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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 30 of Directive 2001/83/EC

Clenil and associated names

INN: beclometasone dipropionate

Procedure number: EMEA/H/A-30/1418

Note:

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

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1. Background information

Due to the divergent national decisions taken by Member States concerning the authorisation of nebulised beclometasone dipropionate (nBDP) 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.

2. Scientific discussion

2.1. Introduction

Beclometasone dipropionate 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 is currently available as metered-dose inhaler (MDI), dry powder formulation (DPI), nasal spray and as nebuliser suspension. Nebulisation allows delivering of BDP to the lung and, with respect to MDI, does not require co-ordination of hand movements during drug administration. For MDIs use of a spacer improves delivery and with inhaled corticosteroids (ICS) reduces the potential for side-effects. When administered as a nasal spray via the intranasal route beclometasone dipropionate is used in the management of vasomotor and allergic rhinitis.

BDP nebuliser 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 nebulised beclometasone dipropionate (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). 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 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.

2.2. Critical Evaluation

Submitted supporting data consisted of published studies conducted with nBDP. These studies, reviews and meta-analyses as well as post marketing safety data have been assessed together with the current relevant guidelines (Global Initiative for Asthma [GINA] Global Strategy for Asthma Management and Prevention, European Respiratory System [ERS] task force).

The PI of nBDP-containing products currently approved in the EU countries and some additional published reviews on the use of the ICS in the management of asthma, wheezing and allergic rhinitis have also been taken into account.

In addition, a third party intervention concerning the indication allergic and idiopathic rhinitis, inflammatory and allergic affections of the nasal cavities and of the rhino-pharyngeal tract has been submitted and taken into account by the CHMP.

It is hereafter summarised the main points discussed for the harmonisation of the different sections of the product information.

2.2.1. Product information

Summary of Product Characteristics

Section 4.1 – Therapeutic indications

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 population in terms of age groups in the EU is adults and children (without a lower age limit) in Italy, Germany, Ireland, and Greece, but children only in France. The MAH defines the paediatric population for which the product is approved to be the overall paediatric population without excluding infants and toddlers.

The CHMP agreed with the indication "in the maintenance treatment of asthma" in line with the available scientific evidence and guideline recommendations where ICS 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.

In support of this indication sixteen clinical studies (twelve of which including paediatric population) have been submitted in asthmatic patients with nBDP. 916 patients were enrolled and 735 included in the Intention-to-treat (ITT) analysis.

The studies include a large number of patients with various severity of disease. These studies showed that nBDP (as other corticosteroids) is an effective and safe treatment for asthmatic patients. These results are in line with the GINA guideline which recommends ICS as first-line treatment for all patients requiring regular anti-inflammatory therapy.

The CHMP noted that it is well known from guidelines that the main aim of the continuous treatment of asthma is to reduce the burden to the patient, the risk of exacerbations and the airway damage. As clearly explained in the recent GINA guideline, asthma treatment is adjusted in a continuous cycle based on initial assessment and on review of the response. Regular daily controller treatment should be initiated as soon as possible after diagnosis of asthma if any of the following conditions are met: symptoms more than twice a month, awakening due to asthma more than once a month, asthma symptoms plus any risk factor for exacerbation (need of oral corticosteroids within the last 12 months, low forced expiratory volume in 1 second (FEV1), admission to intensive care unit for asthma).

The recommendation to use nBDP "when the use of pressurised or dry powder inhalers is unsatisfactory or inappropriate" is in line with GINA recommendations (see table 1 below). stating that nebulizers should be considered (mainly for children less than 5 years) as an alternative device "for the

small number of children who cannot be taught effective use of a spacer device or for those too immature to use one themselves and thus require the assistance of a caregiver (i.e. parent)…".

In addition, the equivalent efficacy and safety of nBDP and BDP administered by pressurised meter-dose inhaler (pMDI) plus spacer has been demonstrated in adult patients in the published studies considered.

Table 1

Age	**Preferred device**	**Alternative device**
0-3 years	Pressurised metered dose inhaler plus dedicated spacer with face mask	Nebuliser with face mask
4-5 years	Pressurised metered-dose inhaler plus dedicated spacer with mouthpiece	Pressurised metered-dose inhaler plus dedicated spacer with face mask or nebuliser with mouthpiece or face mask

The CHMP considered whether the indication should include adults given that in one member state (France) the approved indication of nBDP is restricted to paediatric population. However, according to the provided evidence, the restriction of the use of nBDP to children with severe persistent asthma only is not justified. Adequate scientific evidence has been provided to support the proposed indication in both adults and children.

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.

The following evidence has been presented in support of the different broad wording indication and discussed by the CHMP:

Studies conducted with nBDP

The MAH submitted 5 studies (4 of which had a positive outcome) conducted with nBDP in 858 patients with bronchostenotic conditions to support the proposed indication. Three studies, Maayan et al., 1986, Ghirga et al., 2002 and La Force et al.,1993 are small undersized studies conducted in infants which show a favourable trend in the reduction of wheezing episodes, but require confirmation from adequately powered studies.

