Public Assessment Report

Scientific discussion

Aphiahsone

50 micrograms/actuation nasal spray, suspension

(Mometasone furoate)

DK/H/2337/001/DC

5 February 2015

This module reflects the scientific discussion for the approval of Aphiahsone. The procedure was finalised on 19 December 2013. 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 Aphiahsone 50 micrograms/actuation nasal spray, suspension, from Glenmark Pharmaceuticals Europe.

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

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active.
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.
Mometasone furoate significantly inhibits the release of leukotrienes from leucocytes of allergic patients.
In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6 and TNFα; it is also a potent inhibitor of leukotriene production. In addition, it is an extremely potent inhibitor of the production of the Th2 cytokines, IL-4 and IL-5, from human CD4+ T-cells.

This decentralised procedure concerns a hybrid application claiming essential similarity with the reference product Nasonex 50 micrograms/actuation nasal spray, suspension by Merck Sharp & Dohme B.V., registered in Denmark since 1997.

The marketing authorisation is granted based on article 10.3 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is a nasal spray suspension, containing 51.73 micrograms/actuation of mometasone furoate monohydrate (corresponding to 50 micrograms/actuation of mometasone furoate anhydrous).

The product is a white to off-white viscous suspension with pH between 4.3 and 4.9. The nasal spray is contained in a white, high density polyethylene bottle, that contains 60 actuations (10 g), 120 actuations (16 g) or 140 actuations (18 g) of product formulation, supplied with a metering pump and on which a nasal applicator with cap is fitted. However, not all pack sizes may be marketed.

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

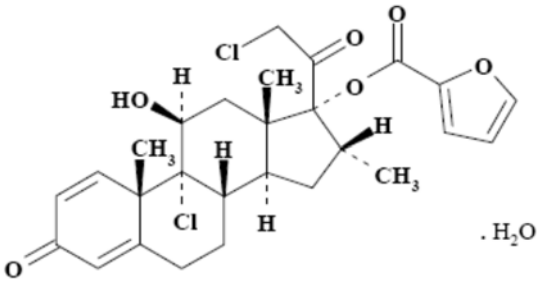
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, mometasone furoate monohydrate, is not described in the European Pharmacopoeia, but the anhydrous substance is described in the European Pharmacopoeia (monograph 1449).

INN: Mometasone Furoate Monohydrate
Chemical name(s): 9,21 -dichloro-11 p-hydroxy-16a-methyl-3,20- dioxopregna-l,4-dien-17-yl furan-2-carboxylate monohydrate
Molecular formula: $C_{27}H_{32}Cl_2O_7$
Molecular mass: 539.4

Molecular structure:



Mometasone furoate monohydrate is a white to almost white powder practically insoluble in water, soluble in acetone and in methylene chloride and slightly soluble in ethanol 96%.

The active substance is obtained from an external supplier and the chemical-pharmaceutical documentation is presented as an Active Substance Master File.

Adequate information on the synthesis and in-process control is provided.
The control tests and specifications for drug substance are adequately drawn up.

Results of stability studies performed according to the ICH guidance have been presented. No significant changes in any parameters were observed. The proposed retest period is justified and no special requirements to the storage conditions are required.

II.3 Medicinal Product

The development of the product is based on investigations of the reference product Nasonex.

No clinical data is provided to support this application and a thorough in-vitro comparison study and a cell permeation test have been presented to show essential similarity to the reference product. The comparison show that the characteristics of the suspension are similar to the reference product and the suspension is delivered through a device (pump) with similar characteristics, therefore the finished product can be considered similar to the reference product regarding efficacy and safety.

A justified finished product specification is provided and the analytical procedures have been adequately described and validated according to EU/ICH requirements.

Batch analysis has been performed on 2 batches (full scale). The batch analysis results show that the finished product meets the specification.

The conditions used in the stability studies are according to the ICH stability guideline. A shelf-life of 2 years, with the storage precaution “do not store above 25°C”, is justified based on long term stability data.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of mometasone furoate are well known. As mometasone furoate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is therefore appropriate.

The non-clinical report refers 22 publications up to year 2011.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is acceptable given the extensive clinical/market experience with mometasone nasal spray.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Aphiahsone 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Safety and efficacy of mometasone furoate are well known. As mometasone furoate is a widely used, well-known active substance, the MAH has not provided additional clinical studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview report refers 26 publications up to year 2011. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

The applicant has not performed any comparative clinical studies of Aphiahsone and the proprietary product Nasonex, but instead argues for a waiver of clinical studies with reference to existing guidelines and their specified criteria to claim bioequivalence for a generic drug in comparison with a reference listed drug.

Efficacy and safety of Aphiahsone is supported with bibliographic references on the brand leader (Nasonex) together with a biowaiver based on a detailed *in vitro* biopharmaceutical qualitative and quantitative comparison of Nasonex and Aphiahsone.

IV.3 Risk Management Plan & Pharmacovigilance system

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

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 Aphiahsone.

The summary of safety concerns is as follows, with routine pharmacovigilance and risk minimisation activities only:

Summary of safety concerns	
Important identified risks	Overdose
Important potential risks	Psychological or behavioural disorders Ocular disorders Hypersensitivity reactions Nasal septum perforation Pregnancy/lactation Infections
Missing information	Special target population (cystic fibrosis patients)

No additional pharmacovigilance or risk minimisation measures apply.

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 language used for the purpose of user testing the PIL was English.
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.

The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

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

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Aphiahsone with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 19 December 2013. Aphiahsone was authorised in Denmark on 29 January 2014.

A European harmonised birth date has been allocated and subsequently the first data lock point for mometasone is 22 May 2017, after which the PSUR submission cycle is 5 years.

The date for the first renewal will be: 19 December 2018.

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

- The MAH commits to follow the outcome of any Article 30 referral for the reference product Nasonex.

Public Assessment Report

Update

Aphiahsone

50 micrograms/actuation nasal spray, suspension

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This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Repeat use with PL and SE	DK/H/2337/001/E/001	N	19 September 2014	18 December 2014	Approval	Y, Annex 1

ANNEX 1 – Repeat use procedure (DK/H/2337/001/E/001)

The repeat use procedure started on 19 September 2014. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states PL and SE on the basis of the data submitted, considered that essential similarity had been demonstrated for Aphiahsone 50 micrograms/actuation nasal spray, suspension with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finalised on 18 December 2014.

The MAH provided an updated dossier. No variations were filed prior to the repeat use procedure.

The date for the first renewal will be: 19 December 2018.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

Commitments made during the initial procedure DK/H/2337/001/DC:

- The MAH commits to follow the outcome of any Article 30 referral for the reference product Nasonex.