CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Mometasonfuroaat Sandoz 50 microgram/dose, nasal spray, suspension Sandoz B.V., the Netherlands

mometasone furoate monohydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2039/001/DC
Registration number in the Netherlands: RVG 107917

21 February 2013

Pharmacotherapeutic group:	decongestants and other nasal preparations for topical use, corticosteroids
ATC code:	R01AD09
Route of administration:	nasal
Therapeutic indication:	treatment of the symptoms of seasonal allergic or perennial allergic rhinitis in adults and children 6 years of age and older; prophylactic treatment initiated up to four weeks prior to the anticipated start of the pollen season in patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis; symptomatic treatment of nasal polyps in adults 18 years of age and older.
Prescription status:	prescription only
Date of authorisation in NL:	23 October 2012
Concerned Member States:	Decentralised procedure with AT, DE and IE.
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

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 date of authorisation was 23 October 2012 in the Netherlands.

The product is indicated for:

- use in adults and children 6 years of age and older 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 mometasone furoate nasal spray may be initiated up to four weeks prior to the anticipated start of the pollen season.
- the symptomatic 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.

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties.
It is likely that much of the mechanism for the anti-allergic and anti-inflammatory effects of mometasone furoate lies in its ability to inhibit the release of mediators of allergic reactions.

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 MRP UK/H/0196/001. In addition, reference is made to Nasonex authorisations in the individual member states (reference product).

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

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for hybrid products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired.
A comparative *in vitro* equivalence study was performed, 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)), which were followed as a premise for the design of the study, with inclusion of additional *in vitro* descriptive parameters which were used for support, and application of statistical evaluation. Based on the results of the *in-vitro* comparison, equivalence is claimed.

In addition, the MAH submitted a clinical study to demonstrate therapeutic equivalence with the originator, Nasonex® nasal spray in patients with seasonal allergic rhinitis (Study 2008-02) to support the application.

Scientific Advice was given prior to the procedure. The MAH was advised that for locally applied, locally acting products, containing known constituents (applicable to the proposed product and the intranasal route for administration), an *in vitro* approach could be used for demonstration of equivalence, following the principles and under the limitations listed and described in the following Guidelines: CPMP/EWP/239/95 final, CPMP/EWP/4151/00 and CPMP/EWP/4151/00 Rev. 1.

No paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is mometasone furoate monohydrate, an established active substance, not described in any pharmacopoeia. The anhydrous form is described in the European (Ph.Eur.*) and US Pharmacopoeia. The active substance is practically insoluble in water, soluble in acetone and in methylene chloride, and slightly soluble in ethanol (96%). Polymorphism has been adequately discussed and controlled. It is stated to be absent as only the monohydrate form is produced consistently. Isomerism is not present.

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 have been provided, including chemical structures and all solvents and reagents.

Quality control of drug substance
The drug substance specification is based on the Ph.Eur. monograph of mometasone furoate anhydrous and the specifications of the manufacturers with an additional test on particle size and microbial contamination. The specifications are 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 from one manufacturer have been provided for three production-scale batches, stored at 25°C/60%RH (2 years), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). All results remain within limits. Based on the stability data presented, the claimed retest period of 3 years is deemed acceptable.
For the other manufacturer, stability data on the active substance have been provided for three pilot-scale batches, stored up to 12 months. No impurities were found and variability was observed for assay. The results demonstrate compliance with the specification .Based on the stability data presented, the claimed retest period of 12 months is deemed acceptable. The storage condition is 'store in a freezer in the original container in order to protect from light'.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The drug 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 (100 mg suspension), 50 µg active substance is administered.

The nasal spray suspension is packed in a white high density polyethylene (HDPE) plastic bottle fitted with a PE/PP nasal spray pump.

Nasal spray pump with nasal actuator, protection cap and dip tube is fixed to the bottle neck. The filling amounts are NLT 17.0 g suspension (120 doses) and NLT 18.0 g suspension (140 doses). Two different spray pump devices are used, The suitability of both types of pumps has been demonstrated.

The excipients are: microcrystalline cellulose (E460), carmellose sodium (E468), glycerol (E442), citric acid monohydrate (E330), sodium citrate dihydrate (E331), polysorbate 80 (E433), benzalkonium chloride and purified water.
The type and amount of excipients are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The particle size and polymorphic form of the active substance have been discussed and are controlled in the MAH's specification of the active substance.
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. Based on the *in vitro* study, it is concluded that the test product can be considered to be comparable to the reference product. The test product has the same qualitative and quantitative composition as the reference product.
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.
The manufacturing process development, the choice and safety of the container closure system and the microbiological attributes have been adequately discussed. The suspension contains the preservative agent benzalkonium chloride which is the same agent and amount as present in the innovator product.

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. For the Avicel mixture (microcrystalline cellulose and croscarmellose sodium), particle size is also controlled..

