COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mometasonfuroaat Cipla 50 micrograms/actuation nasal spray, suspension (mometasone furoate)

NL/H/4435/001/DC

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Mometasonfuroaat Cipla 50 micrograms/actuation nasal spray, suspension. The procedure was finalised in the United Kingdom (UK/H/5169/001/DC). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Mometasone furoate 50 micrograms/actuation nasal spray, suspension

PL 36390/0075

UK/H/5169/001/DC

Cipla (EU) Limited

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Cipla (EU) Limited a Marketing Authorisation for the medicinal product Mometasone furoate 50 micrograms/actuation nasal spray, suspension (product licence number: PL 36390/0075) on 21 December 2012. This medicine is available on prescription only.

Mometasone furoate is a corticosteroid (steroid for short) which has an anti-inflammatory action, reducing the swelling and irritation which causes sneezing, itching and a blocked or runny nose. Each spray provides 50 micrograms of the active ingredient, mometasone furoate.

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 of 6 years and older. It is also used to treat nasal polyps in adults of 18 years and older. 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 polyps to gradually shrink.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of taking Mometasone furoate 50 micrograms/actuation nasal spray, suspension outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about Decentralised Procedure

Name of the product in the Reference Member State	Mometasone furoate 50 micrograms/actuation nasal spray, suspension
Type of application	Article 10.3 (hybrid)
Name of the drug substance	Mometasone furoate
Pharmacotherapeutic classification (ATC code) of the medicinal product	Decongestants and other nasal preparations for topical use – corticosteroids (R01A D09)
Pharmaceutical form and strengths of the medicinal products	Nasal spray, suspension, 50 micrograms/actuation
Reference number for the Decentralised Procedure	UK/H/5169/001/DC
Reference Member State	United Kingdom
Member States concerned	CZ, PL, PT
Start date of the Decentralised Procedure	28 December 2011
End date of the Decentralised Procedure	11 October 2012
Marketing Authorisation number	PL 36390/0075
Name and address of the authorisation holder	Cipla (EU) Limited Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, United Kingdom