The other two studies discussed by the MAH are randomised clinical trials (RCT). One RCT enrolled 276 children aged 1-4 years, with at least 3 wheezing episodes in previous 6 months, which were assigned to three groups of treatment: (1) nBDP plus salbutamol pro re nata (prn, as needed) (2) or placebo plus nBDP/salbutamol combination prn or (3) placebo plus salbutamol prn for 3 months. It was demonstrated that the percentage of symptom-free days (defined as a lack of wheezing, coughing,

shortness of breath and patients/parents nocturnal awakenings in 24 h) was significantly higher with the regular use of nBDP plus salbutamol (69.6 ± 20.89 [SD]; P = 0.034) as compared to placebo plus salbutamol prn (61.0 ± 24.83 [SD]), regardless of the presence of risk factors for developing asthma (Papi et al., 2009).

Another placebo-controlled RCT, enrolled 525 children aged 1-4 years, with at least one episode of wheezing in previous 12 months. The trail was aimed at investigating if nBDP was effective in reducing the incidence of viral wheezing diagnosed by paediatricians during a 10-day treatment period. The risk reduction of wheezing episodes did not reach statistical significance even if the BDP group showed a reduced number of episodes (6.8% vs 11.1%) (Clavenna et al. 2014).

Although indicating a positive trend favouring ICS, the two RCTs provide limited evidence of efficacy either because of methodological bias (lack of unequivocal definition of symptom-free days, Papi 2009) or lower occurrence of events compared to what expected (loss of power, Clavenna et al .2014).

Other evidence provided in support of the claimed indication can be derive from meta-analyses/reviews including studies performed with different ICSs, guidelines and consensus group reports as follows:

Meta-analysis, consensus group reports, reviews and guidelines on ICS.

a) Castro-Rodriguez's meta-analysis included 29 RCTs (published from January 1996 to March 2008) in a total of 3,592 patients with a minimum treatment of 4 weeks of ICS. The primary outcome was the reduction of wheezing/asthma exacerbations. Although limited to only two relevant databases, the meta-analysis appears of good quality, the studies are presented clearly and methods used to pool data seem appropriate. Results show that ICS treatment decreased the proportion of patients with exacerbations compared to placebo (18.0% and 32.1%, respectively), with a RR of 0.59 (95% CI: 0.52–0.67). In addition sensitivity analyses were conducted to explore heterogeneity. Although patients with wheeze who received ICS showed a significant reduction of wheezing/asthma exacerbations compared with those taking placebo, their response to treatment was less pronounced compared with asthmatic patients. Of note, treatment effect was independent of age, atopic status, type of ICS, mode of delivery (metered-dose vs nebulizer) and duration (<12 vs > 12 weeks).

b) The systematic review, by Kaiser et al. published in 2016, provides some evidence to support the use of intermittent ICS (as a therapeutic class) for preventing exacerbations in pre-schoolers (children <6 years of age) with intermittent asthma or recurrent viral-triggered wheezing. However, the results of the meta-analysis cannot be used as a scientific ground to support the claimed indication in the treatment of inflammatory disorders associated with wheezing for the nBDP as the studies conducted with nBDP do not contribute significantly to the total result of the meta-analysis (wide, non significant CI for their risk-ratio).

c) The Cochrane review by McKean and Ducharme, 2000 investigated the efficacy of ICS in reducing frequency, severity and duration of wheezing episodes in children/adolescents under 17 years of age suffering from 'episodic viral wheeze' associated with clinical viral infections. Five RCTs with low-dose maintenance and high-dose episodic ICS therapy were included. Two studies (Wilson et al , 1995 and Duoll, 1997) with maintenance ICS therapy, conducted in pre-school and school children treated with budesonide 400 µg/day by pMDI with spacer or BDP 400 µg /day by DPI, over a period of 4-6 months, did not show any reduction over placebo in the proportion of episodes requiring hospital admission (n=1 trial, RR=0.21, 95% CI: 0.01,4.11) or those requiring oral CS (n=2 trials, RR=0.82, 95%CI:0.23,2.90). The other 3 studies performed in preschool children, investigated the efficacy of budesonide 1600-3200 µg/day by pMDI or BDP 2,250 µg daily pMDI plus spacer, for about 5 days over a period of 6 months-2 years. The pooled results of the 2 cross-over trials by Connettett al. 1993 and Wilson et al.1990, showed a reduced requirement for oral CSs although not quite at the level of statistical significance (RR=0.53, 95% CI: 0.27, 1.04). The pooled results from the 3 studies (Wilson et

al, 1990, Connett et al, 1993 and Svedmyr et al, 1999) showed a 33% reduction in episodes requiring oral CSs with no indication of statistical significance as no methodology is agreed upon on how to combine trials with different design (parallel and cross-over). The review authors conclude that high-dose ICS (1.6-3.2 mg) can provide a partially effective strategy for the treatment of mild episodic viral wheeze.

