COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fluticasone propionate Interdos, 50 microgram/actuation nasal spray, suspension (fluticasone propionate)

NL/H/5286/001/DC

Date: 1 November 2021

This module reflects the scientific discussion for the approval of Fluticasone propionate Interdos, 50 microgram/actuation nasal spray, suspension. The procedure was finalised at 26 August 2021. 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
EVA	Ethylene-vinyl acetate
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PL	Package Leaflet
PP	Polypropylene
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 propionate Interdos, 50 microgram/actuation nasal spray, suspension, from Interdos Pharma BV.

Fluticasone propionate Interdos is indicated for prophylaxis and treatment of seasonal allergic rhinitis and perennial rhinitis.

The product is indicated in adults and adolescents aged 12 years and older and in children aged 4 to 12 years.

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 Flixonase 50 microgram per dosage, nasal spray suspension by Glaxo Smith Kline (RVG 14424), nationally registered since 28 November 1990 in the Netherlands.

The concerned member state (CMS) involved in this procedure was the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. The dossier was submitted as hybrid application because bioequivalence with the reference product cannot be demonstrated through bioavailability studies as it concerns a locally acting product. Therefore, a hybrid application is appropriate.

II. QUALITY ASPECTS

II.1 Introduction

Fluticasone propionate Interdos is a nasal spray, and is a white opaque suspension. The product contains as active substance 50 micrograms of fluticasone propionate per dose.

The suspension is packed in a white polypropylene (PP) bottle with a polythene (PE)/PP/ethylene-vinyl acetate (EVA) spray pump.

The excipients are: benzalkonium chloride, glucose, microcrystalline cellulose (E460i), carmellose sodium (E466), phenylethyl alcohol, polysorbate 80 and purified water.

II.2 Drug Substance

The active substance is fluticasone propionate, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is white or almost white powder and is practically insoluble in water. The polymorphic form of the drug substance is confirmed by the drug substance manufacturer, i.e. polymorphic form I. Therefore, it is not deemed necessary to include a test in the drug substance specifications. The polymorphic form of the active substance was also checked against the reference product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

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., with additional requirements for residual solvents and particle size distribution. In addition, the microbiological quality is controlled. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for three years when stored in double polyethylene bags in triple polyethylene laminated bags, placed in fibre or polyethylene drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The drug substance stability studies in support of the re-test period as stated on the CEP were performed with micronised drug substance.

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 excipients are quantitative and qualitatively the same as those in the reference product. The objective was to formulate and develop an aqueous suspension of fluticasone propionate, suitable for nasal delivery, which matched the currently marketed reference product.

To support bioequivalence between the proposed product and the reference product, *in vitro* tests were performed to compare the drug product with the innovator products (including reference product). The justification for the requested biowaiver will be discussed in section IV.

In order to establish performance standards and overall acceptability of the proposed packaging components several packaging development studies were performed with the drug product, such as shaking, minimum fill, extractables, priming and temperature cycling.

Manufacturing process

The manufacturing process consists of the preparation of a solution, preparation of suspension A, preparation of suspension B, followed by filling and packaging. The manufacturing process is clearly and adequately described. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches and three pack sizes in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. where possible. Phenylethyl alcohol is routinely analysed in accordance with the United Stated Pharmacopoeia. The benzalkonium chloride solution 1% (w/w) is controlled via in-house methods for appearance and assay. The pharmacopoeial and in-house 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, relative density, viscosity, identity and assay of active substance and preservatives (benzalkonium chloride and phenylethyl alcohol), related substances, delivered dose, number of actuations, droplet size distribution, and microbiological purity. The release and shelf-life limits are the same, except for the assay limits for both preservatives 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 from three full-scale batches and three pack size batches 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 on full scale batches and three pack sizes of production scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored upright in commercial PP bottles with nasal spray pump. Three batches were also stored at long term conditions as follows: 13 months upright followed by five months inverted.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. All results remain within the proposed specifications at both storage conditions. The preservative efficacy test results at the end of the proposed shelf-life support the in-use shelf-life.

Overall, all results remain within specification, thus the 18 months data is suitable for extrapolation in accordance with ICH Q1E, Evaluation of Stability Data. Thus, the proposed shelf-life of 30 months can be accepted. No special temperature storage conditions are required. Bottles need to be stored in an upright position, until full data on inverted bottles is available.

No trends are observed in the in-use stability study. The in-use stability data shows that the product remains within specifications during months.

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 propionate Interdos 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)

The RMS concluded that Fluticasone propionate Interdos is intended for generic substitution, therefore, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Flixonase 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fluticasone propionate is a well-known active substance with established efficacy and tolerability. An extensive clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Next to the clinical overview, the MAH has submitted *in vitro* studies to support the application.

IV.2 Pharmacokinetics

Biowaiver

Fluticason propionate Interdos nasal spray, suspension is a locally administered and locally acting (LALA) nasal spray formulation, containing a glucocorticoid suspension. For this LALA formulation bridging based on *in vitro* comparison of the quality of test and reference formulation could, in principle, be acceptable provided that the formulations have the same qualitative and quantitative composition and the same pharmaceutical properties (See Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95 final, Pharmaceutical Quality of Inhalation and Nasal Products (CHMP/QWP/49313/2005).

In vitro bioequivalence with the reference product was calculated for the following parameters: delivered dose, drug substance particle size distribution, viscosity, density, pH, droplet size distribution, spray pattern, surface tension, single actuation content through

container life, and aerodynamic droplet size distribution. The presented data are considered adequate. The suitability of the method to measure the viscosity of thixotropic gels is adequately discussed. Microcrystalline cellulose and carmellose sodium are used in the formulation as thixotropic agent. Such mixtures are dispersible in water and form thixotropic gels that are suitable for stabilising aqueous suspensions. It is acceptable that only the reference product of the Netherlands was used for the determination of the quantities of microcrystalline cellulose, carmellose sodium and polysorbate 80.

In conclusion, the similarity between the test product and the innovator product in qualitative and quantitative composition and pharmaceutical properties was adequately investigated in comparative *in vitro* studies. Therefore, a biowaiver has been granted.

IV.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 propionate Interdos.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Local nasal effects including epistaxis and nasal septum perforation • Ocular events (cataract, glaucoma, raised intraocular pressure) • Potent CYP3A4 inhibitors (ritonavir)
Important potential risks	• Effects on HPA axis • Effects on growth • Psychiatric or behavioural effects (psychomotor, hyperactivity, sleep disorders, anxiety, depression and aggression) • Effects on glucose metabolism • Effects on bone density • Adverse effects from self-diagnosis (i.e. use of intranasal fluticasone propionate for medical conditions with similar symptoms to allergic rhinitis) • Misuse/maladministration (including overdose and off-label use in paediatric patients) • Use in pregnancy
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the safety concerns as approved in RMP.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Flixonase. No new clinical studies were conducted. The MAH demonstrated through comparative *in vitro* data that the qualitative and quantitative composition and the pharmaceutical properties of the test product are similar to that of the reference product. Thus, a biowaiver has been granted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test, followed by two rounds with ten 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fluticasone propionate Interdos, 50 microgram/actuation nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Flixonase 50 microgram per dosage, nasal spray suspension. Flixonase is a well-known medicinal product with an established favourable efficacy and safety profile. Therapeutic equivalence with the reference product has been adequately shown by the comparison of the dosage form and the qualitative and quantitative composition. 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 propionate Interdos with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 August 2021.

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
NL/H/5286 /1/IB/001	Type IB: A.2.b. Change in the (invented) name of the medicinal product: for Nationally Authorised Products.	PL	12 Nov. 2021	Approval	