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3

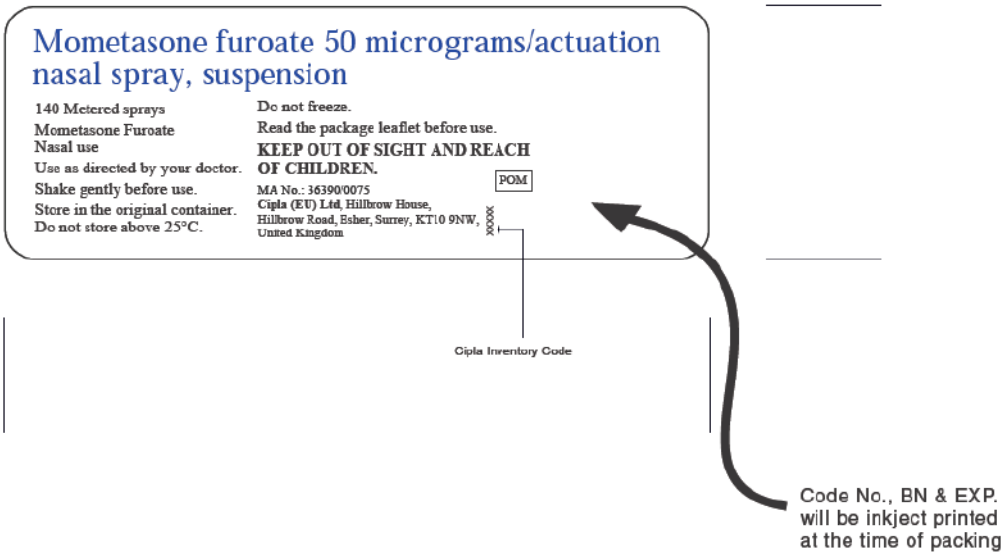
Product Information Leaflet

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

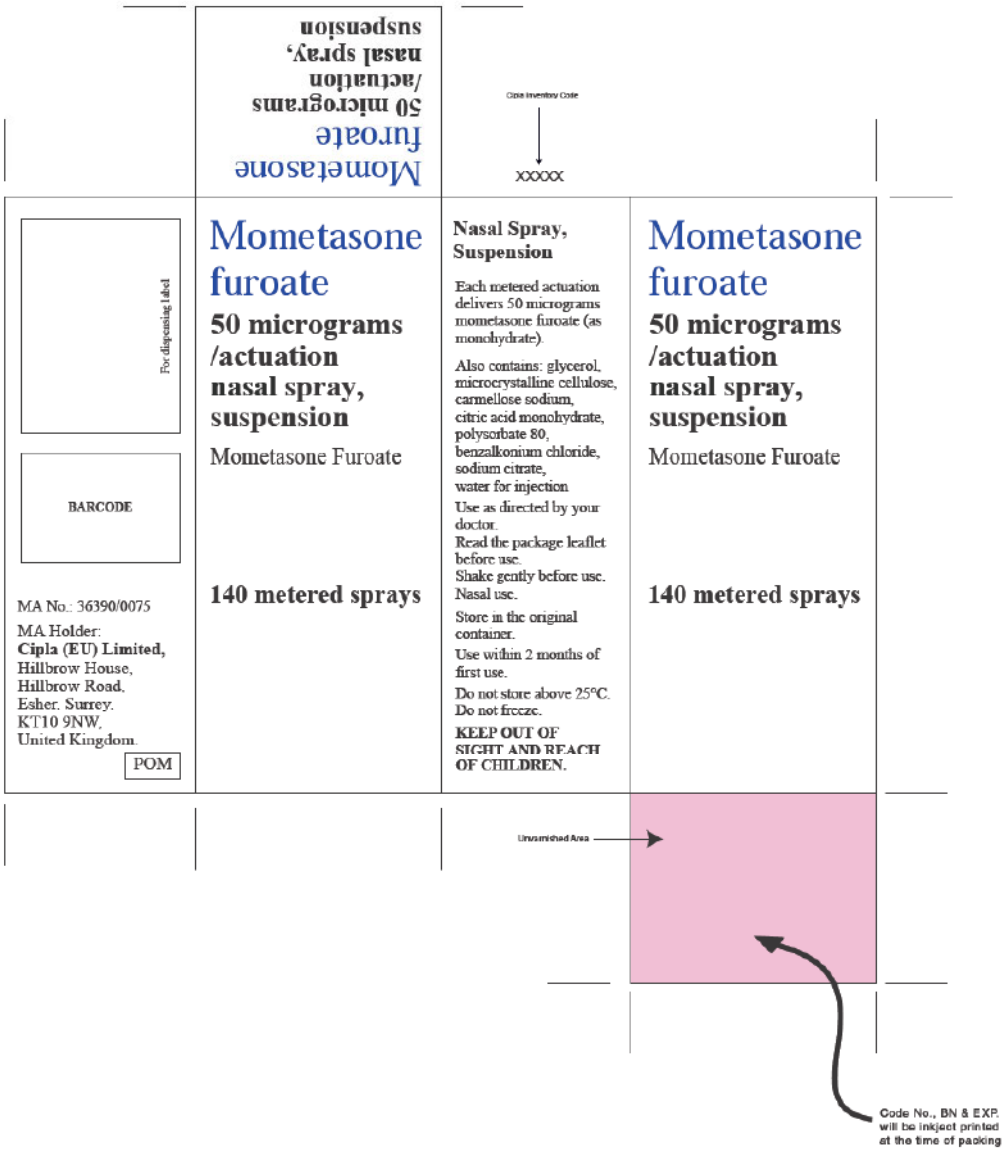
Module 4

Labelling

Label:



Carton:


Mometasone furoate 50 micrograms /actuation nasal spray, suspension
Cipla Inventory Code
XXXXX
For dispensing label
BARCODE
MA No.: 36390/0075
MA Holder:
Cipla (EU) Limited,
Hillbrow House,
Hillbrow Road,
Esher. Surrey.
KT10 9NW,
United Kingdom.
POM
Mometasone furoate
50 micrograms /actuation nasal spray, suspension
Mometasone Furoate
140 metered sprays
Nasal Spray, Suspension
Each metered actuation delivers 50 micrograms mometasone furoate (as monohydrate).
Also contains: glycerol, microcrystalline cellulose, carmellose sodium, citric acid monohydrate, polysorbate 80, benzalkonium chloride, sodium citrate, water for injection
Use as directed by your doctor.
Read the package leaflet before use.
Shake gently before use.
Nasal use.
Store in the original container.
Use within 2 months of first use.
Do not store above 25°C.
Do not freeze.
KEEP OUT OF SIGHT AND REACH OF CHILDREN.
Mometasone furoate
50 micrograms /actuation nasal spray, suspension
Mometasone Furoate
140 metered sprays
Unvarnished Area
Code No., BN & EXP. will be inkjet printed at the time of packing

Module 5

Scientific Discussion

1. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States approved the application for Mometasone furoate 50 micrograms/actuation nasal spray, suspension for the treatment of perennial rhinitis treatment and the treatment and/or prophylaxis of seasonal allergic in those aged 6 years and over as well as nasal polyposis in adults aged 18 years and over.

