COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mometasonfuroaat Interdos, 50 microgram/actuation nasal spray, suspension (mometasone furoate monohydrate)

NL/H/5305/001/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Mometasonfuroaat Interdos, 50 microgram/actuation nasal spray, suspension. The procedure was finalised on 26 October 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
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 Mometasonfuroaat Interdos, 50 microgram/actuation nasal spray, suspension, from Interdos Pharma BV.

Mometasonfuroaat Interdos is indicated in adults and children aged 3 years and older to treat the symptoms of seasonal allergic rhinitis or perennial rhinitis.

Mometasonfuroaat Interdos is indicated to treat nasal polyps in adults aged 18 years and older.

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 reference product Nasonex 50 microgram/actuation, nasal spray, suspension (NL RVG 21613) which has been registered in Sweden by Merck, Sharp & Dohme B.V. since 5 October 1997 (original product). In the Netherlands, Nasonex has been registered since 9 December 1997 by mutual recognition procedure SE/H/1821/001.

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

Mometasonfuroaat is a nasal spray and a white to off-white opaque suspension, with a pH of 4.4 - 5.1. The product contains as active substance 50 microgram of mometasone furoate monohydrate per actuation.

The suspension is packed in white HDPE bottles with a PE/PP/EVA spray pump.

The excipients are benzalkonium chloride, sodium citrate dihydrate (E331(ii)), citric acid monohydrate (E330), microcrystalline cellulose (E460i), carmellose sodium (E466), glycerol (E422), polysorbate 80 and water.

II.2 Drug Substance

The active substance is mometasone furoate monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, soluble in acetone and in methylene chloride and slightly soluble in ethanol 96%. Mometasone furoate monohydrate is a single isomer.

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 is in line with the Ph.Eur. with additional requirements for residual solvents and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 60 months when stored in double polyethylene bags (outer black), placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 are explained. The objective was to formulate and develop an aqueous suspension of mometasone furoate monohydrate, 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. The drug product manufacturer prepares benzalkonium chloride solution 1% (w/w) by diluting benzalkonium chloride solution 50% (w/w) Ph. Eur. with purified water. It is controlled via in-house methods for appearance and assay. The 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, identity and assay of active substance and preservative benzalkonium chloride, related substances, viscosity, density, delivered dose, number of actuations, droplet size distribution and microbiological purity. The release and shelf life limits are the same, except for the benzalkonium chloride assay limit and pH. 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 the proposed production site have been provided on three batches, and three pack sizes, of full scale batches, demonstrating compliance with the release 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 (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The packaging material used in the long term and accelerated stability studies is the same as the proposed commercial packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. However, data shows that the proposed primary packaging material is adequate to protect from light. All results remain within the proposed specifications at both storage conditions.

Overall, all results remain within specification, thus the 18 months data is suitable for extrapolation in accordance with ICH Q1E, Evaluation of Stability Data and the proposed shelf life of 30 months is acceptable. No trends are observed in the in-use stability study.

In addition, the in-use stability study results support the in-use shelf life of three 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 Mometasonfuroaat 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)

Since Mometasonfuroaat Interdos is intended for generic 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 Nasonex 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

Mometasone furoate monohydrate is a well-known active substance with established efficacy and tolerability. A 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

Mometasonfuroaat Interdos is a locally administered and locally acting (LALA) nasal spray formulation. 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). The dose response curve for mometasone nasal products is very flat, therefore, the assay sensitivity of a clinical efficacy study with mometasone is low. Hence, the RMS considers that the concept of demonstrating therapeutic equivalence based on *in vitro* equivalence can be also applicable to mometasone nasal sprays.

In vitro bioequivalence with the reference product was presented 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 droplet size distribution. The presented data are considered adequate. The suitability of the method to measure the viscosity of thixotropic gels is adequately discussed.

In conclusion, the similarity between the test product Mometasonfuroaat Interdos and the innovator product Nasonex 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 Mometasonfuroaat Interdos.

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

Important identified risks	• None
Important potential risks	(Class effects) Possible systemic and local class effects of corticosteroids hypersensitivity reaction: • Adrenal suppression • Hypersensitivity reactions including anaphylactic reaction • Hyperglycaemia • Eye disorders (cataracts, glaucoma, increased intraocular pressure/ocular hypertension, chorioretinal disorder) • Nasal septum perforation (Class effects) Possible systemic effects of corticosteroids at high doses may include: • Psychological or behavioural disorders (psychomotor hyperactivity, sleep disorder, anxiety, depression, aggression [particularly in children])
Missing information	• None

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nasonex. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 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

Mometasonfuroaat Interdos, 50 microgram/actuation nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Nasonex 50 microgram/actuation, nasal spray, suspension. Nasonex 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 Mometasonfuroaat Interdos with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 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