirements, demonstrated that the active substance is not sensitive to light. Based on the data submitted, a retest period could be granted of 36 months. The active substance does not require special storage condition.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The product contains qualitatively and quantitatively the same excipients, formulation and delivery form as the reference. Furthermore, the indicated population for this application is identical to that of the reference. A clinical overview based on literature has been provided. Pharmaceutical equivalence of a sufficient degree to infer therapeutic interchangeability between the test and reference product has been adequately demonstrated. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. A biowaiver has been granted based on *in vitro* studies.

In vitro equivalence studies

To demonstrate similarity between the proposed product and the reference product, analytical *in vitro* tests have been submitted. When establishing equivalence based on in-vitro data only, the *in vivo* correlation of in-vitro parameters should be considered. For that purpose the battery of tested quality attributes should cover all relevant parameters, the acceptance criteria and method of evaluation of the results should be justified and finally the results should comply. For the *in vitro* parameters, the MAH considered the EMA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr).

The parameters tested for this product, are those relevant to evaluate therapeutic equivalence through *in vitro* studies. The used tests were standardized methods or (partially) validated in-house methods. During the development process of the drug product, the particle of size fluticasone furoate was optimised (with a minor change) to match the reference product. The *in vitro* studies were performed with batches produced before this change. New batches with the optimised particle size was produced and used to repeat some of the *in vitro* tests. For the tests that were not repeated (equivalence of polymorphic form, qualitative and quantitative composition, actuator dip length, actuator diameter, viscosity, surface tension and aerodynamic particle size distribution) justification was

submitted to support that the minor difference in particle size has not impact on the study results. The justifications were considered acceptable. *In vitro* bioequivalence was calculated for the parameters that are quantifiable using Average BioEquivalence (ABE) statistics. ABE confirms similarity between test and reference products when the 90% confidence interval of the geometric means ratio of the tested parameters is within the bioequivalence limit of 80-125%. For the other parameters, polymorphic form and viscosity, a comparison was made using the corresponding spectra and figures. For all tests, the product with 120 and/or 60 actuations were compared with the 120 actuations reference product. The tested parameter and the results are described below.

- Delivered dose (single actuation content): the actual amount of drug substance per actuation was determined according to the method for delivered dose uniformity. Recoveries reference versus test product were calculated.
- Drug substance particle size distribution (before and after actuation): determined using spectroscopy. Additional particle size distribution before actuation was determined. Recoveries reference versus test product were calculated.
- Equivalence of polymorphic: three polymorphic forms (I, II, and III) of fluticasone furoate are reported in literature. The test product and reference product contain the polymorphic form I, which is the thermodynamically stabile form at ambient temperature. The manufacturer declared that the single crystalline form I is manufactured and this does not change due to the micronisation process. The presence of the polymorphic forms in the test and reference product was confirmed, XRPD spectra of both products were equivalent.
- Qualitative and quantitative composition: the actual content of fluticasone furoate was determined. The recoveries of the theoretical declared concentrations were calculated. Recoveries reference versus test product were calculated.
- Assay benzalkonium chloride (preservative): the actual amount of benzalkonium chloride was determined. The recoveries of the of the theoretical declared concentrations were calculated. Recoveries reference versus test product were calculated.
- Viscosity: determined according to the standardised method. The method was also used to determine thixotropic behaviour of the test and reference product. Results reference versus test product were compared.
- Relative density: determined with a pycnometer. Results reference versus test product were compared.
- pH: determined (directly in the sample container), according to the standardised method. Recoveries reference versus test product were calculated.
- Droplet size distribution: determined using laser diffraction. Results reference versus test product were compared.
- Surface tension: determined with the Pendant Drop Method. The surface tension of the product is associated with the formulation only and not with the packaging. Therefore, this test was only performed for test product with 120 actuations. Results reference versus test product were compared.
- Single actuation content through container life: the content of a single actuation was determined for one spray (actuation) at the beginning (after priming) and one spray

(actuation) at the end of the same bottle. The recovery fluticasone furoate was calculated by comparing the measured amount with the theoretical declared content of 27.5 µg per actuation.