d) Further evidence comes from the review on wheezing management in pre-school patients by Bush et al., 2014. The review aimed at assessing the role of intermittent montelukast and oral corticosteroids (CSs) and ICS in children with episodic viral wheezing or multiple trigger wheezing. The conclusions of the review on corticosteroids use are mainly based on the results from 4 RCTs conducted with ICS and 2 RCTs investigating oral CSs. The trials with ICS (Bacharier et al., 2008; Ducharme et al., 2009; Zeiger et al., 2011; Wilson et al., 1995) were published recently and were not included in the meta-analysis by Castro-Rodriguez and Rodrigo (2009). They were conducted in children with intermittent viral wheezing, treated for 7-10 days over a time period of about 1 year, and had different primary endpoints (proportion of episode-free days/episode number, rescue oral corticosteroid use, or daily symptom score). The review concludes that in episodic viral wheezing, only high dose ICS proved to be efficacious, when used “on demand” for very short time-periods, although the increased frequency and severity of side effects do not allow the authors to recommend their use. However, the authors are of the opinion that the decision to treat should be based on the frequency and severity of symptoms/episodes, as children with recurrent exacerbations/year and/or multiple trigger wheezing are more likely to benefit from longer treatment periods with standard doses of inhaled corticosteroids.

e) In the consensus report on classification and pharmacological treatment of preschool wheezing (Brand et al., 2014) and in the review by Ducharme et al., 2014, the following treatment strategy is suggested:

- Daily ICS seem to be the most effective therapy for recurrent wheezing in trials of children with intercurrent symptoms or atopy; intermittent high-dose inhaled corticosteroids are effective in moderate-to-severe viral-induced wheezing without interim symptoms (Ducharme et al., 2014)
- ICS remain first-line treatment for multiple-trigger wheeze, but may also be considered in patients with episodic viral wheeze with frequent or severe episodes, or when the clinician suspects that interval symptoms are under reported (Brand et al., 2014).

f) Wheezing in preschool children has been considered in the GINA 2015 and its update version 2016. While high dose ICS for asthma exacerbations or wheezing episodes is not generally encouraged because of substantial concern about the potential long-term systemic side-effects, regular daily, low dose ICS (controller treatment) is recommended as the preferred initial treatment to control asthma in children 5 years and younger. However, a stepwise treatment approach is recommended (regular ICS should be undertaken first plus as-needed SABA as needed) based on symptom patterns, risk of exacerbations and side-effects, and response to initial treatment.

The initial controller treatment should be given for at least 3 months to establish its effectiveness in achieving good asthma control.

On the same view is the European Respiratory System (ERS) Task Force (2014): the two main reasons for starting a ICS therapy in preschool children with wheeze are i) frequent symptoms (on most days of the week, responding to β2-agonists) or ii) frequent and severe acute episodes. If there is no benefit of the controller therapy started after 2-3 months, it should be discontinued and the child investigated further.

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 guideline. 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-schoolers is limited (the only supportive scientific evidence comes from Papi et al., 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 (see duration treatment and need of monitoring in SmPC sections 4.2 and 4.4).

Paediatric age range

BDP 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.

Twelve published studies including paediatric patients were provided by the MAH with nBDP in the treatment of asthma, enrolling patients aged > 6 months to 12 years of age. These trials provide adequate scientific evidence to support the proposed indication in the paediatric population and are in line with the main guidelines which clearly indicate the use of low dose ICS as first-line continuous treatment in children below the age of 5 years.

Regarding infants < 6 months of age, the CHMP noted that limited information is available with Clenil, as such the following reference documents were also taken into account:

i) According to GINA 2015 Guideline (Chapter: children 5 years and younger) although pressurized metered-dose inhaler plus dedicated spacer with face mask are the preferred choice for delivery of medicinal products Inhaled Corticosteroids included, nebulizers with a mouthpiece to avoid the medication reaching the eyes represent the only viable alternative delivery systems in children 0-3 years, when the use of hand-held inhalers is unsatisfactory or considered inappropriate.

ii) "Report of the expert meeting on paediatric asthma" (PDCO 20 October 2010) concludes that "The cut-off age for inclusion of children into clinical trials evaluating anti-asthmatic drugs, was discussed at

some length. There was consensus that inclusion of children < 6 months is not recommended as both classic asthma as well as episodic wheezing triggered by viral infection require an opportunity to observe the clinical pattern with time:....." However, cut-off values "are rather arbitrary as no hard evidence is available to support either of them. The majority of participants therefore thought that 6 months could be recommended."

iii) Draft "Note for guidance on clinical investigation of medicinal products for treatment of asthma" (CHMP/EWP/2922/01 Rev. 1 2013) states that "The inclusion of infants < 6 months in clinical trials to evaluate drugs for the management of asthma is not recommended." and that "Due to differences in asthma pathology extrapolation of data from adults or older children is not considered appropriate."

