Public Assessment Report

Decentralised Procedure

Mometasone furoate 50 micrograms/actuation nasal spray, suspension

(Mometasone furoate monohydrate)

UK/H/5471/01/DC

UK licence no: PL 36390/0157

Cipla (EU) Limited
LAY SUMMARY
Mometasone Furoate 50 micrograms/actuation nasal spray, suspension
(Mometasone furoate monohydrate)

This is a summary of the public assessment report (PAR) for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension (PL 36390/0157). It explains how Mometasone Furoate 50 micrograms/actuation nasal spray, suspension was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Mometasone Furoate 50 micrograms/actuation nasal spray, suspension

For practical information about using Mometasone Furoate 50 micrograms/actuation nasal spray, suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Mometasone Furoate 50 micrograms/actuation nasal spray, suspension and what is it used for?
Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is a generic medicine. This means that Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is similar to a ‘reference medicine’ already authorised in the UK called Nasonex 50 mcg/actuation nasal spray, suspension (Schering-Plough Limited; PL 00025/0587).

This medicine is used to prevent and treat seasonal allergic rhinitis (e.g. hay fever) and perennial rhinitis (e.g. year round rhinitis often due to house dust mites or animal allergies) in adults and children 6 years of age and older.

Hayfever, which occurs at certain times of the year, is an allergic reaction caused by breathing in pollen from trees, grasses, weeds and also moulds and fungal spores. Perennial rhinitis occurs throughout the year and symptoms can be caused by a sensitivity to a variety of things including house dust mite, animal hair (or dander), feathers and certain foods. These allergies cause a runny nose and sneezing and make the lining of the nose swell, causing a stuffy blocked-up feeling.

Mometasone furoate 50 micrograms/actuation nasal spray, suspension is also used to treat nasal polyps in adults 18 years of age and over. Nasal polyps are small growths on the lining of the nose and usually affect both nostrils. The main symptom is a blocked feeling in the nose which may affect breathing through the nose. Watering from the nose, a feeling of something running down the back of the throat and loss of taste and smell may also occur. Mometasone furoate reduces the inflammation in the nose, causing the polyps to gradually shrink.

How is Mometasone Furoate 50 micrograms/actuation nasal spray, suspension used?
Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is sprayed in to the nostrils.

For Seasonal or Perennial Allergic Rhinitis Adults, the elderly and children 12 years of age and older:
The usual dose is TWO sprays into each nostril ONCE a day, taken in the morning.

Use in children 6 – 11 years of age:
The usual dose is ONE spray into each nostril ONCE a day, taken in the morning.

For nasal polyps Adults aged 18 and over:
The usual starting dose is TWO sprays into each nostril ONCE daily. Please refer to the Patient Information Leaflet for more information.

How does Mometasone Furoate 50 micrograms/actuation nasal spray, suspension work?
Mometasone furoate is a corticosteroid which has an anti-inflammatory action, reducing swelling and irritation which causes sneezing, itching and a blocked or runny nose.

How has Mometasone Furoate 50 micrograms/actuation nasal spray, suspension been studied?
Because Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Nasonex 50 mcg/actuation nasal spray, suspension (Schering-Plough Limited; PL 00025/0587). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Mometasone Furoate 50 micrograms/actuation nasal spray, suspension?
As Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is a generic medicine that is bioequivalent to Nasonex 50 mcg/actuation nasal spray, suspension (Schering-Plough Limited), its benefits and risks are taken as being the same as those of Nasonex 50 mcg/actuation nasal spray, suspension (Schering-Plough Limited).

Why is Mometasone Furoate 50 micrograms/actuation nasal spray, suspension approved?
It was concluded that, in accordance with EU requirements, Mometasone Furoate 50 micrograms/actuation nasal spray, suspension has been shown to have comparable quality and to be bioequivalent to Nasonex 50 mcg/actuation nasal spray, suspension. Therefore, the view was that, as for Nasonex 50 mcg/actuation nasal spray, suspension the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Mometasone Furoate 50 micrograms/actuation nasal spray, suspension?
A risk management plan has been developed to ensure that Mometasone Furoate 50 micrograms/actuation nasal spray, suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Mometasone Furoate 50 micrograms/actuation nasal spray, suspension
Austria, Belgium, Croatia, Denmark, Finland, Germany, Italy, Norway, Spain and the UK agreed to grant a Marketing Authorisation for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension on 4th April 2014. A Marketing Authorisation was granted in the UK on 6th May 2014.

