

Public Assessment Report

Scientific discussion

**Flonez 50 microgram/actuation,
nasal spray, suspension**

(mometasone furoate)

NL/H/3085/001/DC

Date: 24 September 2014

This module reflects the scientific discussion for the approval of Flonez 50 microgram/actuation, nasal spray, suspension. The procedure was finalised on 13 April 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Flonez 50 microgram/actuation, nasal spray, suspension from Substipharm développement.

The product is indicated for:

- use in adults and children 12 years of age and older to treat the symptoms of seasonal allergic or perennial allergic rhinitis.
- use in children 6 to 11 years of age to treat the symptoms of seasonal allergic or perennial allergic 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 essential similarity with the innovator product Nasonex nasal spray 50 microgram/actuation. This medicinal product was first registered on 10 April 1997 in the United Kingdom by Schering-Plough Ltd. In the Netherlands, Nasonex (NL License RVG 21613) has been registered since 9 December 1997 through MRP UK/H/0196/001 by Merck Sharp & Dohme B.V.

The marketing authorisation is granted based on article 10(3) (hybrid application) of Directive 2001/83/EC.

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

II. QUALITY ASPECTS

II.1 Introduction

Flonez is white to off-white viscous suspension. Each delivered dose (100 mg suspension) contains mometasone furoate monohydrate equivalent to 50 micrograms of mometasone furoate anhydrous.

The nasal spray is packed in a white, high density polyethylene bottle, that contains 10 g (60 actuations), 16 g (120 actuations) or 18 g (140 actuations) of product formulation, supplied with a PP/PE metering pump and on which a PP nasal applicator with cap is fitted.

The excipients are: benzalkonium chloride, glycerol, polysorbate 80, microcrystalline cellulose and carmellose sodium, citric acid monohydrate, sodium citrate and purified water.

II.2 Drug Substance

The active substance is mometasone furoate monohydrate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.) or any other pharmacopoeia. The anhydrous form is described in both Ph.Eur. and US Pharmacopoeia. The active substance is a white to almost white powder which is practically insoluble in water, soluble in acetone and in dichloromethane, and slightly soluble in ethanol (96%). Mometasone furoate has eight chiral centers, but does not exhibit isomerism and exhibits polymorphism in the form of the hydrate only.

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

A synthetic scheme and a brief description of the manufacturing process of the active substance have been provided, including chemical structures and solvents and reagents. The manufacturing process is described in detail in the restricted part of the ASMF.

Quality control of drug substance

The drug substance specification is based on the Ph.Eur. monograph of mometasone furoate anhydrous and general Ph.Eur. requirements and includes limits for particle size and microbial contamination. The specification is acceptable in view of the route of synthesis and the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance

Stability data on the active substance has been provided for three production-scale batches, stored at 25°C/60%RH (36 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). The stability data presented demonstrate a slight increase in impurities and water content only. All results remain within limits. Based on the stability data presented, the claimed retest period of 36 months can be granted.

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 choice of the active substance is acceptable as the monohydrate form is used, which is the same as the reference.

To demonstrate therapeutic equivalence of the proposed drug product with the reference product, results of *in-vitro* tests have been provided. 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 (EMA/CHMP/QWP/49313/2005 Corr).

The following parameters are the parameters that are relevant to evaluate the therapeutical equivalence by *in-vitro* studies:

- The total dose delivered to the nose (single actuation content) by parameters such as delivered mass, mean delivered dose and delivered dose uniformity.
- The deposition pattern (location and area) in the nose by parameters such as droplet size distribution, small droplets, spray pattern, and plume geometry.
- The similarity of dissolution of the active substance at the site of action by parameters such as particle size distribution, polymorphic form and physicochemical properties (pH, viscosity, density, surface tension, and osmolality).

The quality attributes tested by the MAH are in line with these required parameters.

Based on the analysis of the results of these *in-vitro* tests, therapeutic equivalence is sufficiently demonstrated on chemical-pharmaceutical grounds. The manufacturing process development is described in sufficient detail. The choice and safety of the container closure system have been adequately described. The data on the microbiological attributes demonstrate the suitability of the preservative.

Manufacturing process

The drug product is manufactured by preparation and subsequent filling of the suspension. The provided in-process controls are considered to be justified. The product is manufactured using conventional manufacturing techniques, but given the low concentration of active substance in the drug product and the fact that it concerns a suspension, the manufacturing process is considered as non-standard. The manufacturing process has been adequately validated.

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, microscopic examination, particle size distribution in the spray, pH, viscosity, minimum fill, water loss rate (end of shelf-life), identification (active substance and benzalkonium chloride), assay of mometasone furoate monohydrate per bottle and spray (mean delivered dose, delivered dose uniformity, tail-off profile (end of shelf-life),

degradation products, assay of benzalkonium chloride, microbial limits, droplets < 10µm (skip testing) and droplet size distribution (end of shelf-life). The shelf-life specifications are the same as the release specification, except for the wider limits for assay of benzalkonium chloride and the test on water loss. Batch analytical data from the proposed production site have been provided on the three production-scale validation batches, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the drug product has been provided on two production scaled batches of 600kg, stored at 25°C/60% RH (18-24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 20 mL white HDPE bottles (60 and 120 actuations (24 months), 140 actuations (18 months)). Under all conditions, the parameters remain well within limits. A storage period of 24 months can be accepted based on the provided data. A photostability study has been performed in line with the requirements of the Note for Guidance on photostability testing, ICH Q1B. The results indicate that the product is photosensitive. The suspension is sufficiently protected from light in the bottle. The storage condition 'do not store above 30°C. Do not freeze' can be accepted.