- Aerodynamic droplet size distribution: determine with a Andersen Cascade Impactor (ACI). Theoretically, 10 actuations are equal to 550 mg of drug product and contain 275 µg of drug substance. Results reference versus test product were compared.
- Actuator dip length (in-used): measured with a caliper, considering which part of the actuator is inserted in the nose by the patient. Recoveries reference versus test product were calculated.
- Actuator diameter (top and bottom): the actuator diameter of top and bottom of was measured at the same positions (top and bottom) as used for the determination of actuator dip length. Recoveries reference versus test product were calculated.
- Spray pattern: spray patterns for both reference and test product were determined and compared.

Overall conclusion *in vitro* tests

All recoveries for the different parameter are within the bioequivalence limit of 80% - 125%. Furthermore, the test that are not quantifiable, show similar results when comparing the standard and reference product. Based on the results, pharmaceutical equivalence of a sufficient degree to infer therapeutic interchangeability between the test and reference product has been adequately demonstrated for all parameters. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process includes preparation of different solutions and suspensions in processing vessels by mixing, dispersion, filling and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been submitted for three full-scaled bulk batches (each divided in a drug product batch of 60 and 120 actuations) in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. requirements except for benzalkonium chloride solution 1% w/w for which an in-house specification is provided. The excipient specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, foreign particles, pH, viscosity, relative density, identification of fluticasone furoate and benzalkonium chloride, assay of fluticasone furoate and benzalkonium chloride, related substances, delivered dose, number of actuations, droplet size distribution and microbiological purity. The proposed release and shelf life acceptance criteria are identical except for assay of fluticasone furoate, assay of benzalkonium chloride and related substances. Limits in the specification have been justified

and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data of three full-scale batches of each presentation (60 and 120 actuations) from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full-scale batches of each presentation (60 and 120 actuations) stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The tests were performed in accordance with ICH stability guidelines. The batches were stored in amber coloured glass bottles (10 mL) with a spray pump, upright and inverted for one batch of each presentation. Photostability studies were performed and showed that the product is stable when exposed to light. No differences were observed between pack sizes, no claim on upright storage is required. All results at both conditions were well within the stated shelf life acceptance criteria. Based on the submitted stability data, a shelf life was granted of two years. The labelled storage conditions are *"do not refrigerate or freeze, always keep the dust cap on".*

Furthermore, stability data have been provided demonstrating that the product remains stable for three months following first opening of the spray pump, when stored below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fluticasone furoate Basic Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fluticasone furoate Basic Pharma is a widely used active substance and its pharmacodynamic, pharmacokinetic and toxicological properties are well known and the product is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Avamys which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

III.3 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 Fluticasone furoate Basic Pharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Headache • Nasal Events (including: Epistaxis, nasal ulceration, nasal septum perforation and other nasal events) • Hypersensitivity • Cataracts & glaucoma
Important potential risks	• Taste & Smell disorders • Pyrexia • Systemic corticosteroid effect: Adrenal suppression • Systemic corticosteroid effect: Cataracts/glaucoma • Systemic corticosteroid effect: Growth retardation • Psychiatric effects
Missing information	• Use in pregnancy and lactation • Off-label use (sinusitis and children < 6 years of age)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

III.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Avamys. No new clinical studies were conducted. The MAH demonstrated through *in vitro* studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

IV. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with five participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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. After user testing changes were made to the cleaning instructions in Chapter 3 of the PL in line with development tests, these changes do not affect the outcome of the performed user testing.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fluticasone furoate Basic Pharma, 27.5 microgram/actuation, nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Avamys 27.5 micrograms/spray, nasal spray suspension which is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fluticasone furoate Basic Pharma, 27.5 microgram/actuation, nasal spray, suspension with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 May 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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