Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

Overall summary of the scientific evaluation of Mometasone Furoate Sandoz and associated names (see Annex I)

Mometasone furoate is a topical glucocorticosteroid with local anti-inflammatory properties at doses that are not systemically active. The Applicant submitted an application for Mometasone Furoate Sandoz 50 mcg/dose, in the treatment of the symptoms of seasonal allergic or perennial rhinitis and of nasal polyps, as a nasal spray with two different spray pump devices (Device 1 and Device 2). The Applicant provided *in vitro* data for both devices, however only Device 1 was investigated *in vivo*. While the reference member state considered both devices to be approvable, the objecting concerned member state (CMS) did not consider *in vitro* data to be a valid surrogate of equivalence for nasal suspensions and therefore considered that equivalence had not been demonstrated for Device 2. In addition, the objecting CMS raised concerns regarding the statistical methodology applied. A procedure under Article 29(4) was therefore triggered in February 2012.

The CHMP noted that the Applicant had received scientific advice from the CHMP on the clinical program, stating that for locally applied, locally acting products containing known constituents, an *in vitro* approach could in principle be used for demonstration of equivalence, provided that this approach is justified. Because of the low systemic bioavailability and the poor absorption from the gastrointestinal tract of mometasone furoate, the Applicant decided not to perform any pharmacokinetic or pharmacodynamic studies and instead performed comparative *in vitro* studies between the proposed and the reference products for both spray pump delivery devices. Having assessed the performance of the spray pumps and the properties of the suspension in the spray, the CHMP agreed that there is adequate evidence of comparable particle size distribution of the active substance suspension between the proposed products and reference product, and also agreed that comparable locations and patterns of deposition were demonstrated. Considering that particle size distribution is an adequate indicator of dissolubility, the CHMP therefore concluded that the dissolution properties of the proposed and the reference products are equivalent, 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 further concluded that the data confirmed that potential differences between the proposed and the reference products would not impact the benefit-risk of the proposed products. The CHMP considered that this was supported by the evidence of equivalent therapeutic efficacy obtained from the phase III clinical study comparing the proposed product with the Device 1 spray pump and the reference product.

The CHMP also discussed the objections raised regarding the statistical methodology used for the *in vitro* comparison. The objecting CMS considered that the available *in vitro* data is not a valid surrogate for the equivalence of the products, as the comparison was performed using the Population Bioequivalence (PBE) method, which consists of an aggregate criterion where the differences in means can be compensated by the differences in variability. The PBE method may therefore be more permissive than the Average Bioequivalence (ABE) method described in the CHMP's *Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP).*[1] While noting that the Applicant had presented justifications for the use of PBE and that this use was pre-specified where

[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)

applied, the CHMP considered 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.

Having assessed the entirety of the available data, the CHMP concluded that the evidence of comparable particle size distribution as well as location and pattern of deposition between the proposed and the reference products indicates comparable dissolubility, which is in turn an indicator of comparable safety and efficacy. This was further supported by the clinical data obtained with the Device 1 spray pump. In conclusion, considering the total body of available evidence, the CHMP considered it to be adequately demonstrated that potential differences between the proposed product fitted either with the Device 1 pump or with the Device 2 pump and the reference product do not affect the safety and efficacy of the proposed products and that the benefit-risk of the proposed products is therefore positive.

Grounds for positive opinion

Whereas

- the CHMP assessed the entirety of the data submitted by the Applicant,
- the CHMP considered that the results of the conducted *in vitro* comparisons confirm that the particle size distribution as well as the locations and patterns of deposition of the suspension in the nose of the proposed products and the reference product are comparable,
- the CHMP considered particle size distribution and location and pattern of deposition to be adequate indicators of dissolubility and therefore concluded that the proposed and the reference products have comparable dissolution properties,
- the CHMP therefore considered it adequately demonstrated that potential differences between the proposed product fitted either with the Device 1 pump or with the Device 2 pump and the reference product do not affect the safety and efficacy of the proposed products, based on the available *in vitro* evidence and further supported by the clinical data obtained using the proposed product fitted with the Device 1 spray pump,
- the CHMP considered the benefit-risk of the proposed products to be positive,

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Mometasone Furoate Sandoz and associated names (see Annex I).