The full PAR for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension follows this summary. For more information about treatment with Mometasone Furoate 50 micrograms/actuation nasal spray, suspension, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2014.
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# Module 1

## Information about initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Mometasone Furoate 50 micrograms/actuation nasal spray, suspension</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10(3), Hybrid application</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Mometasone furoate monohydrate</td>
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<tr>
<td><strong>Form</strong></td>
<td>Nasal spray, suspension</td>
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<tr>
<td><strong>Strength</strong></td>
<td>50 micrograms/actuation</td>
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| **MA Holder** | Cipla (EU) Limited  
Hillbrow House,  
Hillbrow Road,  
Esher, Surrey, KT10 9NW,  
United Kingdom |
| **RMS** | UK |
| **CMS** | Austria, Belgium, Croatia, Denmark, Finland, Germany, Italy, Norway and Spain |
| **Procedure Numbers** | UK/H/5471/01/DC |
| **Timetable** | Day 208 – 4th April 2014 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Mometasone furoate nasal spray, suspension
50 micrograms / actuation 140 Metered sprays

Nasal use
Shake gently before use.
Store in the original container.

Cipla Cipla (EU) Ltd. POM PL 36390/0157

Read the package leaflet before use.
Keep out of the sight and reach of children.

Code No.: XXX/DRUGS/XXX
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension (PL 36390/0157, UK/H/5471/01/DC) for the following indications could be approved.

- Mometasone furoate nasal spray, suspension 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.

- Mometasone furoate nasal spray, suspension 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 Mometasone furoate nasal spray, suspension may be initiated up to four weeks prior to the anticipated start of the pollen season.

- Mometasone furoate nasal spray, suspension is indicated for the treatment of symptoms of nasal polyposis in adults 18 years of age and older.

This application was submitted under Article 10(3) of Directive 2001/83/EC (as amended), hybrid application. The applicant has cross referred to Nasonex 50 micrograms/actuation nasal spray, suspension, originally granted to Schering-Plough Ltd (PL 00201/0216) on 10th April 1997. The reference licence has undergone a Change of Ownership procedure to the current Marketing Authorisation Holder, Merck Sharp & Dohme Limited (PL 00025/0587), on 14th January 2011.

With the UK as the RMS in this Decentralised Procedure (UK/H/5471/01/DC), Cipla (EU) Limited applied for a Marketing Authorisation for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension in Austria, Belgium, Croatia, Denmark, Finland, Germany, Italy, Norway and Spain.

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 inhibits the release of leukotrienes from leucocytes of allergic patients.

No new clinical or non-clinical studies were conducted, which is acceptable given that this is a hybrid application, which refer to an originator product that has been licensed for over 10 years.
The applicant has provided two bioequivalence studies to support the claim of generic equivalence of the test product (Mometasone Furoate 50 micrograms/actuation nasal spray, suspension) with the reference product (Nasonex 50 mcg Nasal Spray, suspension).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within and outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 208 – 4th April 2014). After a subsequent national phase, the UK granted a Marketing Authorisation for this product on 6th May 2014 (PL 36390/0157).
# II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Mometasone Furoate 50 micrograms/actuation nasal spray, suspension |
| Name(s) of the active substance(s) (INN) | Mometasone furoate monohydrate |
| Pharmacotherapeutic classification (ATC code) | Decongestants and Other Nasal Preparations for Topical Use-Corticosteroids, ATC code: R01A D09 |
| Pharmaceutical form and strength(s) | 50 micrograms/actuation nasal spray, suspension |
| Reference numbers for the Decentralised Procedure | UK/H/5471/01/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | Austria, Belgium, Croatia, Denmark, Finland, Germany, Italy, Norway and Spain |
| Marketing Authorisation Number(s) | PL 36390/0157 |
| Name and address of the authorisation holder | Cipla (EU) Limited Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Mometasone furoate monohydrate

Chemical Name: 9,21-dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl-furan-2-carboxylate monohydrate

Structure:

![Structure of Mometasone Furoate Monohydrate]

Molecular Formula: C_{27}H_{30}Cl_{2}O_{6} . H_{2}O

Molecular Weight: 539.4 g/mol

Appearance: white to almost white powder.

Solubility: It is soluble in acetone and methylene chloride.

Mometasone furoate monohydrate is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients glycerol, microcrystalline cellulose, carmellose sodium, citric acid monohydrate, polysorbate 80, benzalkonium chloride, sodium citrate dihydrate and water for injection.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

Pharmaceutical Development
The objective of the development programme was to produce a robust formulation of Mometasone Furoate 50 micrograms nasal spray, suspension that will be qualitatively and quantitatively equivalent in composition and also therapeutically equivalent to the reference medicinal product, Nasonex® 50 mcg/actuation nasal spray, suspension (Schering Plough Ltd).