Overall, the CHMP agreed that the use of Clenil in very young children (infant and toddlers) is justified by the indication to use nBDP in cases when the use of hand-held inhalers is unsatisfactory or considered inappropriate. In addition since clinical development of medicinal products for asthma treatment is only possible from 6 months of age as the diagnosis of asthma requires an opportunity to observe the clinical pattern with time, development of inhaled product will never be performed in children < 6 months of age, therefore data will never become available. However, this does not exclude the possible need of nBDP below 6 months of age. Of note, there is no contraindication for use of beclometasone in children less than 6 months.

As regards the indication in wheezing, the term “preschool” as proposed by the MAH is not informative and not in line with the SmPC guideline. The most supportive evidence for the treatment of recurrent wheezing children (Papi et al., 2009) 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 it more appropriate to leave it open.

Allergic and idiopathic rhinitis, inflammatory and allergic affections of the nasal cavities and of the rhino-pharyngeal tract

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

The evidence provided by the MAH in support of this indication consisted of 4 studies, only one of which is a RCT (Profita et al., 2013). This study is a randomized, double-blind, placebo-controlled study aimed at assessing the efficacy of nBDP versus placebo, conducted in children between 8 and 14 years with concomitant allergic mild intermittent asthma and allergic rhinitis. As the authors underlined, no differences were observed between the group treated with nBDP and with the placebo for symptom score of rhinitis, whereas, the treatment was shown to be useful in children with concomitant allergic asthma, a condition where the use of nBDP has been well established. Furthermore, in the conclusion, the author suggested to add a nasal steroid spray to increase the impact of upper airway inflammation on nasal symptoms if those patients did not reach a satisfactory symptoms control.

The other 3 studies quoted by the MAH are uncontrolled and conducted in adolescents and adult patients.

According to the most recent guidelines (i.e. Allergy 2008 and Allergic Rhinitis and its Impact on Asthma (ARIA) 2015), 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. 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 et al., 2013 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 nebulization is able to deliver drugs to paranasal sinuses while nasal sprays are not. However, the study which the MAH (Möller et al., 2010) referred to enrolled 5 healthy adults, which is not a representative sample. No evidence is therefore available to support the expert's theory.

Finally, there is evidence that distribution of topical solution to the non-operated sinuses is limited, with nebulization being ineffective with <3% sinus penetration.

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.

Third party Intervention

A letter from two physicians was submitted for review by the CHMP. Referring to the ongoing referral procedure, the letter supports the role of nBDP in the clinical treatment of allergic and vasomotor rhinitis (idiopathic rhinitis).

The beneficial effect of intranasal BDP in the treatment of allergic and vasomotor rhinitis (idiopathic rhinitis) in adults and children as well as the mechanism of action for the anti-inflammatory activity of corticosteroids (both systemic and topic use) is widely discussed by the experts who declare that they regularly use nBDP to treat allergic and vasomotor rhinitis in their department.

Besides a quotation of the "joint task force on practice parameters" which states that "intranasal corticosteroids are effective in the treatment of vasomotor rhinitis", no scientific evidence in support to nBDP suspension were provided.

On review of the information and argumentation provided in the letter the CHMP concluded that the provided experts' opinion is acknowledged, but will not change the CHMP position that the indication of nBDP in the treatment of allergic rhinitis is currently not acceptable.

In conclusion, the final agreed wording for section 4.1 is hereafter:

Clenil is indicated for the:

- maintenance treatment of asthma, when the use of pressurised metered dose or dry powder inhalers is unsatisfactory or inappropriate, in adults and children up to 18 years of age;
- treatment of recurrent wheezing in children up to 5 years of age (see sections 4.2 and 4.4 paediatric population).

Section 4.2 – Posology and method of administration

Maximum daily dose

The minimum and maximum daily dosages currently approved in the EU Countries where Clenil is authorised are:

- 800 micrograms in children, 1600 to 3200 micrograms in adults and adolescents in Germany, Ireland and Greece
- 400 to 800 micrograms in children, 800 to 1600 micrograms in adults and adolescent in Italy
- 800 to 1600 micrograms in infants in France

The CHMP noted that in clinical practice, the actual corticosteroids posology range varies significantly and is strictly related to the therapeutic indications and severity of the disease. The GINA guideline recommends a wide dose range of beclometasone dipropionate (chlorofluorocarbon propellant) per day from 200 micrograms to > 1000 micrograms of in adolescents and adults, from 100 micrograms to >400 micrograms for children 6-11 years of age, and 100 micrograms hydrofluoralkane propellant in children < 5 years of age. Although most of the benefit from inhaled corticosteroids is achieved at relatively low doses, usually very high doses of inhaled corticosteroids continue to be used and there are also reports of significant side effects occurring with high dose inhaled corticosteroids use.

