Public Assessment Report

Decentralised Procedure

Mometasone Furoate 0.1% w/w Cream

Mometasone Furoate 0.1% w/w Ointment

Procedure Numbers: UK/H/5755-5756/001/DC

UK Licence Numbers: PL 04416/1421-1422

Sandoz Ltd

LAY SUMMARY

Mometasone Furoate 0.1% w/w Cream
Mometasone Furoate 0.1% w/w Ointment

This is a summary of the public assessment report (PAR) for Mometasone Furoate 0.1% w/w Cream and Mometasone Furoate 0.1% w/w Ointment. These medicines will be referred to as Mometasone Cream and Mometasone Ointment in the remainder of this summary.

This summary explains how Mometasone Cream and Mometasone Ointment were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Mometasone Cream and Mometasone Ointment.

For practical information about using Mometasone Cream and Mometasone Ointment patients should read the package leaflets or contact their doctor or pharmacist.

What are Mometasone Cream and Mometasone Ointment and what are they used for?
Mometasone Cream and Mometasone Ointment are 'hybrid medicines'. This means that they are similar to 'reference medicines' already authorised in the European Union (EU). The reference products for Mometasone Cream and Mometasone Ointment are Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment, respectively.

Mometasone Cream and Mometasone Ointment are used to reduce symptoms caused by certain inflammatory skin disorders such as psoriasis (excluding widespread plaque psoriasis) and atopic dermatitis in adults and children aged 2 years and over. These preparations are generally used to treat very dry, scaly and cracked skin complaints. They are not cures for these conditions, but should help to relieve symptoms.

How do Mometasone Cream and Mometasone Ointment work?
Mometasone furoate belongs to a group of medicines called topical corticosteroids (or steroids). Topical corticosteroids can be divided into four degrees of strength or potency: mild, moderate, potent and very potent. Mometasone Cream and Mometasone Ointment are classified as "potent corticosteroids".

The way that corticosteroids work is not fully understood; although it is thought that they increase levels of a type of protein which reduces inflammation.

How are Mometasone Cream and Mometasone Ointment used?
A thin layer of cream or ointment should be gently applied to the affected area of skin once daily. Patients only need to use a small amount of these preparations. One fingertip unit (a line from the tip of an adult index finger to the first crease) is enough to cover an area twice the size of an adult hand. Patients should never apply more than this quantity nor should they apply the cream or ointment more often than advised by their doctor or pharmacist.

These medicines should not be applied to the face without the close supervision of a doctor and should not be used on the face for more than 5 days. Patients should not use a large amount of cream or ointment on large areas of the body (over 20% of body surface area) or use the cream or ointment for a long time (for example every day for over 3 weeks). The cream or ointment should not be applied in or around the eyes, including the eye-lids. Use in children should be for no more than 5 days. Use is not recommended in children below 2 years of age.

The cream or ointment should not be used under a child's nappy, as this makes it easier for the active substance (mometasone furoate) to pass through the skin and possibly cause some unwanted effects. Unless advised by a doctor, patients should not cover treated areas with a bandage or plaster. Treated areas on the face or in children should not be covered with a bandage or plaster.

These medicines can only be obtained with a prescription.

What benefits of Mometasone Cream and Mometasone Ointment have been shown in studies?
Studies to establish therapeutic equivalence between Mometasone Cream and Elocon 1% w/w Cream and therapeutic equivalence between Mometasone Ointment and Elocon 0.1%w/w Ointment were submitted with these applications. The results of these studies indicate that Mometasone Cream and Mometasone Ointment have similar levels of safety and efficacy as Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment, respectively.

What are the possible side effects of Mometasone Cream and Mometasone Ointment?
For the full list of all side effects reported with Mometasone Cream and Mometasone Ointment, see section 4 of the package leaflets.

For the full list of restrictions, see the package leaflets.