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 (TLC and HPLC for API and HPLC for benzalkonium chloride), assay (API and benzalkonium chloride), 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 have been provided on seven production-scale batches, stored at 25°C/60% RH (up to 12 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 plastic bottles. The data support a shelf-life of 24 months. A photostability study has been performed. Compliance with the NfG on photostability testing, ICH Q1B, has been demonstrated. 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" can be accepted. The in-use stability data support the claimed shelf-life after first use of 2 months and the transportation stability data show relative stability of the product when exposed to 50°C or 2-8°C.

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.2 Non-clinical aspects

This product is a generic formulation of Nasonex nasal spray 50 µg/actuation, which is available on the European market. 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.
The available preclinical information suggests that mometasone furoate has a safety pharmacology and toxicity profile that will not preclude its clinical use according to the restrictions addressed in the SmPC. The characteristics of mometasone furoate are adequately reflected in the SmPC and the indications and precautions for the use of this drug are justified by its pharmacological properties. The benefit-risk profile of mometasone furoate is considered to remain favourable from a non-clinical point of view, provided that this medicinal product is used according to the SmPC. Overall it can be stated that the investigations performed on mometasone furoate cover all aspects of safety assessment required, and can therefore demonstrate an acceptable level of safety for mometasone furoate under the conditions stipulated in the SmPC.

Environmental risk assessment
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.

II.3 Clinical aspects

Mometasone nasal spray is a locally applied, locally acting product. For a generic application of a locally acting product such as mometasone nasal spray, comparability should be demonstrated. In general comparability 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 MAH submitted an application for Mometasonfuroaat Sandoz 50 mcg/dose, in the treatment of the symptoms of seasonal allergic or perennial rhinitis and of nasal polyps, as a nasal spray with two different spray pump devices (Device 1 and Device 2). The MAH provided *in vitro* data for both devices, however only Device 1 was investigated *in vivo*.

For mometasone nasal spray, the RMS has considered proof of therapeutic equivalence based on *in vitro* comparison 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)[1] have studied the pharmacokinetics of mometasone nasal spray following 8 actuations per nostril every 8 hours for 4 days. Subjects were administered 2400 µg/day during 4 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. Therefore, the RMS considers a pharmacokinetic equivalence study using mometasone nasal spray 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 RMS considers and agrees with the EMA advice, that the concept of demonstrating therapeutic equivalence based on *in vitro* equivalence can be also applicable to mometasone nasal sprays.
For Device 1 a clinical randomized, placebo controlled, four week parallel study comparing Mometasonenasal spray with Nasonex® nasal spray and placebo in patients with seasonal allergic rhinitis (study 2008-02) was provided in order to prove therapeutic equivalence. After a two week run in period, symptomatic patients were treated for four weeks. The primary endpoint was the change from baseline in the reflective total nasal symptoms score (rTNSS). The TNSS is the composite variable calculated as the sum of 4 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. mean 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 EMA 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 demonstrated.
During the study, no differences in local and systemic adverse events 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.

Product information

SmPC
The content of the SmPC approved during the decentralised procedure is in accordance with those accepted for other mometasone furoate products.

Readability test
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 of testing including a pilot test. The tested population was on average overqualified.

[1] 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.

The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. No weaknesses have been identified. Overall, each and every question meets the criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Mometasonfuroaat Sandoz 50 microgram/dose, nasal spray, suspension has a proven chemical-pharmaceutical quality and is a generic form of Nasonex nasal spray 50 µg/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 generic application of a locally acting product such as mometasone nasal spray, it is exempted for a biostudy. Comparability has been demonstrated based on *in vitro* data. Furthermore, a clinical study was performed to establish therapeutic equivalence with the innovator. The study demonstrated no significant difference between the test and the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other mometasone containing products.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Mometasonfuroaat Sandoz 50 microgram/dose, nasal spray, suspension with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 6 February 2012. Mometasonfuroaat Sandoz 50 microgram/dose, nasal spray, suspension was authorised in the Netherlands on 23 October 2012.

The date for the first renewal will be: 16 December 2016.

The following post-approval commitments have been made during the procedure:

<u>Quality - active substance</u>

- As the specification of the drug substance of the ASMF-holder has changed, the MAH should include additional tests and limits in the drug substance specification.
- The microbiological tests will be validated and the validation data and batch analysis results submitted as soon as available.

<u>Quality - medicinal product</u>

- The MAH commits to continue the long term stability testing up to the approved shelf-life. The authorities will be informed immediately in case out of specification results are observed.
- The MAH commits to start an in-use study at the end of the shelf-life in order to confirm the suitability of the approved in-use period. The authorities will be informed immediately in case out of specification results are observed.
- The MAH commits to evaluate the preservative efficacy at the end of shelf-life and after simulated in-use stability. The authorities will be informed immediately in case out of specification results are observed.
- The tests for droplet size distribution and mean delivered dose will be performed at the 24-month time-point and results will be submitted.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMDh	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
DCP	Decentralised procedure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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