In most of the clinical studies provided to support the efficacy and safety of the nBDP in the proposed therapeutic indications, the maximum daily dose ranges from 800 to 1600 microgram.

A dose of 2400 microgram was used in the study comparing efficacy and safety of nBDP 2400 ug/die (twice daily) with nebulised fluticasone propionate 1000 microgram/die (twice daily) (Terzano 2003).

A maximum daily dose of 3200 microgram was used only in one sponsored single-dose PK study (Poli et al., 2003) in healthy adults showing comparable AUC values of the active metabolite B17MP when nBDP 3200 microgram or BDP 1600 microgram administered via pMDI, were used. Consistently, no significant differences were found with respect to the serum or urinary cortisol PK parameters, demonstrating equivalent systemic effects on the hypothalamic-pituitary-adrenal (HPA)-axis of BDP 1600 microgram given via MDI and BDP 3200 microgram given via nebuliser.

The CHMP agreed that the clinical trial data alone do not allow to conclude that higher doses of BDP are needed when used as nebuliser suspension compared to pressurised suspension for inhalation, however the data suggest that no relevant differences in the safety profile should be observed following the administration of a maximum daily dose of BDP 3200 micrograms given via nebuliser.

The CHMP further noted that a maximum daily dose of BDP 3200 micrograms dose has been authorised in 3 countries in the EU with no evidence of emerging safety concerns. However, it must be recognised that the lack of safety signals could be due to under-reporting, considering that the dose is usually down-titrated once disease control is achieved.

In order to be able to conclude on this matter, the CHMP requested the MAH to provide post-marketing safety data confirming that the maximum dose of 3200 micrograms in adults and adolescents has been used over a long period of time with no emergence of relevant safety signals. A total of 312 cases (592 Adverse Drug Reactions, ADRs) were cumulatively collected up to 30 September 2015. In most of the cases (246 cases, 513 ADRs), the daily dose range was below 3200 micrograms. In only 4 cases (8 ADRs), the daily dose is ≥ 3200 micrograms. Two of these cases may suggest an overdose based on the reported ADRs. In addition, the MAH has reviewed 62 cases (71 ADRs) with missing information on the daily dose.

The analysis did not raise any concern regarding the potential for systemic complications associated with long-term treatment. Taking into account these data the CHMP concluded that a maximum of 3200 micrograms 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 micrograms daily dose in children, which is in line with the current recommendation in France, is acceptable.

Once daily vs twice daily administration

Adults

Currently only in Italy, the regimen "once or twice" daily dosing is approved; in Germany, Ireland, Greece and France (for children only) only the regimen twice daily is approved.

One randomised cross-over trial performed in 24 well-controlled asthma patients compared the efficacy of once-daily and twice-daily regimen of ICS administered for 16 weeks in terms of changes in several lung function parameters (FEV1, morning and evening peak expiratory flows, PEF), asthma symptoms, health-related quality of life and fractional exhaled nitric oxide levels. The same level of clinical control and lung functions was observed in patients receiving once- and twice-daily administration. However, the difference in fractional exhaled nitric oxide level between the beginning and end of the treatment was significantly higher only at the end of the once-daily treatment (33.87 and 39.38ppb, respectively, $p < 0.001$) (Hasegawa, 2008).

A comparable control of asthma symptoms for once- and twice-daily regimen of inhaled BDP was observed both in a 2-month study enrolling 42 patients with stable mild to moderate asthma (Gagnon, 1994) as well as in a 2-month RCT trial enrolling 201 patients with mild to moderately severe asthma (Gillissen, 2007).

In a 12-week, randomized, double-blind, double-dummy, parallel-group study, 617 patients with mild to moderate persistent asthma (not optimally controlled on inhaled corticosteroids) were randomized to once-daily budesonide/formoterol (80/4.5 mg, 2 inhalations in the evening), twice-daily budesonide/formoterol (80/4.5 mg, 1 inhalation), or a corresponding dose of budesonide once-daily. (200 mg, 1 inhalation in the evening). Changes in mean morning PEF as well as in all lung function parameters investigated were similar for once daily and twice daily regimens (Kunaa et al., 2007).

Further evidence is available for comparable efficacy in asthma symptom control of once-daily 'evening' dosing and twice-daily regimen both for mometasone furoate-DPI given to patients previously dependent on twice a day ICS therapy (D'Urzo et al., 2005) and fluticasone furoate-DPI given to patients with persistent asthma maintained on ICS for ≥ 3 months (Woodcock, 2011, D'Urzo et al., 2005).

Moreover, the improvement in treatment adherence achieved with the once daily dosing regimen has been demonstrated in a 12-week open-label study in patients ≥12 years old with mild-to-moderate persistent asthma receiving mometasone furoate-DPI 400 µg once-daily in the evening or mometasone furoate-DPI 200 micrograms twice daily. The mean adherence rates, as measured by the automatic dose counter, were significantly better ($P < 0.001$) with MF-DPI 400 micrograms once daily in the evening (93.3%) than with MF-DPI 200 micrograms twice daily (89.5%) (Price et al.,2010).

