CBG MEB

Public Assessment Report

Scientific discussion

Mometasonfuroaat Sandoz 50 microgram/dose, nasal spray, suspension

(mometasone furoate monohydrate)

NL/H/3882/001/DC

Date: 28 May 2019

This module reflects the scientific discussion for the approval of Mometasonfuroaat Sandoz. The procedure was finalised on 2 November 2017. 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
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 Sandoz 50 microgram/dose, nasal spray, suspension from Sandoz 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 generic application claiming essential similarity with the innovator product Nasonex nasal spray 50 µg/actuation by Schering-Plough Ltd., registered since 10 April 1997 in the United Kingdom. In the Netherlands, Nasonex (NL License RVG 21613) has been registered since 9 December 1997 through a mutual recognition procedure (UK/H/0196/001). In addition, reference is made to Nasonex authorisations in the individual member states.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

The product is a white homogenous nasal spray suspension, containing mometasone furoate monohydrate equivalent to 0.05 w/w% of mometasone furoate calculated on anhydrous basis. Per actuation 50 µg active substance is administered.

The drug product is packed in a HDPE plastic bottle fitted with a PE/PP nasal applicator. The nasal spray pump with nasal actuator, protection cap and dip tube are fixed to the bottle neck.

The excipients are glycerol, microcrystalline cellulose and croscarmellose sodium (Avicel mixture), citric acid monohydrate, sodium citrate dihydrate, polysorbate 80, benzalkonium chloride and purified water.

II.2 Drug Substance

The active substance is mometasone furoate monohydrate an established active substance, not described in any pharmacopoeia at the time of assessment. The anhydrous form is currently described in the European Pharmacopoeia (Ph.Eur.) monograph 9.5. The active substance is practically insoluble in water, soluble in acetone and in methylene chloride, 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 Active Substance Master File (ASMF) procedure is used by three manufacturers 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
A synthetic scheme and a description of the manufacturing process have been provided, including chemical structures and all solvents and reagents.

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. The specification also includes additional tests on particle size and microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
Stability data on the active substance of *manufacturer-I* have been provided for three production scaled batches, stored at 25°C/60% RH (five years), 30°C/65% RH (12 months) and 40°C/75% RH (six months). All results remain within limits. Based on the stability data presented, the claimed retest period of five years is deemed acceptable.

Stability data on the active substance of *manufacturer-II* have been provided for three pilot scaled batches, in a freezer up to 60 months and at 25ºC/60% RH for 48 months. No impurities were found and variability was observed for assay. Based on the stability data presented, the claimed retest period of 48 months is acceptable. The storage condition is 'store in a freezer in the original container in order to protect from light'.

Stability data on the active substance of *manufacturer-III* have been provided for twelve batches stored up to 66 months at 30°C/65% RH and up to six months at 40°C/75% RH. The results support the retest period of 24 months.

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 manufacturing process development, the choice and safety of the container closure system and the microbiological attributes have been adequately discussed. The suspension contains an acceptable preservative agent. The single actuation content, mean delivered dose, delivered dose uniformity, spray pattern (plume geometry, ovality, area), nasal deposition by artificial nose studies, droplet size distribution and particle size distribution have been demonstrated to be similar between the test and reference product, tested over the entire container life, where necessary, using validated analytical methods and models. It is noted that both proposed nasal spray pumps of the test and reference product have different dimensions, but the suitability of both pumps has been demonstrated. Furthermore, it has been demonstrated that the proposed drug products are suitable in use with respect to in use stability, efficacy of preservative, tail-off profiles, priming and repriming instructions, cleaning, shaking and robustness.

Comparability of the test product with the reference product has been tested on *in vitro* parameters as it concerns a nasal spray with local action. The results of a comparative *in vitro* equivalence study were submitted, in accordance with European Medicines Agency guidelines (Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CHMP/EWP/239/95)).
In addition, the MAH submitted a clinical study to demonstrate therapeutic equivalence with the originator, Nasonex nasal spray in patients with seasonal allergic rhinitis to support the application.

Manufacturing process
The drug product is manufactured by preparation and subsequent filling of the suspension. The provided in-process controls are deemed acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques, but given the low concentration of active substance in the drug product, the manufacturing process is considered as non-standard. The maximum batch size is acceptable.

Control of excipients

All excipients are tested in accordance with their respective Ph.Eur. monograph. These specifications are acceptable.

Quality control of drug product
The drug product specification includes tests for appearance, pH, relative density, number of actuations per container, average dose, delivered dose uniformity, viscosity, droplet size distribution, identification, assay, related substances and microbiological requirements. The shelf-life specifications are the same as the release specification, except for the wider limits for assay of benzalkonium chloride and related substances. The shelf-life limit for assay of the active substance is the same as the release limit. A test on the particle size distribution of the active substance is included in the drug product specification. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the drug product has been provided on ten production scaled batches, stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (6 months) and three production scaled batches, stored at 25°C/60% RH (up to 18 months) and 40°C/75% RH (6 months). Additionally also in-use stability studies (two months) and photostability studies were performed. The conditions used in the stability studies are according to the ICH stability guideline. The product was stored in the proposed packaging. The stability data mainly demonstrates a decrease in preservative only. Under accelerated storage conditions a slight increase in impurities could be observed. The data support a shelf-life of 24 months. The drug product is sensitive to light outside the packaging, but light-protection of the container has been demonstrated. The storage condition “Do not freeze” is acceptable. The in use stability data support the claimed shelf-life after first use of two 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 Sandoz 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 product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of mometasone furoate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Nasonex nasal spray 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. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH referred to one clinical randomised, placebo controlled, four week parallel study comparing Mometasonfuroaat Sandoz nasal spray with Nasonex nasal spray and placebo in patients with seasonal allergic rhinitis in order to provide therapeutic equivalence.

