

Annex II

Scientific conclusions

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Beclometasone dipropionate (BDP) is a glucocorticoid and a prodrug of the active metabolite, beclometasone-17-monopropionate. Beclometasone dipropionate exerts local anti-inflammatory action in the control of bronchial asthma.

BDP nebuliser (nBDP) suspension products are authorised in five EU member states including France, Germany, Greece, Ireland and Italy under different invented names: Sanasthmax, Becloneb, Beclospin, Clenil. Clenil (and associated names) monodose was first approved through national procedure in Italy in 1991, then was approved through national procedures in France, while in Ireland, Germany and Greece through Mutual Recognition procedure with Ireland as Reference Member State.

In Italy nBDP is currently indicated in both adults and children for the treatment of asthma, and other respiratory conditions with the narrowing of the airways in the lungs (bronchostenotic condition), specifically when the use of pressurised or dry powder inhalers is unsatisfactory or inappropriate. nBDP is also indicated in allergic and idiopathic rhinitis, inflammatory and allergic affections of the nasal cavities and of the rhino-pharyngeal tract.

In France nBDP is indicated as anti-inflammatory treatment of severe persistent asthma in children.

In Ireland, Germany and Greece nBDP is indicated in both adults and children for the treatment of bronchial asthma where use of a pressurised or dry powder inhaler is unsatisfactory or inappropriate.

Due to the divergent national decisions taken by Member States concerning the authorisation of nBDP-containing products, Italy notified the CHMP/European Medicines Agency on 19 June 2015 of a referral under Article 30 of Directive 2001/83/EC for Clenil and associated names, in order to resolve divergences amongst the nationally authorised product information and thus harmonise its divergent product information across the EU.

Overall summary of the scientific evaluation by the CHMP

Maintenance treatment of asthma

This indication of the maintenance treatment of asthma when the use of pressurised or dry powder inhalers is unsatisfactory or inappropriate is currently approved in all five member states where the product is authorised.

The CHMP agreed with the indication "in the maintenance treatment of asthma" in line with the available scientific evidence and guideline recommendations where inhaled corticosteroids are considered the first-line treatment when a diagnosis of asthma has been done and nebulizers are recommended when the use of other hand-held inhalers is not appropriate.

Other respiratory conditions with the narrowing of the airways in the lungs (bronchostenotic condition)

Clenil is currently indicated for the treatment of other respiratory conditions with the narrowing of the airways in the lungs (bronchostenotic condition) in Italy. This indication is not currently authorised in the other four EU member states (Greece, Germany, France and Ireland).

The evidence and argumentation provided by the MAH on the beneficial effect of nBDP in the treatment of the broad proposed indications (bronchostenotic condition as initial one, inflammatory disorders of the respiratory tract in particular associated with wheezing as second one) was considered by the CHMP unsatisfactory in identifying the medical need and the target population (lack of adequately designed and sized trials). Thus the proposed broad indications were considered unacceptable.

Following the negative position of the CHMP on the broad indication, the MAH proposed a narrowed one "symptomatic treatment of recurrent wheezing in preschool children" that was agreed with some changes.

Most wheezing in preschool children (≤ 5 years of age) is associated with viral upper respiratory tract infections, which recur frequently in this age group. The cumulative prevalence of wheeze is almost 50% at the age of 6 years. Pre-schoolers with recurrent wheezing are at high risk of developing asthma during school age; in this population asthma and wheezing do not always overlap and deciding when recurrent wheezing is the initial presentation of asthma is difficult.

A confident diagnosis of asthma in children ≤ 5 years of age is difficult, because episodic respiratory symptoms such as wheezing and cough are also common in children without asthma, particularly in those 0–2 years old. The nBDP indication in wheezing would allow paediatricians to treat young children suffering from recurring wheezing when a clear asthma diagnosis is not achievable, in line with GINA guideline¹. Indeed, the CHMP noted that restricting the indication to only "asthma" might lead to an under-treatment of children ≤ 5 years of age with recurrent wheezing without any other apparent risk factors for asthma.

It is acknowledged that the scientific evidence on the benefit of nBDP in the treatment of recurrent wheezing in pre-schooler is limited (the only supportive scientific evidence comes from Papi and colleagues (2009) in which methodological bias is noted); however, high standard studies, as per today criteria, are not expected to be available for nBDP to support indication that has been granted in Italy many years ago.

Overall, the CHMP agreed on the final indication wording "treatment of wheezing in children up to 5 years of age".

The CHMP also agreed that there is a need to give adequate information in the PI on the risk of long-term exposure in children below the age of 5 years. As such recommendations regarding the duration treatment and the need of monitoring are included in sections 4.2 and 4.4 of the SmPC.

Paediatric age range

Beclomethasone dipropionate is currently indicated in children in all EU member states where the product is authorised. The paediatric population for which the product is approved is intended to be the overall paediatric population without excluding infants and toddlers. Taking into account the available data and guidelines the CHMP agreed that there should not be a lower age limit recognising that there is a possible need of beclomethasone below 6 months of age.

As regards the indication in wheezing, the term "preschool" as proposed by the MAH was not considered as informative by the CHMP and not in line with the SmPC guideline. The most supportive evidence for the treatment of recurrent wheezing children (Papi et al., 2009)² enrolled children aged 1–4 years. In GINA guideline, low dose ICS (controller treatment) is recommended as the preferred initial treatment to control asthma in children 5 years and younger. Due to the difficulty to set a lower age limit for the treatment of asthma/wheezing condition in the paediatric population, the CHMP considered more appropriate to leave it open.