This Decentralised application was submitted under as a hybrid application under Article 10(3) of Directive 2001/83/EC, as amended. The innovator product is Nasonex 50 micrograms/actuation Nasal Spray, Suspension originally licensed on 10 April 1997 to Schering-Plough Ltd and currently licensed to Merck Sharp & Dohme Ltd (through product licence PL 00025/0587) following a Change of Ownership on 14 January 2011. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

With the UK acting as Reference Member State (RMS) in the Decentralised Procedure (DCP), Cipla (EU) Limited sought Marketing Authorisations in the Concerned Member States (CMS) Czech Republic, Poland and Portugal.

The RMS and CMS considered that the application could be approved at the end of the procedure on 11 October 2012. After a subsequent national phase, the Marketing Authorisation was granted in the UK on 21 December 2012.

About the Product

Mometasone furoate is a synthetic corticosteroid with local anti-inflammatory properties and high affinity for the glucocorticoid receptor.

General Comments on the Submitted Dossier

The submitted documentation in relation to the proposed products is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

General Comments on Compliance with GMP, GLP, GCP and Agreed Ethical Principles

GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out

letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP and GCP
The bioequivalence studies are stated to have been conducted in accordance with GLP, GCP and the Declaration of Helsinki.

2. QUALITY ASPECTS

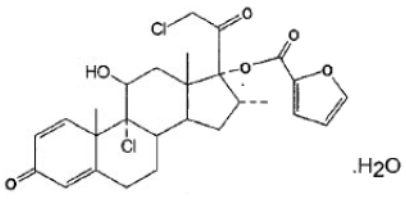
DRUG SUBSTANCE

General information
Nomenclature

rINN:	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

Molecular formula:	$C_{27}H_{30}Cl_2O_6 . H_2O$
Relative molecular mass:	539.4
Structural formula:	



General Properties
Mometasone furoate is a white to off white powder. It is practically insoluble in water, sparingly soluble in 96% ethanol and soluble in methylene chloride and acetone. The structure of mometasone contains eight chiral centres and is controlled by a specific optical rotation of +56.00 - +62.00. It has a melting point of 220 °C.

Manufacture of the Drug Substance
Synthesis of the drug substance from the designated starting material 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.

Control of the Drug Substance
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.

Appropriate proof-of-structure data have been supplied for the drug substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

Container Closure System
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 foodstuffs.

Stability of the Drug Substance
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Description and Composition
The drug product is a white to off-white coloured homogeneous re-dispersible, nasal spray suspension. Each actuation delivers 50 micrograms of mometasone furoate (as the monohydrate) and 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 Ph Eur monographs. Satisfactory Certificates of Analysis are provided for each excipient showing compliance with their respective monographs.

None of the excipients contain materials of animal or human origin. No genetically modified organisms have been used in the preparation of these excipients.

Pharmaceutical Development of the Drug Product
Details of the pharmaceutical development of the drug products have been supplied and are satisfactory. The objective was to develop a formulation of mometasone furoate 50 micrograms/actuation nasal spray suspension which would be therapeutically equivalent to the reference product Nasonex 50 micrograms/actuation Nasal Spray, Suspension.

Manufacture of the Drug Product
A satisfactory batch formula has been provided for the manufacture of the drug products, together with a description and flow-chart of the manufacturing method. In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies have been conducted on pilot scale batches and results were acceptable. A process validaton scheme for commercial scale batches is also presented in accordance with CPMP/QWP/848/96 and is acceptable.

Control of the Drug Product
Finished product specification provided is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as

appropriate. Satisfactory batch analysis data are provided; the data demonstrate that the batches are compliant with the proposed release specifications.

Container Closure System
The drug product is licensed for marketing in a white, opaque, high density polyethylene bottle fitted with a metered dose, manual, polypropylene spray actuator. Each bottle contains 18.0 g suspension, which is equivalent to 140 metered sprays. Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation concerning materials in contact with food.

Stability of the Drug Product
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved. After first use, the product should be used within 2 months.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for batches of the test and reference products used in the bioequivalence studies. Refer to the clinical assessment report for further details.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and product labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory.