Although long-term effects on inflammatory and remodelling parameters have not been investigated for the once daily regimen of ICS treatment (Boulet 2004) considering the improvement in patient adherence and all the available evidence of similar efficacy between once and twice daily regimen of ICS, a once daily regimen, once the asthma symptoms are under control, is endorsed by CHMP.

Children

Few controlled clinical trials have been performed in asthmatic children comparing the efficacy of once versus twice daily dosing of ICS. Except for budesonide, for which several studies showed similar efficacy in controlling childhood asthma following once daily administration using a DPI or a nebuliser and twice daily administration (Moller et al., 1999; Shapiro et al., 2001), only preliminary results have been published on effective childhood asthma control with once daily administration of other ICSs. In adult patients with asthma, once daily doses of 1000 micrograms BDP given via a pressurised pMDI provided contrasting results. Of note, review by Kelly et al. 2009, performed through a MEDLINE and PubMed search limited to the time period 2001-2008, concluded that ICS demonstrate efficacy with once daily dosing, but all are more effective when dosed twice daily.

The MAH cites a double-blind, double dummy, randomised, multicentre study on nBDP, performed by La Grutta et al., 2007, in which asthmatic children, not treated with ICS for at least a month preceding

the study and using short-acting bronchodilators more than once a week were enrolled. After a two-week run-in period on nBDP twice daily 400 micrograms, patients were randomly assigned to twelve weeks of treatment with 800 micrograms nBDP daily, either in single dose (once daily group) or divided into two 400 micrograms doses (twice daily group). Sixty five children (mean age 8.6 years, mean FEV1 81% of predicted) were valuable for intention to treat.

A significant increase in FEV1 and Forced vital capacity (FVC), both evaluating the children as a whole group or as twice daily and once daily groups, was observed at the end of the run in period and maintained in both treatment groups throughout the duration of the study period without significant difference between visit 2 (randomization) and visit 5 (end of treatment) or between the two treatment groups.

Morning and evening PEF showed a progressive increase and PEF diurnal variability showed a progressive reduction in the two treatment groups during the whole study period without reaching statistical significance.

The study was designed to show superiority but failed to detect a significant difference between once daily and twice daily group, and was not able to show assay sensitivity since only one dose level was investigated. Although from a methodological point of view, it is not possible to conclude that BDP once daily was not inferior to BDP twice daily, the evaluation of the FEV1 and FVC curves over time show very similar efficacy patterns, and equally sustained effect in both groups during the 12-week study period.

Although the CHMP acknowledge the paucity of data, both once daily and twice daily dose regimens are considered 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 due to the once-daily administration.

Duration of Therapy

Asthma and wheezing

No treatment duration is proposed in the harmonised product information by the MAH as the medicinal product is intended for both long-term treatment, when used in the management of asthma, and short-term treatment, when used for recurrent wheezing. Therefore, a case-by-case decision should be taken by the physician taking into account the severity and frequency of symptoms.

In addition, it is argued that other nebulised ICS product information do not include any information on the treatment duration (Pulmicort-budesonide, Flixotide-fluticasone, Forbest-flunisolide).

Indeed GINA guidance states that regular daily controller asthma treatment should be initiated as soon as possible after the diagnosis is made and that the patient's response should be reviewed and treatment stepped down once good control is achieved.

Considering young children (up to 5 years of age), GINA guideline states that the initial ICSs controller treatment should be given for at least 3 months to establish its effectiveness in achieving good asthma control. On the same view is the ERS Task Force (2014) which reports that if there is no benefit of the controller therapy started after 2-3 months, it should be discontinued and the child investigated further. As reported by a recent review on the managing of multiple trigger wheeze in preschool children (Bush et al., 2014), prophylactic inhaled corticosteroids for a defined period, reasonably 4 to 8 weeks, is suggested.

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.

For the recurrent wheezing indication in young children, the CHMP concluded that if no treatment benefit 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 because a comparative in-vitro study between the proposed branded nebulizers and the PARI LC Plus used in the clinical and pharmaceutical development of nBDP as well as statistical data to demonstrate that the variability in the delivery performance of the different nebulizers falls within acceptable ranges were not provided. In addition, in-vitro data describing the delivery characteristics of the nebulizers were not informative and did not allow concluding on their comparable performance. As such reference is not made to a brand rather to a “jet nebuliser” in the product information.

The final agreed wording for section 4.2 is specified in the attached SmPC Annex III

Section 4.3 – Contraindications

Clenil is currently contraindicated in case of hypersensitivity to the active substance or to any of the excipients. Minor rewording to be in line with QRD template has been made to this section.