Why are Mometasone Cream and Mometasone Ointment approved?
It was concluded that, in accordance with EU requirements, Mometasone Cream and Mometasone Ointment have been shown to be therapeutically equivalent to Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment, respectively. Therefore, the MHRA decided that, as for Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment, the benefits of Mometasone Cream and Mometasone Ointment are greater than their risks.

What measures are being taken to ensure the safe and effective use of Mometasone Cream and Mometasone Ointment?
A risk management plan has been developed to ensure that Mometasone Cream and Mometasone Ointment are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Mometasone Cream and Mometasone Ointment, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously as well.

Other information about Mometasone Cream and Mometasone Ointment
Marketing Authorisations for Mometasone Cream and Mometasone Ointment were granted on 23 June 2015.

The full PAR for Mometasone Cream and Mometasone Ointment follows this summary.

This summary was last updated in August 2015.

SCIENTIFIC DISCUSSION

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I Introduction

Based on the review of the data on quality, safety and efficacy, the Competent Authorities of Bulgaria, the Czech Republic, Germany, Estonia, Finland, France, Croatia (for the cream only), Hungary (for the ointment only), Latvia, Lithuania, Malta, the Netherlands, Poland, Romania, Slovenia, Slovakia and the UK considered that the applications for Mometasone Furoate 0.1% w/w Cream (PL 04416/1421) and Mometasone Furoate 0.1% w/w Ointment (PL 04416/1422) could be approved. These prescription-only medicines (POM) are indicated for use in adults, adolescents and children aged 2 years and above for the symptomatic treatment of inflammatory skin conditions which respond to external treatment with glucocorticoids, such as atopic dermatitis and psoriasis (excluding widespread plaque psoriasis).

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, the Czech Republic, Germany, Estonia, Finland, France, Croatia (for the cream only), Hungary (for the ointment only), Latvia, Lithuania, Malta, the Netherlands, Poland, Romania, Slovenia and Slovakia as Concerned Member States (CMS).

The applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference medicinal products for the application for the cream and ointment are Elocon 1% w/w Cream (PL 00025/0577) and Elocon 0.1%w/w Ointment (PL 00025/0578) which have been authorised to Merck Sharp & Dohme Limited, UK since a change of Marketing Authorisation ownership on 22 December 2010. These reference medicinal products were first authorised in the UK on 19 November 1991 to Schering-Plough Limited.

Mometasone furoate is a synthetic, non-fluorinated glucocorticoid with a furoate ester in position 17. Like other corticosteroids for external use, mometasone furoate exhibits marked anti-inflammatory activity and marked anti-psoriatic activity in standard animal predictive models.

No new non-clinical data have been submitted, which is acceptable given that these are hybrid application based on originator products that have been in clinical use for over 10 years.

Given the topical nature and negligible systemic absorption of these medicinal products, equivalence studies using the pharmacodynamic surrogate endpoint of skin-blanching were submitted in support the applications, rather than conventional pharmacokinetic studies. The use of equivalence methodology using this surrogate endpoint is acceptable. The studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (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.

The MHRA considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has 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. The MA holder has provided a Risk Management Plan (RMP).

An ERA based on environmental data available on the reference products has been provided.

The UK, Bulgaria, the Czech Republic, Germany, Estonia, Finland, France, Croatia (for the cream only), Hungary (for the ointment only), Latvia, Lithuania, Malta, the Netherlands, Poland, Romania, Slovenia and Slovakia considered that the applications could be approved on Day 208 of the procedure (22 May 2015). After a subsequent national phase, Marketing Authorisations were granted to Sandoz Ltd in the UK on 23 June 2015.

II Quality aspects

II.1 Introduction

Mometasone Furoate 0.1% w/w Cream is white to off-white and smooth. One gram of cream contains 1 mg of mometasone furoate and the excipients hexylene glycol, purified water, white beeswax, propylene glycol monopalmitostearate, stearyl alcohol, macrogol 20, cetostearyl ether, titanium dioxide (E171), aluminium starch octenylsuccinate, phosphoric acid 10% solution and white soft paraffin (contains butylhydroxytoluene (E321).