Quality Overall Summary
A satisfactory Quality Overall Summary prepared by an appropriately qualified expert has been provided. The CV of the expert has also been supplied.

Quality Conclusion
There are no objections to approval of Mometasone furoate 50 micrograms/actuation nasal spray, suspension from a quality point of view.

3. NON-CLINICAL ASPECTS

As the pharmacological, pharmacokinetic and toxicological properties of mometasone furoate are well known, no non-clinical studies are required and none have been provided.

Non-clinical Overview
The Non-clinical Overview has been written by a suitably qualified expert. The overview, dated 4 November 2011, refers to 7 references from the published literature dated up to 2011. In view of the fact that the pharmaco-toxicological properties of mometasone furoate are well known, the overview is acceptable

Environmental Risk Assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this product onto the market is unlikely to result in an increase in the combined sales of all mometasone furoate-containing products, which, in turn, is unlikely to increase exposure of the environment to mometasone furoate.

Product Literature
The product literature is acceptable from a non-clinical point of view.

Non-clinical Conclusion
There are no objections to the approval of Mometasone furoate 50 micrograms/actuation nasal spray, suspension from a non-clinical point of view.

4. CLINICAL ASPECTS

Clinical Study Reports
This application is supported by two randomised, single-dose, open label, crossover bioequivalence studies of Mometasone furoate 50 micrograms/actuation nasal spray, suspension compared to the reference product Nasonex 50 micrograms/actuation Nasal Spray, Suspension have been conducted: one without charcoal blockade (Study 1) and one with charcoal blockade (Study 2).

Study 1
A randomised, single-dose, open label, two way crossover, bioequivalence study comparing the systemic exposure of test Mometasone furoate 50 micrograms/actuation nasal spray, suspension and the reference Nasonex 50 micrograms/actuation Nasal Spray, Suspension administered as a total dose of 400 mcg in healthy adult male human subjects under fasting conditions.

Study 2
A randomised, single-dose, open label, two way crossover, bioequivalence study comparing the systemic exposure of test Mometasone furoate 50 mcg/actuation nasal spray, suspension of Cipla Limited, India and the reference Nasonex 50 micrograms/actuation Nasal Spray, Suspension administered as a total dose of 400 mcg in healthy adult male human subjects under fasting conditions using charcoal blockade method.

Methods

Design of the studies
In both studies, after an overnight fast of at least 10 hours, subjects self-administered 4 sprays (200mcg) of study drug into each nostril, in accordance with the

randomisation schedule. This was carried-out in the standing position, under supervision.

In Study 2, 80 ml (approximately 10 g) 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 1 (without charcoal blockade): pre-dose then at intervals up to 72 hours post-dose.

Study 2 (with charcoal blockade): pre-dose then at intervals up to 36 hours post-dose.

The design of the studies is acceptable and the wash-out period and blood sampling schedules considered to be adequate

Populations studied
In both studies eligible subjects were healthy males aged ≥ 18 years who fulfilled standard entry criteria, in accordance with the protocol. To allow for any dropouts 48 and 54 subjects were enrolled, respectively.

Analytical methods
Concentrations of plasma mometasone furoate were determined using a validated Liquid Chromatography Mass Spectrometry (LC-MS/MS) methodology. The Calibration Curve and Quality Control Standards are considered to be satisfactory and the linearity range for mometasone furoate spanned appropriate values. Satisfactory analytical reports have been provided.

Pharmacokinetic Variables
A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentration versus time profiles. The pharmacokinetic parameters are appropriate.

Statistical methods
ANOVA, two one-sided tests for bioequivalence and ratio analysis for untransformed and ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were conducted. Statistical comparison of the pharmacokinetic parameters for both test and reference products were performed and assessed for bioequivalence. Bioequivalence was to be concluded if the 90% CIs for C_{max} and AUC_{0-t} fell within the standard 20-125% limits.

T_{max} was evaluated by non-parametric Wilcoxon Rank-Sum two-sample test procedure.

The statistics have been adequately described and the methodology is considered to be acceptable.

Results

Study 1 (without charcoal blockade)

Plasma samples from 47 of the 48 enrolled subjects were analysed and the plasma samples for the 45 subjects who completed both dosing arms were considered for final pharmacokinetic and statistical evaluations.

Study 2 (with charcoal blockade)

Plasma samples from 52 of the 54 enrolled subjects were analysed and pharmacokinetically/statistically evaluated.