Comparative impurity profiles and qualitative composition of the reference and test products have been provided.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated using the minimum commercial scale batch sizes and has shown satisfactory results. The applicant has committed to perform further process validation on three full scale commercial-scale batches.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in a white opaque high density polyethylene bottle fitted with a -metered dose, manual polypropylene spray actuator, with a pack size of 1 bottle containing 18.0 g suspension, equivalent to 140 metered sprays.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with relevant EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, shelf-lives of 2 years before opening and 2 months after first use with storage conditions “Do not store above 25°C”, “Do not freeze” and “Store in the original container” are set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and label are acceptable from a pharmaceutical perspective.
User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Mometasone Furoate 50 micrograms/actuation nasal spray, suspension (Cipla (EU) Limited). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

**Marketing Authorisation Application (MAA) Form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**
The pharmacodynamic, pharmacokinetic and toxicological properties of mometasone furoate monohydrate are well-established and the non-clinical dossier is based on a review of published literature.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for not submitting an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.

**III.3 CLINICAL ASPECTS**
The applicant has conducted two bioequivalence studies comparing Mometasone furoate 50 mcg/actuation nasal spray, suspension with Nasonex 50 mcg/actuation nasal spray, suspension with charcoal blockade (Study 11-04-17) and without charcoal blockade (Study 11-04-16).

**Study 11-04-16**
A randomised, single-dose, open label, two way crossover, bioequivalence study comparing the systemic exposure of the test product, Mometasone furoate 50 mcg/actuation nasal spray, suspension, (Cipla Limited, India) and the reference product Nasonex (delivering mometasone furoate 50 mcg/actuation) nasal spray, suspension (Schering-Plough Limited, UK) administered as a total dose of 400 micrograms in healthy adult male human subjects under fasting conditions.

**Study 11-04-17**
A randomised, single-dose, open label, two way crossover, bioequivalence study comparing the systemic exposure of the test product, Mometasone furoate 50 mcg/actuation nasal spray, suspension, (Cipla Limited, India) and the reference product Nasonex (delivering mometasone furoate 50 mcg/actuation) nasal spray, suspension (Schering-Plough Limited,
UK in healthy adult male human subjects under fasting conditions using charcoal blockade method.

In both studies, after an overnight fast of at least 10 h, subjects self-administered 4 sprays of study drug into each nostril, in accordance with the randomisation schedule. This was carried-out in the standing position, under supervision.

In Study 11-04-017, 80 ml of activated charcoal suspension was administered orally approximately 2 minutes prior to dosing then at 0.50, 1.00 and 1.50 h post-dosing. A minimum 7 day washout-period separated dosing occasions.

Blood samples for plasma mometasone furoate assay were collected during each study period at the following times:

Study 11-04-016 (without charcoal blockade): pre-dose (within 1 hour of dosing) then at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose.

Study 11-04-017 (with charcoal blockade): pre-dose then at 2, 4, 8, 12, 24 and 36 hours after dosing.

Results

### Geometric Least Square Means, Ratios and 90% Confidence Interval of mometasone furoate monohydrate without charcoal blockade (N=45)

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<th>PK Parameters</th>
<th>Geometric Mean</th>
<th>90% Confidence Interval</th>
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<tr>
<td>C\text{\textsubscript{max}} (pg/ml)</td>
<td>Test (T): 15.71</td>
<td>Reference (R): 16.67</td>
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<td></td>
<td>AUC\text{\textsubscript{0-t}} (hr.pg/ml)</td>
<td>174.12</td>
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<tr>
<td></td>
<td>AUC\text{\textsubscript{0-\infty}} (hr.pg/ml)</td>
<td>204.93</td>
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### Geometric Least Square Means, Ratios and 90% Confidence Interval of mometasone furoate monohydrate with charcoal blockade (N=52)

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<th>PK Parameters</th>
<th>Geometric Mean</th>
<th>90% Confidence Interval</th>
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<tr>
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<td>Reference (R): 14.68</td>
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<td></td>
<td>AUC\text{\textsubscript{0-t}} (hr.pg/ml)</td>
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<td></td>
<td>AUC\text{\textsubscript{0-\infty}} (hr.pg/ml)</td>
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The 90% confidence intervals for C\text{\textsubscript{max}} and AUC were within the pre-defined limits acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Mometasone furoate 50 mcg/actuation nasal spray, suspension) and the reference formulation (Nasonex 50 mcg/actuation nasal spray, suspension) under fasting conditions, with and without charcoal blockade.

Efficacy

No new data on efficacy have been submitted and none are required for this type of application.
Safety
No new safety data were submitted and none are required.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has access to the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable risk management plan has been provided for this product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Mometasone Furoate 50 micrograms/actuation nasal spray, suspension are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
This application has been supported by two bioequivalence studies which compared the low level of systemic absorption derived from the proposed generic formulation compared to the established innovator, Nasonex nasal spray, suspension. One study included charcoal blockade to exclude gastrointestinal absorption and the demonstration of bioequivalence on standard criteria in both studies can be taken to confirm that nasal mucosal penetration, and hence mucosal absorption, of the actives from the proposed and innovator formulations are equivalent.

No new or unexpected safety concerns arose from this application.

The SmPC and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has been submitted.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with mometasone furoate monohydrate is considered to have demonstrated the therapeutic value of the product. The benefit-risk balance is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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