IV.2 Pharmacokinetics

Mometasone nasal spray is a locally applied, locally acting product. For a hybrid application of a locally acting product such as mometasone nasal spray, therapeutic equivalence should be demonstrated. In general therapeutic equivalence for locally acting products is demonstrated in clinical studies. The EMA Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents for demonstration of therapeutic equivalence, however, allows to use *in vitro* models as alternatives for clinical trials.

The results of a comparative *in vitro* equivalence study were submitted, in accordance with European Medicines Agency guidelines (Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CHMP/EWP/239/95)). Based on the results of the *in vitro* comparison, equivalence is claimed. It is concluded that the test product is comparable to the reference product. The test product has the same qualitative and quantitative composition as the reference product.

For mometasone nasal spray, proof of therapeutic equivalence based on *in vitro* comparison is considered valid because the dose response curve for mometasone nasal products is very flat, hence the assay sensitivity of a clinical efficacy study with mometasone is low. In contrast to orally inhaled products, a nasal spray is released at the site of action. A pharmacokinetic study will not provide information on the local pattern of deposition in the nose, and a pharmacokinetic study can only support equivalence with respect to safety but can not support equivalence with respect to efficacy.

Daley-Yates et al. (2004)[2] have studied the pharmacokinetics of mometasone nasal spray following eight actuations per nostril every eight hours for four days. Subjects were administered 2400 µg/day during four days in order to obtain plasma levels above the detection limit. Maximal recommended dose of mometasone nasal spray is 400 µg/day. The contribution of absorption of mometasone in the nose vs. oral absorption of mometasone is not known. A pharmacokinetic equivalence study using mometasone nasal spray is considered technically very challenging due to the very low mometasone plasma concentrations and the high number of actuations needed. Moreover, a pharmacokinetic equivalence study with mometasone nasal spray could only support equivalence with respect to safety but could not support equivalence with respect to efficacy.

The MAH provided one clinical randomised, placebo controlled, four week parallel study comparing Mometasone nasal spray with Nasonex nasal spray and placebo in patients with seasonal allergic rhinitis in order to provide therapeutic equivalence. After a two week run in period, symptomatic patients were treated for fours week. The primary endpoint was de change from baseline in the reflective total nasal symptoms score (rTNSS). The TNSS is the composite variable calculated as the sum of four nasal symptoms; the rTNSS is a reflection of the mean, overall intensity of the symptoms over the last 24 hours.

The study demonstrated no significant difference between the test and the reference product for both primary endpoints i.e. means change rTNSS (difference LS mean (± SE) 0.09 (95% CI (-0.44, 0.62) in the PP populations and difference in LS mean -0.11 (95% CI (-0.65, 0.43) in the ITT population. The 95% CI is within the pre-specified equivalence limits of -1.0 to +1.0 as agreed with EMEA in the scientific advice of 2009 (EMEA/CHMP/SWAP/288058/2009). A statistically significant effect between

both active treatments and placebo (Nasonex nasal spray p=0.0019; Mometasone p=0.0053 ITT population) was demonstrated, so the study is assay sensitive. As a result, therapeutic equivalence for efficacy is considered as demonstrated. During the study, no differences in local and systemic adverse events (AEs) were observed. No major safety issue emerged. In the urine cortisol no statistically significant difference between the test and the reference product has been demonstrated.

Proof of therapeutic equivalence has been discussed in the past (Article 29(4) of Directive 2001/83/). Assessed by the CHMP (EMEA/H/A-29/1332), it was considered that the evidence of comparable particle size distribution as well as location and pattern of deposition between the proposed and the reference products indicates comparable dissolubility, which is in turn an indicator of the therapeutic equivalence of the proposed and the reference mometasone furoate-containing products.

---

[2] Daley-Yates PT, Kunka RL, Yin Y, Andrews SM, Callejas S, Ng C. 'Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays', Eur J Clin Pharmacol. 2004 Jun;60(4):265-8.

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 Sandoz.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Overdose • Systemic effects • Ocular disorders • Hypersensitivity reactions, including severe reactions • Nasal septum perforation
Important potential risks	• Psychological or behavioural disorders • Infections
Missing information	• Use in the treatment of unilateral polyps, polyps associated with cystic fibrosis, or polyps that completely obstruct the nasal cavities (not applicable for OTC) • Use during pregnancy and lactation

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 nasal spray. No new clinical studies were conducted. Therapeutic equivalence between the product at issue and Nasonex nasal spray has been demonstrated *in vitro* which is confirmed for efficacy by a clinical study. The issue has been discussed and assessed by the CHMP (EMEA/H/A-29/1332) in the past. It was considered that the evidence of comparable particle size distribution as well as location and pattern of deposition between the proposed and the reference products indicates comparable dissolubility, which is in turn an indicator of the therapeutic equivalence of the proposed and the reference mometasone furoate-containing products. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The proposed package leaflet is accepted. A new user testing is not necessary as the wording is identical to the leaflet registered in the earlier approved procedure NL/H/2038/001/DC for Mometasonfuroaat Sandoz.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mometasonfuroaat Sandoz 50 microgram/dose, 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.

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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 November 2017.

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/3882/001/1//IB/001	Update product information regarding psusa april 2017		24-5-2018	Approval	
NL/H/3882/001/1//IB/002	Implement the outcome of a PRAC signal recommendation. PRAC recommendation on signals adopted at the 24-27 October 2016 PRAC meeting EMA/PRAC/700146/2016 from 10 November 2016. Update in line with new annex of excipients guideline the text with benzalkonium chloride warning.		6-9-2018	Approval	