The final agreed wording for section 4.3 is specified in the attached SmPC Annex III

Section 4.4 – Special warnings and precautions for use

The content of this section is currently broadly the same across member states.

A new paragraph has been added in line with the indication of treatment of wheezing in children up to 5 years, to warn that regular follow-up is essential to review the treatment response. If no treatment benefit is observed within 2-3 months or if a diagnosis of asthma is not likely, Clenil should be discontinued to avoid unnecessary long-term exposure to inhaled corticosteroids and associated risks in children including growth retardation with cross-reference to section 4.8.

Furthermore a paragraph has been included to be in line with the SmPC of other corticosteroids that warns that the increasing use of bronchodilators, in particular short-acting inhaled beta2-agonists to relieve symptoms indicates deterioration of asthma control. In this situation patients should be re-assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids).

The final agreed wording for section 4.4 is specified in Annex III of the CHMP opinion.

Section 4.5 – Interaction with other medicinal products and other forms of interaction

The CHMP noted that currently across member states there is no information reported on PK interaction. The MAH confirmed that no data is available and this section now reflects the fact that no formal PK drug-drug interaction studies have been conducted according to the SmPC guideline.

The final agreed wording for section 4.5 is specified in Annex III of the CHMP opinion.

Section 4.6 – Fertility, pregnancy and lactation

The content of this section is currently broadly the same across member states. Available data in animal and humans suggest reproductive toxicity.

Although safety data on high dose inhaled BDP therapy during pregnancy are sparse, in light of some literature evidence on the positive association between high doses of inhaled glucocorticoids (≥ 1000 micrograms) and incidence of malformations, a recommendation that the lowest effective dose of BDP to control asthma symptom has been included.

To be in line with the SmPC guideline the paragraph on pregnancy was re-arranged to start with human data, followed by the results from the animal studies. Reference has be made to section 5.3 where the information on teratogenic effects and fertility in animals is mentioned.

With regards to breast feeding, PK data show that the main active metabolite of BDP, beclometasone-17- monopropionate (17-BMP), has a bioavailability of 62 % after inhalation, as such it can be assumed, that after high inhaled doses of BDP the infant may be exposed to significant amounts of the substance via breast milk. Therefore, a recommendation on avoiding breast-feeding for 4 h (mean elimination half-life of 2.7 hours for the active metabolite 17-BMP) after inhalation of high dose inhaled BDP is made.

The final agreed wording for section 4.6 is specified in Annex III of the CHMP opinion.

Section 4.7 – Effects on ability to drive and use machines

Information in this section consistently reflects across member states that Clenil does not affect the ability to drive or use machines.

No changes have been made to the SmPC in this section.

Section 4.8 – Undesirable effects

The most common adverse reactions observed during clinical trials using inhaled BDP were laryngitis, pharyngitis and oral candidiasis.

A number of discrepancies were noted between the nationally authorised SmPCs, notably ADRs where reported in some SmPCs but missing in others. In addition there was a need to re-calculate the frequency and re-define some ADRs according to MedDRA 18.1. The CHMP also noted this section is currently not in line with the SmPC guideline in all the member states where Clenil is approved.

As a result the whole section has been reworded and updated according to SmPC guideline.

The final agreed wording for section 4.8 is specified in Annex III of the CHMP opinion.

Section 4.9 – Overdose

The MAHs made a proposal that “the use of Clenil in doses exceeding 4,000 micrograms per day over a long period of time could lead to adrenal suppression”. However CHMP noted that currently in the Irish SmPC doses exceeding 3,000 micrograms per day are cited. As the MAH did not justify this increase the following statement has been agreed: “The use of beclometasone dipropionate nebuliser suspension in doses exceeding those recommended over a long period of time could lead to suppression of hypothalamic-pituitary-adrenal (HPA)-axis function."

The final agreed wording for section 4.9 is specified in Annex III of the CHMP opinion.

Section 5.1 – Pharmacodynamic properties

Section 5.1 has been reworded in order to be in line to the SmPC guideline and to avoid inconsistencies among information reported in different sections.

The main supportive published data for indications in asthma and wheezing were reported under "Clinical efficacy and safety" section including bibliographic reference.

The final agreed wording for section 5.1 is specified in Annex III of the CHMP opinion.

Section 5.2 – Pharmacokinetic properties

The CHMP noted that relatively few quantitative data are presented in this section, e.g. information on clearance rate, distribution volume and elimination half-life of BDP and its major metabolite is not yet given.

As such this information has been added and a paragraph included regarding PK of BDP in special populations has been included.

The final agreed wording for section 5.3 is specified in Annex III of the CHMP opinion.

Section 5.3 – Preclinical safety data

Generally there were no significant divergences across the national SmPCs.

The final agreed wording for section 5.3 is specified in Annex III of the CHMP opinion.