The pharmacokinetic results of the study are summarised below:

Study 1 (without charcoal blockade)

The results are summarised in Table 1:

Table 1: 90% Confidence Intervals (CIs) of ln-transformed pharmacokinetic parameters of mometasone furoate (without charcoal blockade

Pharmacokinetic Parameters	Geometric mean		*(%)T/R	90% Confidence Interval
	Test (T)	Reference (R)		
N	45	45	--	--
C_{max} (pg/ml)	15.71	16.67	93.98	85.61-103.17
AUC_{0-t} (hr.pg/ml)	174.12	164.96	105.56	96.17-115.87
$AUC_{0-\infty}$ (hr.pg/ml)	204.93	199.73	102.76	94.12-112.18

***(%) T/R is ratio of TestGeoLSM/ RefGeoLSM.**

Study 2 (with charcoal blockade)

The results are summarised in Table 2:

Table 2: 90% Confidence Intervals (CIs) of ln-transformed pharmacokinetic parameters of mometasone furoate (with charcoal blockade)

Pharmacokinetic Parameters	Geometric mean		*(%)T/R	90% Confidence Interval
	Test (T)	Reference (R)		
N	52	52	--	--
C_{max} (pg/ml)	14.93	14.68	101.86	93.57-110.89
AUC_{0-t} (hr.pg/ml)	65.71	66.09	99.58	90.45-109.63
$AUC_{0-\infty}$ (hr.pg/ml)	84.87	86.47	98.43	87.17-111.14

***(%) T/R is ratio of TestGeoLSM/ RefGeoLSM.**

Summary of pharmacokinetic findings

As can be seen, the 90% confidence intervals for the test/reference (T/R) mean ratios of ln-transformed pharmacokinetic variables C_{max} and AUC_{0-t} in both studies are completely contained within the conventional bioequivalence 90% CI limits of 80% to 125%. Therefore, the proposed product can be considered bioequivalent to Nasonex under fasting conditions, with and without charcoal blockade.

The applicant considers that having demonstrated bioequivalence in the presence of charcoal blockade, the same bioavailability of the drug can be expected at the nasal mucosa (in order to bind to nasal glucocorticoid receptors and exert local anti-inflammatory effects). Therapeutic equivalence can therefore be expected for the proposed generic product compared to the innovator Nasonex Nasal Spray.

In terms of safety findings, both the test and reference formulations were well tolerated. Reported adverse events were non serious, and apart from one fainting attack following administration of the reference formulation in study 2 were only mild to moderate in severity and considered to be unrelated to study medication. They resolved without sequelae. There are therefore no new safety concerns in relation to momestasone furoate and, in particular, the proposed new generic formulation arising from these studies.

Bioequivalence has been shown for the proposed mometasone furoate nasal spray and innovator Nasonex both with and without charcoal blockade. The former confirms that the absorption from the nasal mucosa is, itself, equivalent and hence equivalent absorption and thereapeutic effect within the nasal mucosa can be anticipated.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for this application.

Clinical Efficacy
No new efficacy data are presented for this application and none is required. However the applicant has provided a review of clinical trials published in the literature regarding the efficacy of mometasone furoate.

Clinical Safety
With the exception of the data generated during the bioequivalence studies, no new safety data are presented for this application and none is required. No new or unexpected safety issues arose during the bioequivalence studies. The applicant has provided a review of clinical trials published in the literature regarding the safety of mometasone furoate.

Pharmacovigilance System
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

Post Marketing Experience
No post marketing data are available. The medicinal product has not been marketed in any country.

Clinical Overview
A Clinical Overview written by an appropriately qualified physician has been provided and is a satisfactory summary of the clinical part of the dossier.

Product Literature
All product literature (SmPC, PIL and labelling) is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of Mometasone furoate 50 micrograms/actuation nasal spray, suspension from a clinical point of view.

5. 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 these type.

EFFICACY
With the exception of the bioequivalence studies, no new clinical data were submitted and none are required for an application of this type. Bioequivalence has been demonstrated between the applicant's product and the reference product.

SAFETY
With the exception of the bioequivalence studies, no new clinical data were submitted and none are required for an application of this type. No new or unexpected safety concerns arise from the bioequivalence studies.

PRODUCT LITERATURE
The SmPC and PIL are satisfactory and consistent with those of the reference product. Satisfactory product labelling has also been submitted.

BENEFIT: RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with mometasone furoate is considered to have demonstrated the therapeutic value of the compound. The benefit: risk balance is, therefore, considered to be acceptable. A Marketing Authorisation should be granted