IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Beclospin 400 micrograms/1 ml nebuliser suspension
Beclometasone dipropionate
PA0584/004/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considered that the application for Beclospin (beclometasone dipropionate anhydrous) 400mcg/1ml Nebuliser Suspension, by Chiesi Farmaceutici S.p.A.,in the treatment of:

- 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.

is approvable. A national marketing authorisation was granted on 01 April 1979.

This application concerns a mutual recognition procedure with Ireland acting as RMS and Italy as the Concerned Member State (CMS). The application is submitted according to Article 10a of Directive 2001/83/EC, so called well-established use, based on an original marketing authorisation in the RMS and bibliographic application.

This medicinal product is available on prescription only, which may be renewed.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Beclospin 400 micrograms/1 ml nebuliser suspension
Name(s) of the active substance(s) (INN)	Beclometasone dipropionate anhydrous
Pharmacotherapeutic classification (ATC code)	R03BA01 beclometasone
Pharmaceutical form and strength(s)	400 micrograms/1 ml nebuliser suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA0584/004/001
Marketing Authorisation Holder	Chiesi Farmaceutici SpA
MRP/DCP No.	IE/H/160/01/E/001
Reference Member State	IE
Concerned Member State	IT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Beclospin 400mcg/1ml Nebuliser Suspension.

II.2 Drug substance

The active substance is Beclometasone dipropionate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each ampoule contains 400 micrograms beclometasone dipropionate anhydrous in 1 ml.
Each ampoule contains 800 micrograms beclometasone dipropionate anhydrous in 2 ml.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to <relevant European/ICH guidelines> and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for preparations for inhalation, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Beclospin 400mcg/1ml Nebuliser Suspension.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for 14 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Pharmacodynamic, pharmacokinetic and toxicological properties of beclomethasone dipropionate are well known. As beclomethasone dipropionate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment

Beclomethasone dipropionate is already used in existing marketed products and no significant increase in environmental exposure is anticipated considering this is a line extension to add an additional pharmaceutical form that will dispense a lower quantity of beclomethasone dipropionate.

Therefore, the introduction of beclomethasone dipropionate is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

No nonclinical studies have been provided which is appropriate for a widely used, well-known active substance. There are no objections to approval of Beclospin 400 micrograms/1 ml nebuliser suspension from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Beclometasone dipropionate anhydrous (BDP) is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the MR procedure is in accordance with that accepted for the currently authorised national product Beclospin (PA0584/004/001**;** Chiesi Farmaceutici S.p.A.).

The applicant provided a comprehensive clinical overview (dated February 2018) of the development of the active substance and its efficacy and safety in use, for more than 25 years, in the treatment of asthma. The clinical overview provides a critical analysis of the clinical data published on BDP, based on a literature search with publication dates ranging from 1986 to late 2017.

This overview adequately supports the product's authorised indications and posology.

The evidence presented for demonstrating that the constituents of BDP have well established use, with an acceptable level of safety and efficacy, is acceptable. This document effectively summarises the results of BDP clinical studies published since original regulatory approval.

IV.2 Pharmacokinetics

BDP is a pro-drug that is hydrolysed via esterase enzymes to its main active metabolite, beclometasone monopropionate (B17MP), the most abundant metabolite in plasma.

Absorption
Following inhalation, systemic absorption of unchanged BDP occurs mainly through the lungs. Oral absorption of the swallowed dose is negligible. Systemic absorption of the main active metabolite B17MP arises from both lung deposition and oral absorption of the swallowed dose. Bioavailability of orally administered BDP is negligible; pre-systemic conversion to B17MP results in absorption of approximately 40% of the swallowed portion as B17MP. The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for BDP and B17MP respectively.

Distribution
Plasma protein binding is moderately high. Following intravenous dosing, the disposition of BDP and its active metabolite, B17MP, are characterised by high plasma clearance (150 and 120 L/h respectively), with a small volume of distribution at steady state for BDP (20 L) and a larger tissue distribution for its active metabolite (424 L).

Biotransformation
The main product of metabolism is the active metabolite (B17MP). Minor inactive metabolites, beclometasone-21-monopropionate (B21MP) and beclometasone (BOH), are also formed but contribute little to the systemic exposure.

Elimination
BDP is cleared very rapidly from the systemic circulation by metabolism mediated via esterase enzymes that are found in most tissues. Faecal excretion is the major route of BDP elimination, mainly as polar metabolites; renal excretion of BDP and its metabolites is negligible. The terminal elimination half-lives are 0.5 h and 2.7 h for BDP and B17MP

respectively.

Linearity/non-linearity
There is an approximately linear increase in systemic exposure of the active metabolite B17MP with increasing inhaled dose.

Special populations
The pharmacokinetics of BDP in patients with renal or hepatic impairment has not been studied. As BDP undergoes a very rapid metabolism via esterase enzymes present in intestinal fluids, serum, lungs and liver to originate more polar products B21MP, B17MP and BOH, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of BDP. As BDP or its metabolites have not been traced in urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

IV.3 Pharmacodynamics

Mechanism of action
BDP is a glucocorticoid with potent anti-inflammatory activity and limited mineralocorticoid activity. Following administration to the respiratory system by inhalation a local effect in the lower respiratory tract is obtained. BDP and its main active metabolite (B17MP), have affinity for the human glucocorticoid receptor. As the potency of B17MP is approximately 30-fold higher than that of the parent compound, the majority of the effect is related to B17MP systemic exposure.