Other sections of the SmPC

In section 1 the denomination has been changed from "Clenil 400 micrograms/1 ml nebuliser suspension" and "Clenil 800 micrograms/2 ml nebuliser suspension" to "CLENIL 400 micrograms nebuliser suspension" and "CLENIL 800 micrograms nebuliser suspension", in line with QRD recommendations on the expression of strength in the name of centrally authorised human medicinal products (EMA/707229/2009).

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 the 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 micrograms ampoule.

Currently in Italy Clenil 800 micrograms /2 ml ampoule is authorised to be used for two doses and the ampoule has a graduation mark. In the majority of other member states Clenil is only authorised for single use even in the presence of the graduation mark (Ireland and Greece).

The CHMP took into account the following available data on the multiuse of the 800 micrograms /2 ml ampoule.

The ampoules of Clenil do not contain preservatives and they are sterile. The primary packaging of both the presentation of Clenil is supplied with a twist-off cap which allows the patient to close the ampoule once opened. A large amount of data has been provided on a representative sample showing that the present closure system prevents the microbial contamination of the product. The acceptance criteria used are those for inhalation use, listed in the Ph.Eur. 5.1.4 Microbiological Quality of non-sterile pharmaceutical preparations and substances for pharmaceutical uses. All the obtained results comply with the Ph.Eur. requirements.

The suitability of both 1 and 2 ml ampoules to prevent microbial contamination during the storage and use in the short term has been demonstrated through an in-use simulation study performed on 120 second half-doses of three batches stored both at room temperature and at 2-8°C for 12, 24 and 48 hours and tested for Total Aerobic Microbial Count and Total Yeast Mould Counts values and for the absence of Staphylococcus aureus, Pseudomonas aeruginosa and Bile-tolerant Gram-negative Bacteria in accordance to Ph.Eur. 5.1.4.

One study challenging microbial contamination has also been performed to show that the suspension does not provide a suitable growth substrate to micro-organisms and chemical stability of the half-dose stored at 2-8 °C for 18 hours has been investigated and compliance to specification limits for assay and related substances demonstrated.

Taking into account that the product has been safely used according to the approved storage instructions in Italy for more than 14 years and based on a large amount of data showing an extremely low microbial growth both at room temperature and at the proposed storage conditions of 2-8°C even up to 48 hours, the use of the half-dose for 800 micrograms ampoule is endorsed. Thus, the ampoule closure system is considered suitable to prevent microbial contamination at the proposed storage and in-use conditions. 400 micrograms ampoule remains for single use.

Moreover, the graduation mark demonstrated to allow accurate and precise dispensing of two half-doses.

In SmPC section 6.3 is reported that the ampoules should be used within 3 months from the first opening of the pouch; for 800 micrograms ampoule only, it is stated that after the first opening of the ampoule, it should be stored it in a refrigerator (2°C – 8°C) and that the remaining quantity has to be used within 12 hours after first opening.

The MAH has provided suitable justification for the recommended storage conditions of the ampoules in the in the upright position in the original package (carton box) in order to minimize the possibility that the solid particles are not properly re-dispersed in case patients do not shake the ampoules before use.

The suitability of the test to detect microbial contamination in the 800 micrograms ampoule should be provided in the harmonised Module 3 after the conclusion of the referral.

Furthermore the finished product specification for the product contained in the 800 micrograms ampoule should be updated to include the test ‘Uniformity of Mass of Dose Delivered from multi-dose container’ and details on the primary containers with the graduation mark should be included if not present (French presentation). Harmonization of relevant sections of Module 3 is needed after the conclusion of the referral.

Labelling

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

2.2.1.1. Package Leaflet (PL)

The PL was amended in accordance with the changes made to the SmPC. The MAH has committed to carry out a user testing on the PL.

2.2.2. Risk Management Plan

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

3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Clenil and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

4. Grounds for 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 recommended the variation to the terms of the marketing authorisations for which the product information is set out in Annex III for Clenil and associated names (see Annex I).

The CHMP as a consequence concluded that the benefit-risk balance of Clenil and associated names remains favourable, subject to the agreed changes to the product information.

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Appendix 1

Divergent positions

Article 30 of Directive 2001/83/EC

Procedure No: EMEA/H/A-30/1418

Clenil and associated names (INN: beclometasone dipropionate)

Divergent statement

The following CHMP members consider that the benefit risk of Clenil in the indication of treatment of recurrent wheezing in children up to 5 years of age is not favourable based on the following grounds:

The proposed indication “treatment of recurrent wheezing in children up to 5 years of age” as a separate indication for Clenil” is not supported. There is evidence of benefit for use of ICS in asthma. Nevertheless, post-viral wheezing can recur 2-3 times/year in normal children. In these patients benefits and risks remain highly uncertain.

CHMP members expressing a divergent opinion:

Sinan B.Sarac	15 September 2016	Signature: .....
Pierre Demolis	15 September 2016	Signature: .....
Piotr Fiedor	15 September 2016	Signature: .....
Jana Schweigertova	15 September 2016	Signature: .....