The cream is supplied in a latex-lined aluminium collapsible tube, lacquered with an epoxy phenolic resin, fitted with a white high density polyethylene piercing screw cap. 10g, 15g, 20g, 30g, 50g, 60g and 100g tubes have been authorised, although not all packs sizes may be marketed.

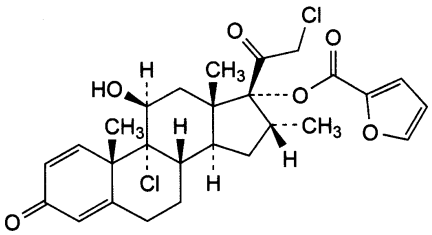
Mometasone Furoate 0.1% w/w Ointment is translucent, white, soft, uniform and smooth. One gram of ointment contains 1 mg of mometasone furoate and the excipients hexylene glycol, phosphoric acid 10% solution, propylene glycol monopalmitostearate, white beeswax, white soft paraffin (contains butylhydroxytoluene (E321)) and purified water.

The ointment is supplied in a latex-lined aluminium collapsible tube, lacquered with an epoxy phenolic resin, fitted with a white high density polyethylene piercing screw cap. 10g, 15g, 20g, 30g, 50g, 60g and 100g tubes have been authorised, although not all packs sizes may be marketed.

II.2 Drug Substance

INN: Mometasone furoate

Structure:



Molecular formula: $C_{27}H_{30}Cl_2O_6$

Molecular mass:	521.4
Appearance:	Mometasone furoate is a white or off-white powder
Solubility	Practically insoluble in water, slightly soluble in ethanol (96 percent), soluble in acetone and in methylene chloride.

Mometasone furoate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance mometasone furoate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical development
The objective of the development programme was to formulate stable topical preparations that are comparable in performance to the reference products Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment (Merck Sharp & Dohme Limited, UK).

Suitable pharmaceutical development data have been provided for these applications.

Comparative viscosity, assay, tube uniformity and impurity profiles have been provided for these products and the reference products.

All of the excipients in the cream comply with their respective European Pharmacopoeia monographs, with the exception of aluminium starch octenylsuccinate, which is controlled in line with suitable in-house specifications, and hexylene glycol, which is controlled according to the USP/NF specification.

All of the excipients in the ointment comply with their respective European Pharmacopoeia monographs, with the exception of hexylene glycol, which is controlled according to the USP/NF specification.

Satisfactory Certificates of Analysis have been provided for all excipients.

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

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, together with an appropriate account of the manufacturing processes. The manufacturing processes have been validated with commercial-scale batches and have shown satisfactory results.

Control of Finished Product
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished products in the packaging proposed for marketing. Based on the results, a

shelf-life of 2 years for the products stored in the unopened tubes has been set. The shelf-life after first opening a tube is 12 weeks. The storage instructions for the cream are “Do not store above 25°C” and “Do not refrigerate or freeze” and for the ointment is “Do not store above 30°C”.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

