COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mometasonfuroaat BPM 50 micrograms/ actuation, nasal spray, suspension

(mometasone furoate monohydrate)

NL/H/5099/001/DC

Date: 26 August 2021

This module reflects the scientific discussion for the approval of Mometasonfuroaat BPM 50 micrograms/actuation, nasal spray, suspension. The procedure was finalised on 21 January 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 BPM 50 micrograms/actuation, nasal spray, suspension from Basic Pharma Manufacturing B.V.

The product is indicated for:

- use in adults and children three years of age and older to treat the symptoms of seasonal allergic or perennial rhinitis.
- the treatment of nasal polyps in adults 18 years of age and older.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product Nasonex nasal spray 50 µg/actuation. In the Netherlands, Nasonex (NL License RVG 21613) has been registered by Merck Sharp & Dohme B.V. since 9 December 1997 through a mutual recognition procedure (SE/H/1821/001).

The concerned member states (CMS) involved in this procedure were Denmark and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Mometasonfuroaat BPM 50 micrograms/actuation is a white to off-white opaque suspension, with a pH of 4.4 – 5.1. After initial priming of the spray pump, each actuation delivers approximately 100 mg of mometasone furoate suspension, containing mometasone furoate monohydrate equivalent to 50 micrograms mometasone furoate.

The drug product is packed in a White HDPE bottle 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, 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 white or almost

white powder. It is practically insoluble in water, soluble in acetone and in methylene chloride and slightly soluble in ethanol (96%). Mometasone furoate exhibits polymorphism in the form of the hydrate only. The stability of the polymorphic form has been adequately discussed and controlled.

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 in line with the Ph.Eur. with additional requirements for residual solvents and particle size distribution. The proposed drug substance specifications are acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions 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.

Results of bioequivalence studies have not been submitted. However, therapeutical equivalence has adequately been substantiated based on demonstrated similar quantitative composition, active substance and excipients, and similar results for the relevant physico-chemical characteristics of the nasal suspension spray, i.e. delivered dose, drug substance particle size distribution, polymorphic form, viscosity, density, pH, droplet size distribution, surface tension, and spray pattern. *In-vitro* bioequivalence was calculated for the parameters that are quantifiable. These are delivered dose uniformity, assay mometasone furoate monohydrate, assay benzalkonium chloride, density, pH, droplet size distribution, and spray pattern. For the other parameters, drug substance particle size distribution drug

polymorphism, and viscosity a comparison was made with the results/range observed in the reference product.

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

Manufacturing process

The manufacturing process has been described in sufficient detail. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches and three pack sizes.

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 product 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. The specifications are acceptable.
The proposed analytical methods have been adequately described and validated. 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 has 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 are suitable for extrapolation in accordance with ICH Q1E, Evaluation of Stability Data. A shelf-life of 30 months has been granted.

No trends are observed in the in-use stability study. The in-use stability was only performed with the product at start of shelf-life. The current data show that the product remains within specifications during these first three months. The results of preservative efficacy testing and 3 months in-use stability testing at the end of shelf-life should confirm the earlier obtained results.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Mometasonfuroaat BPM 50 micrograms/actuation, nasal spray, suspension 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 BPM 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

Mometason furoate 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. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The MAH claims therapeutic equivalence of Mometasonfuroaat BPM 50 micrograms/ actuation to the innovator product based on *in vitro* equivalence data. The dose response curve for mometasone nasal products is very flat, hence the assay sensitivity of a clinical efficacy study with mometasone is low. The member states consider that the concept of demonstrating therapeutic equivalence based on *in vitro* equivalence can be also applicable to mometasone nasal sprays. It is considered that Mometasonfuroaat BPM has the same pharmaceutical properties as the reference product Nasonex and equivalence has been demonstrated sufficiently. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 BPM.

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 - 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 equivalence to the reference product based on chemical-pharmaceutical attributes. Risk management is adequately addressed. This generic 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 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mometasonfuroaat BMP 50 micrograms/actuation, nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Nasonex nasal spray 50 µg/actuation. Nasonex nasal spray 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.

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 BMP with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 January 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