Allergic and idiopathic rhinitis, inflammatory and allergic affections of the nasal cavities and of the rhinopharyngeal tract

This indication is currently only authorised in Italy, one out of the five EU member states where the product is licensed.

¹ GINA: From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: <http://www.ginasthma.org/>.

² Papi A. et al., 'Regular vs prn nebulized treatment in wheeze preschool children'. Allergy 2009; 64: 1463–1471.

The evidence provided by the MAH in support of this indication consisted of 4 studies, only one of which is a randomised clinical trial (Profita et al., 2013)³. According to the most recent guidelines⁴, the use of corticosteroids is recommended for mild-moderate rhinitis via intranasal route. The studies in allergic rhinitis were actually carried out using intranasal spray. In fact, pharmaceutical formulations for nebulization are intended for asthma treatment as they deliver particles with particle size distribution less than 5 microns that can reach lower airways using facial masks; the fact that a nebuliser suspension administered through the facial mask is not suitable for administration to the nasal cavity is also proven by the cited article by Profita and colleagues where no differences were observed between the nBDP provided by facial mask and the placebo group for symptom score of rhinitis.

The MAH stated that nebulisation is able to deliver drugs to paranasal sinuses while nasal sprays are not. However, the study referred to enrolled 5 healthy adults, which is not a representative sample.

Finally, recent evidence reports that distribution of topical solution to the unoperated sinuses is limited, with nebulization being also ineffective with <3% sinus penetration. Cain and colleagues.⁵

In conclusion, the CHMP considered that the available evidence does not support the proposed indications in "allergic and idiopathic rhinitis, inflammatory and allergic affections of the nasal cavities and of the rhino-pharyngeal tract" for nBDP.

Section 4.2 – Posology and method of administration

Maximum daily dose

The MAH proposed harmonised dosing recommendations based on the doses studied in clinical trials and in line with GINA guidelines.

On review of all available data including post marketing safety data the CHMP concluded that a maximum of 3200 ug daily dose of BDP in adults and adolescents, which is in line with the current recommendation in Germany, Ireland and Greece and of a maximum of 1600 ug daily dose in children, which is in line with the current recommendation in France, is acceptable.

Once daily vs twice daily administration

Based on a review of the available data, the CHMP considered that both once daily and twice daily dose regimens are acceptable. In the clinical managing of asthma, patient adherence to long-term inhaled therapy is of extreme importance and the possibility of a once daily administration should not be precluded. More importantly, ICS therapy is always patient-tailored and closely monitored by the physician in terms of symptom controls, thus precluding the occurring of prolonged unsatisfactory symptom control because of once-daily administration.

Duration of Therapy

Asthma and wheezing

The CHMP concluded that for asthma treatment no indication of duration of therapy should be reported in the SmPC; the duration of treatment should be based on clinical judgement on the basis on the severity and frequency of symptoms and patient conditions on a case-by-case basis.

³ Profita M. et al 'Effect of Nebulized Beclomethasone on Airway Inflammation and Clinical Status of Children with Allergic Asthma and Rhinitis: A Randomized, Double-Blind, Placebo-Controlled Study'. Int Arch Allergy Immunol 2013; 161:53–64.

⁴ Allergic Rhinitis and its Impact on Asthma (ARIA) guideline 2015: Available from <http://www.whear.org/Documents&Resources.php>

⁵ Cain et al. 'European Position Paper on Rhinosinusitis and Nasal Polyps' 2012; Update on the management of chronic rhinosinusitis. 2013; Infect Drug Resist.

For the recurrent wheezing indication in young children, the CHMP concluded that if no treatment benefit of is observed within 2-3 months, Clenil should be discontinued. In addition, the duration of treatment of recurrent wheezing should not exceed 3 months, unless diagnosis of asthma is confirmed to avoid an unnecessary long-term exposure. Cross-reference with section 4.4 is also mentioned.

Method of administration

The MAH proposed to revise the SmPC section 4.2 to include more detailed information on the nebuliser systems. The CHMP considered that the inclusion of the brand nebulisers in section SmPC 4.2 was not acceptable as the data to support this were not available. As such reference is not made to a brand rather to a “jet nebuliser” in the product information.

Other sections of the SmPC

Sections 4.3 Contraindications to 5.3 Preclinical safety data have been harmonised to include the relevant available information, or amend wording according to the attest QRD template.

Section 1, (name of the medicinal product) Sections 2 (qualitative and quantitative composition), 6.1 (list of excipients), and 6.2 (incompatibilities) have been updated with minor changes to be in line with QRD template.

Sections 6.3 (shelf life), 6.4 (special precautions for storage) 6.5 (nature and contents of container) and 6.6 (Special precautions for disposal and other handling) have been updated in line with the recommendation for multi-use of the 800 ug ampoule.

Labelling

Changes introduced in the SmPC were consistently reflected in the labelling where relevant, however most sections were left to be completed nationally.

Package Leaflet

The package leaflet has been amended to reflect the changes of the SmPC

Grounds for the CHMP opinion

Whereas

- the scope of the referral was the harmonisation of the product information,
- the product information proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,
- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the divergences identified in the notification for Clenil and associated names, as well as the remaining sections of the product information.
- The committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information.
- The committee agreed on a harmonised product information for Clenil and associated names.