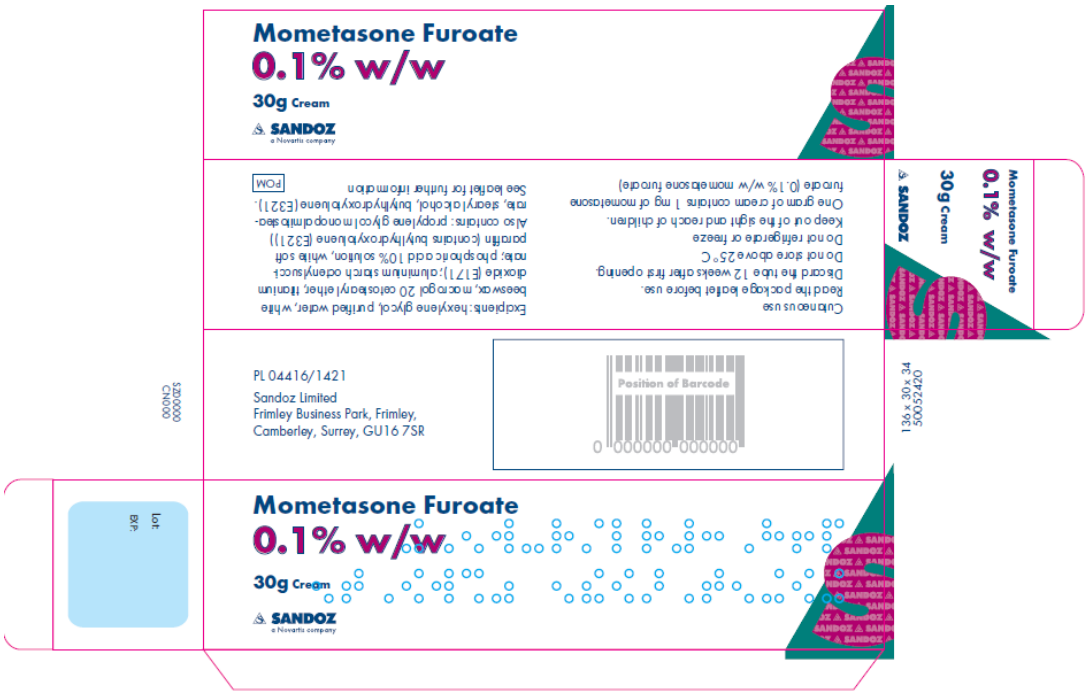
The SmPCs, PILs and labelling are satisfactory and in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The UK approved labelling for the cream is as follows.

The label text for the ointment is in line with that for the cream. No label mock-ups have been provided for the ointment. In accordance with medicines legislation, the ointment shall not be marketed in the UK until approval of the label mock-ups has been obtained:

Label:

Carton:



III Non-clinical aspects

III.1 Introduction

No new non-clinical data have been submitted and none are required for applications of this type.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology

No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)

An ERA based on environmental data available on the reference products has been provided. No new data have been generated in support of these applications and none are needed.

III.6 Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV. CLINICAL ASPECTS

Clinical studies

Conventional pharmacokinetic bioequivalence studies are not possible due to the negligible systemic absorption of these topical preparations. However, skin blanching is a known pharmacodynamic property of dermally applied topical corticosteroids and equivalence studies using this surrogate pharmacodynamic endpoint has been conducted.

Methods

The pivotal study satisfactorily established equivalence between Mometasone Furoate 0.1% w/w Cream and Elocon 1% w/w Cream. A pilot (dose finding) study was also conducted.

The pivotal study was a single-blind, one period, single exposure vasoconstriction response study in healthy male and female subjects. One 5.0 µL/cm^2 application of each cream was applied to regions of each forearm. 90 subjects were enrolled in the study and results from 60 subjects were used in the statistical analysis. Assessment of Skin Blanching at various time periods following dose removal was assessed by visual score (screening only) and by chromameter measurement (study assessment period). Evaluators had been trained in their respective tasks.

Pivotal and pilot studies were also conducted using the ointment formulation. These studies were open-label, one period, randomised vasoconstriction studies. One 5.0 µL/cm^2

application of each ointment was applied to regions of each forearm. Twenty four subjects participated in the pilot (dose ranging) and data for all 24 subjects were used in the statistical analysis. Twenty four subjects participated in the pilot (dose ranging) study and data from all 24 subjects were used in the statistical analysis. Sixty subjects participated in the pivotal study and data from 47 subjects were used in the statistical analysis. Assessment was as described above for the cream formulation.