In-use testing was performed by simulating use for 15 days (4 sprays, lowest dosing advice), keeping the bottle for 45 days and then re-using of the spray. The time period covered is 60 days (2 months) which is the recommended period of use as per SmPC. The in-use stability data support the claimed shelf-life after first use of 2 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 Flonez has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to repeat the test for efficacy of the preservative at the end of the shelf-life.
- The MAH committed to submit results of additional *in-vitro* testing with more samples per batch and statistical analysis with inclusion of more results per batch, in order to confirm equivalence with the reference product Nasonex.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Flonez 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 nasal spray 50 microgram/actuation, 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 is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active. It is available commercially in oral inhaler, nasal inhaler, and topical cream and ointment dosage forms. Mometasone has a very low systemic bioavailability.

As the active substance is well known and widely used, the MAH has not provided additional studies and further studies are not considered necessary. Overview based on literature review is appropriate. The provided clinical overview is of acceptable quality.

IV.2 Pharmacokinetics

Mometasone nasal spray is a locally applied, locally acting product. For a generic application of a locally acting product, 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 the use *in vitro* models as an alternative for clinical trials.

For mometasone nasal spray, the RMS considers the proof of therapeutic equivalence based on *in vitro* comparison valid because establishing therapeutic equivalence in clinical studies is difficult due to the insensitive endpoints and/or difficulties with exposure due to the seasonal influence. A nasal spray is released at the site of action. A pharmacokinetic study would not provide information on the local pattern of deposition in the nose, and therefore could only support equivalence with respect to safety but not regarding efficacy. Therefore, the RMS considered that the concept of demonstrating therapeutic equivalence based on *in vitro* equivalence can be also applicable to mometasone nasal sprays.

Based on the analysis of the results of the *in-vitro* tests as described in the quality section, therapeutic equivalence is sufficiently demonstrated. Therefore bioequivalence studies are not required for this application.

IV.3 Clinical efficacy and safety

Mometasone furoate nasal spray (MFNS) contains mometasone furoate in an aqueous suspension for nasal inhalation via a metered-manual pump spray. MFNS is indicated for use in adults and children 12 years of age and older to treat the symptoms of seasonal allergic or perennial rhinitis. It is also indicated for use in children 6 to 11 years of age to treat the symptoms of seasonal allergic or perennial allergic rhinitis. In patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis, prophylactic treatment with MFNS may be initiated up to four weeks prior to the anticipated start of the pollen season. This indication is included in the SmPC of some other mometasone containing nasal sprays. However, a prophylactic indication is not supported by all Member States. The MAH therefore decided to drop this indication.

The dose recommendations regarding the use of mometasone in the treatment of nasal polyps are also different in a number of Member States. Review of literature provided evidence that the higher dose performed somewhat better than the lower dose, but no clear dose response has been observed. Therefore it is recommended to start with a low dose, and provide a higher dose if symptoms do not improve. The following is included in the SmPC:

The usual recommended starting dose for polyposis is two actuations (50 micrograms/actuation) in each nostril once daily (total daily dose of 200 micrograms). If after 5 to 6 weeks symptoms are inadequately controlled, the dose may be increased to a daily dose of two sprays in each nostril twice daily (total daily dose of 400 micrograms).

IV.4 Risk Management Plan

The MAH has justified the absence of a Risk Management Plan (RMP). At the time this application was made, submission of an RMP was not required. The Member States considered this acceptable as:

- There is more than 10 years post-authorisation experience with the active substance.
- The safety profile of mometasone furoate monohydrate can be considered as well established.
- No safety concerns requiring additional risk minimisation activities have been identified with the reference medicinal product.
- The MAH has a pharmacovigilance system that fulfils the requirements.

Routine pharmacovigilance activities are sufficient to identify actual or potential risks.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nasonex nasal spray 50 microgram/actuation. No new clinical studies were conducted. The MAH demonstrated therapeutic equivalence based on *in-vitro* data. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 package leaflet 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

Flonez 50 microgram/actuation, nasal spray, suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Nasonex nasal spray 50 microgram/actuation. Nasonex is a well-known medicinal product with an established favourable efficacy and safety profile.

Mometasone nasal spray is a locally applied, locally acting product. For a hybrid generic application of a locally acting product such as mometasone nasal spray, a biowaiver can be granted.

In the Board meetings of 28 June 2012 and 3 April 2014, the comparison of the *in vitro* data was discussed. The Board concluded that based on these data, therapeutic equivalence has been sufficiently demonstrated.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The therapeutic indications were agreed on the posology was restricted as required.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Flonez 50 microgram/actuation with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 April 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached