EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Mometasone Furoate Sandoz and associated names

Pursuant to Article 29(4) of Directive 2001/83/EC

INN: mometasone

Procedure no: EMEA/H/A-29(4)/1332

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Sandoz B.V. submitted an application for decentralised procedure of Mometasone Furoate Sandoz and associated names, 50 microgram/dose, nasal spray, suspension on 1 July 2010.

The application was submitted to the reference Member State (RMS): The Netherlands and the concerned Member States (CMS): BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LU, NO, PL, PT, RO, SE, SI, SK, UK

The Decentralised procedure NL/H/2038/001/DC started on 30 September 2010.

On day 210, according to CMS Spain, Potential Serious Risks to public health (PSRPHs) on safety and efficacy, as set out under section 2.2 below, remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by The Netherlands on 8 December 2011. The CMD(h) 60 Day procedure was initiated on 25 December 2011.

Day 60 of the CMD(h) procedure was on 23 February 2012 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by the Netherlands on 23 February 2012. Spain raised public health objections to the *in vitro* methodology used, considering that it was inadequate to provide evidence of *in vivo* equivalence between the proposed and the reference products. In addition, Spain raised concerns with regard the statistical method used.

2. Scientific discussion during the referral procedure

2.1. Introduction

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active. Intranasal corticosteroids are used to treat allergic rhinitis for which the symptoms include chronic obstruction, hyposmia, post-nasal mucous discharge, and nasal hyper-reactivity. The Applicant submitted an application under the decentralised procedure for Mometasone Furoate Sandoz 50 mcg/dose, as a nasal spray (suspension) and applied for the following indications:

- use in adults and children of 6 years and older to treat the symptoms of seasonal allergic or perennial rhinitis.

- prophylactic treatment in patients who have a history of moderate to severe symptoms of seasonal allergic rhinitis up to four weeks prior to the anticipated start of the pollen season.

- symptomatic treatment of nasal polyps in adults 18 years of age and older.

The Applicant submitted an application for two different spray pump devices (Device 1 and Device 2) fitted to containers containing identical mometasone furoate suspensions and provided *in vitro* data for both devices, however only Device 1 was investigated *in vivo*. While the reference member state (RMS) considered both devices to be approvable, based on the available *in vitro* data, the objecting concerned member state (CMS) did not consider *in vitro* data to be a valid surrogate of *in vivo* equivalence for nasal suspensions and therefore considered that equivalence had not been

demonstrated for Device 2, due to insufficient evidence regarding the *in vivo* dissolution of the drug particles in the nose, which is critical for efficacy. In addition, the objecting CMS raised concerns regarding the statistical methodology applied, as the *in vitro* comparison was performed using Population Bioequivalence (PBE) instead of Average Bioequivalence (ABE), as described in the CHMP's *Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP)*[1].

As these concerns could not be resolved by Day 60 of the CMD(h) procedure, the objecting CMS raised concerns of Potential Serious Risks to Public Health and a procedure under Article 29(4) was therefore triggered in February 2012. A CHMP list of questions was addressed to the Applicant, requesting further justification of the adequacy of the *in vitro* data used to support the equivalence between the originator and Device 2. The Applicant was also asked to comment on the adequacy of the parameters used in the *in vitro* approach and the statistical analysis used.

The CHMP consulted its Biostatistics Working Party (BSWP) and Quality Working Party (QWP) in the context of this procedure.

2.2. Critical evaluation

The CHMP noted that the Applicant had received the following scientific advice from the CHMP on the clinical program during the development of the proposed application: "*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; CHMP/EWP/4151/00 and CPMP/EWP/4151/00 Rev 1"*. The advice further stated that "*Since the characteristics of the spray (speed, droplet size) could have an important impact on the deposition of the spray, these aspects of the device should be well characterized. For therapeutic purposes the ideal size of the droplets is > 7 µm, which will guarantee that they stay in the nasal passages, producing the desired effect. If the average diameter of the generated droplets is different or if the generic droplets are much smaller than the ones of the originator, this could produce a problem from a safety point of view, due to the better penetration of the drug to the lower airways*".

The CHMP noted that the SmPC of reference product Nasonex states that '*Mometasone furoate, administered as an aqueous nasal spray, has a negligible (<0.1%) systemic bioavailability and is generally undetectable in plasma, despite the use of a sensitive assay with a lower quantitation limit of 50 pg/ml; Mometasone furoate suspension is very poorly absorbed from the gastrointestinal tract, and the small amount that may be swallowed and absorbed undergoes extensive first-pass hepatic metabolism prior to excretion in urine and bile*'. The Applicant did therefore not perform any pharmacokinetic or pharmacodynamic studies and instead performed comparative *in vitro* studies between the EU reference product Nasonex and the proposed products for both spray pump delivery devices. In addition, supportive data from a Phase III clinical study was submitted during the DCP procedure.

The CHMP considered that this was in line with the approach described in the Note for Guidance on Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents (CPMP/EWP/235/95), which states: "*if possible pharmacodynamic studies or local availability studies; possibly in vitro studies or argumentation in case of minor differences. Otherwise clinical studies. Any safety issue has to be addressed appropriately".* The CHMP agreed that in the case of mometasone

[1] Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1, January 2009).

furoate nasal spray, an *in vitro* approach is acceptable in principle, due to the very low systemic bioavailability, provided that the approach is justified and that any differences observed with the proposed product do not impact the benefit-risk negatively. The CHMP noted that the scientific advice received by the Applicant did not provide any detailed guidance on the test methods to be applied and acceptance criteria to be met. The CHMP also noted that no harmonized European guidance document or reflection paper on the equivalence testing of nasal spray suspensions is available.

***In vitro* tests**

The CHMP reviewed the *in vitro* data provided by the Applicant, taking into account the limited sensitivity of clinical testing for this type of product (for bioequivalence and efficacy testing). The performance of the spray pump was determined based on the *Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products* (EMEA/CHMP/QWP/49313/2005 Corr). The CHMP was of the opinion that the results demonstrate that both devices are suitable for the intended use and that the in-use requirements defined in the SmPC are supported by the data and in line with those of the reference product. The Applicant carried out a battery of *in vitro* tests to compare the properties of the suspension in the container and the properties of the suspension in the spray and then discussed the effects of these properties on the delivery in the nose.

1) Comparison of the suspension in the container

The Applicant stated that the composition of the proposed drug product is qualitatively and quantitatively the same as for the reference product and that the proposed product suspension is identical, regardless of the type of pump fitted to the container. The Applicant supported this by providing a comparison between the suspensions of the proposed and the reference product. The CHMP agreed that the results were comparable between the proposed and the reference product.

As the drug product is a suspension and because the particle size of the active substance is critical, given the low solubility of mometasone furoate (about 0.1 µg/mL), the Applicant analysed the particle size distribution (PSD) of the drug substance in the suspension. Because the drug product contains excipients that are also suspended in the formulation, additional testing was carried out to differentiate between the particles of suspended excipients and suspended drug substance. The CHMP assessed the PSD data provided by the Applicant and agreed that the comparability in particle size distribution of the proposed and reference product suspensions had been demonstrated. In the absence of a harmonized EU guideline on the comparison of PSD, the CHMP agreed with the approach taken by the Applicant. Overall, the CHMP therefore considered the suspensions to be comparable. The CHMP noted that the Applicant did not discuss the PSD of the suspended excipients, beyond stating that the same grade of excipients were used and that the physico-chemical properties of the proposed drug product were comparable to the reference product. Nonetheless, the CHMP considered this to be sufficient, in line with the position of the QWP.

2) Comparison of the spray pattern of the suspension

The Applicant stated that the way the suspension is sprayed by the spray pump determines the delivery of the formulation to the nose and therefore carried out a battery of *in vitro* tests to analyse the impact of the spray pumps on the delivery of the product. The CHMP Scientific Advice defined droplets below 7 µm in size as indicators of safety, as particles below this threshold could potentially reach the lungs. The Applicant therefore investigated the incidence of droplets below10 µm in size. The results showed low incidences for all batches tested, with comparable results between the proposed and the reference product.

The Applicant also demonstrated that the dose delivered with the proposed product is comparable to the dose delivered using the reference product. The parameters were tested in the first and last sprays of the container to ensure accurate dose delivery throughout container life.

Having assessed the available data, the CHMP agreed that the proposed product and the reference product achieved comparable spray patterns and dose delivery.

3) Discussion on the effects of the properties on the delivery in the nose

The Applicant identified three critical stages for establishing the comparability of the delivery of the formulations of the proposed product with the reference product: the dose delivered to the nose, the location of deposition in the nose and the dissolution of the drug substance at the site of action.

a) Delivered dose

The delivered dose of the proposed product was demonstrated to be comparable to that of the reference product, using the ABE statistical analysis approach.

b) Location and pattern of deposition

The location where the sprayed suspension is deposited in the nose is determined mainly by the droplet size distribution (DSD), including small droplets below 10 µm, and spray pattern. In order to confirm the *in vitro* results already obtained, the Applicant performed an additional study to support the fact that the proposed drug product achieves a similar area and location of deposition of the spray in the nose as that of the reference product. The Applicant acknowledged that this is not a generally accepted method in the EU, but was of the view that the data can be assessed as supporting data to demonstrate that the spray pumps of the proposed and reference products achieve similar deposition patterns regardless of the similarity of the spray pattern and DSD between the proposed and reference product. The Applicant provided the summarised results of this study, including deposition area for both proposed devices compared to the reference device.

Considering the totality of the analyses carried out by the Applicant, the CHMP agreed that the deposition location and the deposition pattern of the proposed and the reference products were comparable. The CHMP was therefore reassured that the spray pump used did not impact on the deposition of the suspension in the nose.

c) Dissolution of the drug substance at the site of action

The CHMP noted that no solubility studies were performed by the Applicant but agreed that the PSD of mometasone furoate is an adequate indicator of dissolubility and considered that the total body of available data on PSD confirms that the proposed and the reference products have comparable PSD.

The CHMP therefore considered the dissolution properties to be comparable between the proposed and the reference products, independently of the spray pump device used. As the CHMP considered the rate of dissolution to determine the availability of the active substance locally, the CHMP concluded that the data provided sufficient confirmation that potential differences between the proposed and the reference products would not impact the benefit-risk of the proposed products.

***In vivo* test**

The CHMP noted that equivalence in therapeutic efficacy was demonstrated in a clinical study performed with the proposed product fitted with the Device 1 pump and considered this *in vivo* data to be supportive of the *in vitro* data.

Discussion on the statistical methodology used

The CHMP discussed the objections raised regarding the statistical analysis applied during the *in vitro* comparison and the relation of the *in vitro* data towards the *in vivo* dissolution of the drug substance at the site of action. The objecting CMS considered that the available *in vitro* data is not a valid surrogate for the equivalence of the products, as the *in vitro* comparison was performed using the Population Bioequivalence (PBE) statistical method, which consists of an aggregate criterion where the differences in means can be compensated by the differences in variability. The objecting member state therefore considered the PBE method to be more permissive than the average bioequivalence (ABE) methodology for *in vitro* comparison, as described in the orally inhaled product (OIP) guideline, which uses a 15% acceptance range. The PBE method was described in a draft FDA *Guidance to Industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* at the time of submission but not in the EU guidelines. The CHMP noted that the EU guidelines did not provide guidance on the statistical approaches to be used for *in vitro* comparison but did also not explicitly preclude the use of the PBE methodology.

The CHMP noted the position of the Biostatistics Working Party (BSWP), which considered that the use of the PBE approach to demonstrate equivalence is not acceptable, as the absence of consensus on limits and approaches to be applied in this PBE methodology may in certain situations lead to the conclusion of bioequivalence even in case of large mean differences. In addition, in the context of this procedure, the BSWP considered the proposed PBE approach to be inappropriate to show *in vitro* similarity as no justification for the use of PBE in this specific situation was provided and because the use of the PBE approach was not pre-specified and only performed in the presence of a failed ABE analysis, inflating the type I error and casting doubts on the validity of the PBE results. The BSWP considered that changing the method of analysis *post hoc* is not acceptable in general.

The CHMP noted that the ABE approach was used for most of the *in vitro* parameters tested and that comparability with the reference product was demonstrated in all cases where applied. The Applicant only applied the PBE approach when comparing the results of DSD and spray pattern, stating that DSD and spray pattern have an inherent high variability. To support this approach, the Applicant tested two batches of the reference product, showing comparability of the DSD and spray pattern using the PBE approach, whereas the ABE approach could not demonstrate bioequivalence. The Applicant therefore pre-specified the use the PBE approach for these parameters.

While noting that the Applicant had presented justifications for the use of PBE and that this use was pre-specified where applied, the CHMP agreed with the BSWP position that the use of PBE in bioequivalence studies is not desirable as it may lead to the acceptance of higher levels of variability between drug products. However, in this specific case, the CHMP considered the adequacy of the applied statistical methods to be of secondary importance compared to the evaluation of the available *in vitro* data, as supported by the available *in vivo* data, which was considered sufficient to reach a conclusion. The CHMP noted that further discussions are needed on the criteria for equivalence using *in vitro* methodology.

