IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Budesonide Azure 1 mg/2 ml Nebuliser Suspension
Budesonide
PA22871/035/002

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 HPRA has granted a marketing authorisation for Budesonide Azure 0.5mg/2ml & 1mg/2ml Nebuliser Suspension, from Azure Pharmaceuticals Ltd, on 6th February 2026 indicated for:

- use in bronchial asthma, in patients where use of a pressurised inhaler or dry powder formulation is unsatisfactory or inappropriate
- use in infants and children with croup (acute viral upper respiratory tract infection also known as viral laryngotracheobronchitis or laryngitis subglottica), in which hospitalisation is indicated.

This application for a marketing authorisation was submitted in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a 'hybrid' application. The reference medicinal product was Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser), AstraZeneca AB. Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension has the same qualitative and quantitative composition in terms of active substance and the same pharmaceutical form as Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser).

With Ireland as the Reference Member State in this decentralised procedure, Azure Pharmaceuticals applied for a marketing authorisation for Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension in Concerned member State, Malta.

The legal status for this marketing authorisation is subject to medical prescription, which may be renewed.

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

Name of the product	Budesonide Azure 1 mg/2 ml Nebuliser Suspension
Name(s) of the active substance(s) (INN)	Budesonide
Pharmacotherapeutic classification (ATC Code)	R03BA02
Pharmaceutical form and strength(s)	1 mg/2 ml Nebuliser Suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/035/002
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd. 12 Hamilton Drive The Rock Road Blackrock Dundalk Co. Louth A91 T997 Ireland
MRP/DCP No.	IE/H/1362/002
Reference Member State	IE
Concerned Member State(s)	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Budesonide Azure 0.5mg/2ml & 1mg/2ml Nebuliser Suspension.

II.2 Drug Substance

The active substance is budesonide, 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

The product contains 0.5 mg of budesonide per 2 ml & or 1 mg of budesonide per 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 the dosage form, 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 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 Budesonide Azure 0.5mg/2ml & 1mg/2ml Nebuliser Suspension.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Pulmicort Respules on the Irish market. As the pharmacodynamic, pharmacokinetic and toxicological properties of Budesonide are well known, the Applicant has not provided additional non-clinical studies, and further studies are not required. The overview based on literature review is appropriate.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Budesonide Azure is intended for generic substitution, an increased environmental exposure is not anticipated. Additional environmental risk studies are therefore not requested.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Budesonide are well known since it has been marketed for several decades and resulting clinical experience is extensive. As Budesonide is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies, and further studies are not required. The non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Budesonide is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference medicinal product Pulmicort Respules® (0.5 mg/1 mg; suspension for inhalation via a nebuliser), marketed by AstraZeneca AB.

The 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) states that when solutions for nebulisation have the same qualitative and quantitative composition as the reference medicinal product the requirement for clinical studies may be waived. In vitro data have been provided by the applicant in support of therapeutic equivalence compared to the reference medicinal product. Therapeutic equivalence has been demonstrated based on Quality data and thus the absence of clinical studies is accepted in line with the OIP guideline.

IV.2 Pharmacokinetics

Absorption

In adults the systemic availability of budesonide following administration of budesonide nebuliser suspension via a jet nebuliser is approximately 15% of the nominal dose and 40-70% of the dose delivered to the patients. A minor fraction of the systemically available drug comes from swallowed drug. The maximal plasma concentration, occurring about 10 to 30 min after start of nebulisation is approximately 4 nmol/L after a single dose of 2 mg.

Distribution

Budesonide has a volume of distribution of approximately 3 L/Kg. Plasma protein binding averages 85-90%.

Biotransformation

Budesonide undergoes an extensive degree (≈90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Elimination
The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has high systemic clearance (approximately 1.2 L/min) in healthy adults, and the terminal half-life of budesonide after i.v. dosing averages 2-3 hours.

Linearity
The kinetics of budesonide are dose-proportional at clinically relevant doses.

Paediatric population
Budesonide has a systemic clearance of approximately 0.5 L/min in 4-6 year old asthmatic children. Per kg body weight children have a clearance which is approximately 50% greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2.3 hours in asthmatic children. This is about the same as in healthy adults. In 4-6 years old asthmatic children, the systemic availability of budesonide following administration of budesonide nebuliser suspension via a jet nebuliser (Pari LC Jet Plus® with Pari Master® compressor) is approximately 6% of the nominal dose and 26% of the dose delivered to the patients. The systemic availability in children is about half that in healthy adults. The maximum plasma concentration, occurring approximately 20 min after start of nebulisation is approximately 2.4 nmol/L in 4-6 year old asthmatic children after a 1 mg dose.

The exposure (Cmax and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6 year old children is comparable to that in healthy adults given the same delivered dose by the same nebuliser system.

IV.3 Pharmacodynamics
Budesonide is a gluococorticosteroid with a high local anti-inflammatory effect.

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions involving T-cells, eosinophils and mast cells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

A clinical study in asthmatics comparing inhaled and oral budesonide at similar plasma concentrations demonstrated statistically significant evidence of efficacy with inhaled but not oral budesonide compared with placebo. Thus, the therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has shown anti-anaphylactic and anti-inflammatory effects in provocation studies in animals and patients, manifested as decreased bronchial obstruction in the immediate, as well as the late, allergic reaction.

IV.4 Clinical Efficacy
Therapeutic equivalence with the reference medicinal product Pulmicort Respules® (0.5 mg/1 mg; suspension for inhalation via a nebuliser) was demonstrated through in vitro data, in line with the 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).

In addition, the applicant provided bibliographic data on the efficacy of the active substance.

The data provided supports the use of Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension for the claimed indications.

No company efficacy studies have been submitted and this is acceptable in keeping with the legal basis of this application.

IV.5 Clinical Safety
The reference medicinal product for this application, Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser) has been on the market in the EU for 27 years and licensed in IE since 2001. Therefore, budesonide has an established clinical safety profile.

The applicant provided a satisfactory overview on the safety of the active substance.

The SmPC captures the known relevant safety information.

No new clinical studies were completed which is acceptable for an abridged/hybrid application.

IV.6 Discussion on the clinical aspects

As this is a hybrid application under Article 10(3) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension has proven chemical-pharmaceutical quality and is a hybrid form of a suitable approved reference medicinal product; Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser). Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser) is a well-known medicinal product with an established favourable efficacy and safety profile.

The 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) states that when solutions for nebulisation have the same qualitative and quantitative composition as the reference medicinal product the requirement for clinical studies may be waived. In vitro data have been provided by the applicant in support of therapeutic equivalence compared to the reference medicinal product. Therapeutic equivalence has been demonstrated based on Quality data and thus the absence of clinical studies is accepted in line with the OIP guideline.

The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension is a hybrid form of Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser). Pulmicort Respules® (0.5 mg / 1 mg; suspension for inhalation via a nebuliser) is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference medicinal product Pulmicort Respules® (0.5 mg/1 mg; suspension for inhalation via a nebuliser), marketed by AstraZeneca AB.

In vitro data have been provided by the applicant in support of therapeutic equivalence compared to the reference medicinal product. Therapeutic equivalence has been demonstrated based on Quality data and thus the absence of clinical studies is accepted in line with the OIP guideline.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Budesonide Azure 0.5mg/ml & 1mg/2ml Nebuliser Suspension was the same as the reference medicinal product and therefore granted a marketing authorisation.

VI. REVISION DATE

21.01.2031