Pharmacodynamic effects
The systemic pharmacodynamic effects of BDP and its active metabolite B17MP are assessed by measuring effects on hypothalamo-pituitary adrenal (HPA)-axis function. In healthy males a single dose of 1600 µg beclometasone dipropionate by nebulisation had no effect on 24-h urinary cortisol excretion; a single dose of 3200 µg produced a urinary cortisol excretion reduction of about 10% without any significant differences between the two dosage treatments. No significant effect on morning serum cortisol levels was reported in asthmatic patients after a 3-week treatment period of 1600 and 3200 µg per day b.i.d. via a nebulizer.

IV.4 Clinical Efficacy

BDP is indicated for:

- 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.

Asthma, a chronic inflammatory disease of the airways, is characterized by variable symptoms (wheezing, breathlessness, chest tightness, coughing, particularly night or early morning) and variable expiratory airflow limitation (over time and in intensity). Management involves prophylactic measures to reduce inflammation and airway resistance to maintain airflow, and treatment of acute attacks. Inhaled corticosteroid drug therapy in treatment of asthma delivers the drug directly to the desired site of action, allowing higher local concentrations, smaller doses and reduced systemic exposure.

The use of BDP in clinical practice for the above indications is well established from an efficacy perspective and there are many publications in the literature. As summarised by the applicant and detailed in the currently approved SmPC for Beclospin (PA0584/004/001**;** Chiesi Farmaceutici S.p.A.). the following are the main supportive published data.

Asthma
A study, in which the objective was to compare the efficacy and safety of nebulised BDP versus fluticasone propionate suspension for nebulization, was conducted in 205 adult patients aged 18-65 years with asthma, randomized to a 12-week treatment period. Comparable efficacy in controlling asthma was demonstrated by the two
treatments at study end in terms of pulmonary function tests, asthma exacerbations, symptoms and the use of rescue salbutamol (Terzano et al., 2003).

Paediatric population
Asthma
A double-blind, double-dummy, multicentre, randomized, parallel-group study compared the efficacy and safety of nebulised BDP and BDP administered with metered-dose inhalation in 151 patients, aged 6-16 years, with moderate to severe asthma, for 4 weeks. Comparable improvements over baseline were reported at study end for the two treatment groups in morning pulmonary expiratory flow rate (primary endpoint), clinical symptom scores and the use of rescue salbutamol. The two

treatments were equally well tolerated (Bisca et al., 2003).

Efficacy and safety of nebulised BDP in the treatment of severe persistent asthma in infants and young children aged 6 months to 6 years, in comparison to budesonide suspension for nebulization, was assessed in a multicentre, randomized, controlled open-labelled study for 14 weeks. In the study 40.4% and 51.7% patients in the nebulised BDP and budesonide groups respectively did not experience any major exacerbation (primary endpoint). Both treatments were associated with a marked reduction in night-time wheezing and number of days of steroid use. Urinary cortisol and the time course of height and weight were unaffected by both treatments; nebulised BDP was confirmed to have a neutral effect on bone metabolism (Delacourt et al., 2003).

Wheezing
Nebulised BDP was evaluated in 276 children aged 1-4 years with frequent wheezing in a randomized, double-blind, 12-week controlled trial. Regular nebulised BDP plus rescue salbutamol significantly increased the percentage of symptom-free days (primary endpoint, defined as a lack of wheezing, coughing, shortness of breath and patients'/parents' nocturnal awakenings in 24 h) (69.6 ± 20.89 [SD]; P = 0.034) vs placebo/rescue salbutamol (61.0 ± 24.83 [SD]) but not vs combination nebulised BDP/rescue salbutamol (64.9 ± 24.74 [SD]) regardless of the presence of risk factors for developing asthma. The time to first exacerbation was longer in children treated with nebulised BDP. In terms of safety, no change in the values of morning salivary cortisol was detected (Papi et al., 2009).

IV.5 Clinical Safety

The safety profile of BDP is well known and well established over many years (see section IV.4 Clinical Efficacy), when used as an inhaled corticosteroid by nebulised suspension, as indicated and at the recommended dose. BDP has an adverse event profile that is clinically acceptable in light of its mechanism of action, indications and patient profile.
The most common adverse drug reactions are oropharyngeal candidiasis, hoarseness, and/or sore throat, consistent with local adverse of effects of inhaled corticosteroids as a class. Systemic adverse effects of inhaled corticosteroids as a class are noted as very rare when this product is used as indicated and at the recommended dose. Hypersensitivity to BDP or to any of the other ingredients in the formulation can occur; known hypersensitivity is a contra-indication for use of the product.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks.

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

IV.6 Discussion on the clinical aspects

As the use of beclometasone dipropionate (BDP) is well established and supported by many publications on safety and efficacy over the years, no new clinical studies to evaluate the benefit/risk balance were submitted by the applicant. With reference to the scientific literature provided, the overall benefit risk for this product from a clinical perspective remains positive.

V. OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the overall benefit risk for this product remains positive for the indications authorised and the HPRA considers the product approvable.
The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

The marketing authorisation has been granted unlimited validity in the RMS.

VII. UPDATES