Results
Data for the cream formulation derived from the pivotal study are tabulated below:

Means of Negative AUEC (0-24 Hr.), Ratio of Means, and 94% Confidence Interval (Locke) Mometasone Furoate Cream 0.1% N=60			
Test	**Reference**	**% Ratio**	**94% CI**
20.61	19.30	106.81	(96.99, 117.08)

Data for the ointment formulation derived from the pivotal study are tabulated below:

Summary Mean Negative a-Scale Areas under the Response Curve (24 Hr. Areas)	
Mometasone Furoate	**Negative AUEC**
Test Product Geometric Mean	23.70
Reference Product Geometric Mean	21.28
% Ratio	111.40
90% Confidence Interval	(102.90, 120.80)

Based on the pharmacodynamics surrogate methodology, these results confirm that the test and reference products for both the cream and ointment formulations can be considered bioequivalent.

Safety
The equivalence studies raised no safety concerns for these products. The well-established safety profile of topical mometasone furoate has been adequately summarised by the Clinical Experts and there are no new pharmacovigilance safety concerns under consideration at this time. The proposed SmPCs, are consistent with those of the reference formulations and adequately address known safety aspects of these medications.

Risk Management Plan
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 Mometasone Furoate 0.1% w/w Cream and Mometasone Furoate 0.1% w/w Ointment.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Skin hypersensitivity	Warnings in sections 4.3 "Contraindications", 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC of Mometasone both formulations to prevent skin hypersensitivity reactions and to prevent the usein patients who are sensitive to mometasone furoate with the purpose of avoiding skin hypersensitivity reactions.	None
Secondary infections or worsening of existing infections	Warnings in sections 4.3 Contraindications, 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC to avoid secondary skin infections.	None
Rebound on withdrawal of long-term treatment	Warning in section 4.4 "Special warnings and precautions for use" of the SmPC to avoid sudden discontinuation of treatment and use a slow reduction of the treatment.	None
Systemic absorption manifesting as: Hyperglycaemia/ glycosuria Adrenal suppression Cushing's syndrome Growth and development retardation in children	Warning in sections 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SmPC in order to avoid the hypothalamic-pituitaryadrenal axis suppression.	None
Glaucoma and/or cataract associated with use on or near the eyes	Warning in section 4.4 "Special warnings and precautions for use" of the SmPC to prevent the very rare risk of glaucoma simplex or subcapsular cataract.	None
Intracranial hypertension (in paediatric patients)	Warning in section 4.8 "Undesirable effects" of the SmPC to avoid Intracranial Hypertension (bulging fontanelles, headaches and bilateral papilloedema).	None
Safety in pregnancy	Warning in section 4.6 "Fertility, pregnancy and lactation" of the SmPC to avoid the potential risk to the mother or the foetus.	None
Safety during lactation	Warning in section 4.6 "Fertility, pregnancy and lactation" of the SmPC to avoid potential systemic absorption to produce detectable quantities in breast milk.	None
Safety in paediatric patients	Warning in section 4.2 "Posology and method of administration" of the SmPC due to insufficient data on safety.	None

Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Mometasone Furoate 0.1% w/w Cream and Mometasone Furoate 0.1% w/w Ointment**.**

V. USER CONSULTATION

The package leaflets are based on an approved package leaflet that 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 results showed 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 package leaflets for the proposed products are, therefore, satisfactory.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Mometasone Furoate 0.1% w/w Cream and Mometasone Furoate 0.1% w/w Ointment 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. As the pharmacokinetics, pharmacodynamics and toxicology of mometasone furoate are well-known, no additional data were required.

EFFICACY
With the exception of the data submitted in the pilot and pivotal pharmacodynamic studies, no new clinical data were submitted and none are required for this type of application.

Therapeutic equivalence has been demonstrated between the applicant's Mometasone Furoate 0.1% w/w Cream and Mometasone Furoate 0.1% w/w Ointment and the reference products Mometasone Cream and Ointment are Elocon 1% w/w Cream and Elocon 0.1%w/w Ointment, respectively.

SAFETY
The safety profile of mometasone furoate is well-known. With the exception of the safety data generated during the clinical studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the clinical studies.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and consistent with those for the reference products and consistent with current guidelines.

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

RECOMMENDATION
The grant of Marketing Authorisations is recommended.

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval / non approval	Assessment report attached