Conclusion

Having assessed the entirety of the *in vitro* data, the CHMP concluded that there is adequate evidence to confirm that the particle size distribution as well as the location and pattern of deposition are comparable for the proposed products and the reference product, independently of the spray device used. The CHMP considered that any uncertainties regarding the comparability of droplet size distribution and spray pattern between the proposed and reference product were adequately addressed. As the CHMP considered particle size distribution to be an adequate indicator of dissolubility, which is in turn an indicator of comparable safety and efficacy, the CHMP therefore concluded that the overall available data adequately demonstrated that potential differences between the proposed product fitted either with Device 1 or with Device 2 and the reference product do not

affect the efficacy or safety of the proposed products and that the benefit-risk of the proposed products is therefore positive.

This was further supported by the evidence of equivalent therapeutic efficacy obtained from the phase III clinical study comparing the proposed product fitted with the Device 1 spray pump and the reference product.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan

2.4. Recommendation

The CHMP considered all the objections raised by the objecting concerned member state to be adequately addressed and that they should not prevent the authorisation of the product. The CHMP was of the opinion that the application is approvable.

2.5. Conclusions and benefit risk assessment

Based on:

- the rapporteur's and co-rapporteur's assessment reports
- the positions of the Biostatistics Working Party and the Quality Working Party
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit-risk ratio of Mometasone Furoate Sandoz and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation. The summary of product characteristics, labelling and package leaflet are as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion. The divergent positions are presented in the appendix.

Appendix

Divergent positions

Article 29(4) referral of Council Directive 2001/83/EC, as amended

Procedure No: EMEA/H/A-29/1332

Mometasone Furoate Sandoz and associated names (INN: mometasone)

Divergent statement

The approval of the Device 2 nasal pump is not supported as it has not shown to be equivalent to the reference product. Only the Device 1 pump should be approved since it is the only one that has shown to be therapeutically equivalent with the reference product. Therefore, the approval in the same marketing authorisation of two devices that have not demonstrated to be equivalent is not endorsed.

The *in vitro* methodology used by the Applicant to show equivalence with the reference product is not considered able to address the *in vivo* dissolution of the drug particles in the nose. Dissolution is critical for efficacy because if dissolution were slower, the particles in suspension would be removed by mucociliary clearance and no or less effect would be obtained. The particle size analyses performed by the Applicant in order to distinguish the excipient from drug particles have not been validated as a surrogate of *in vivo* dissolution. The methodology described in the FDA draft guideline that was employed by the Applicant has never been considered validated as surrogate of therapeutic equivalence for nasal suspensions. As a consequence the FDA also requires pharmacokinetic bioequivalence and therapeutic equivalence studies.

More importantly, even if the *in vitro* methodology were considered surrogate of the clinical outcome, the statistical methodology used for *in vitro* comparison is not considered acceptable either. The Applicant has used the Population Bioequivalence (PBE) methodology described in a draft FDA guideline while the statistical approach recommended in the European guideline for Orally Inhaled Products (OIP) is based on the average bioequivalence (ABE) with an acceptance range of 15%. The use of the PBE approach applied by the Applicant is considered unacceptable given that the PBE methodology led to the conclusion of bioequivalence even in case of large mean differences (2-fold difference in the average spray pattern and more than 20% difference in the average median particle size). This view has been supported by the Biostatistics Working Party that was of the opinion that the proposed PBE approach is not appropriate to show in vitro similarity. The use of the PBE approach cannot be justified based on high variability since the variability observed in the in vitro parameters (7-26%) was always smaller than the limit considered as highly variable (30%).

CHMP members expressing a divergent opinion:

Pierre Demolis (FR)	19 July 2012	Signature: ……
Andrea Laslop (AT)	19 July 2012	Signature: ……
Emilia Mavrokordatou (CY)	19 July 2012	Signature: ……
Jan Mazag (SK)	19 July 2012	Signature: ……
Daniela Melchiorri (IT)	19 July 2012	Signature: ……
Pieter Neels (BE)	19 July 2012	Signature: ……
Concepcion Prieto Yerro (ES)	19 July 2012	Signature: ……
Sol Ruiz (co-opted)	19 July 2012	Signature: ……
Nela Vilceanu (RO)	19 July 2012	Signature: ……