IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution
Ipratropium bromide monohydrate
Salbutamol sulfate
PA22871/033/001

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.

CONTENTS

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution, from Azure Pharmaceuticals Ltd on 6th March 2026 for management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) in adults who require regular treatment with both ipratropium bromide and salbutamol.

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.

With Ireland as the Reference Member State in this decentralised procedure, Azure Pharmaceuticals applied for a marketing authorisation for Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution in Malta.

The reference product is Combivent Unidose 0,52 mg/2,5 ml + 3 mg/2,5 ml solução para inalação por vaporização.

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	Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution
Name(s) of the active substance(s) (INN)	Ipratropium bromide monohydrate, salbutamol sulfate
Pharmacotherapeutic classification (ATC code)	R03AL02
Pharmaceutical form and strength(s)	0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/033/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1343/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

QUALITY ASPECTS

II.1. Introduction

This application is for Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution.

II.2 Drug substance

There are two active substances in this medicinal product.

One of the active substances is salbutamol sulfate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The other active substance is ipratropium bromide, 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 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 pharmacopeial 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(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 have been provided, assuring consistent quality of Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Ipratropium Bromide and Salbutamol both alone and in combination have been available on the European market for many years. As the pharmacodynamic, pharmacokinetic and toxicological properties of Ipratropium Bromide and Salbutamol are well known, the applicant has not provided additional nonclinical studies, and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Ipratropium Bromide 0.5mg-Salbutamol (as sulphate) 2.5mg/2.5ml solution for aerosol therapy is intended for generic substitution, this will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not required.

III.6 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Ipratropium bromide and Salbutamol sulfate are 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 product is Combivent Unidose 0,52 mg/2,5 ml + 3 mg/2,5 ml solução para inalação por vaporização marketed by Boehringer Ingelheim.

IV.2 Pharmacokinetics

Ipratropium

Absorption
Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 4% of an inhaled dose. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 9% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution
Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed.
The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

Biotransformation
The half-life of the terminal elimination phase is approximately 1.6 hours.
Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Salbutamol

Absorption
Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or the gastric route and has an oral bioavailability of approximately 50%. Mean peak plasma salbutamol concentrations of 492 pg/mL occur within three hours after inhalation of combination ipratropium bromide – salbutamol sulfate.

Distribution
Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg). Only 8% of the drug is bound to plasma proteins. In nonclinical trials, levels of approximately 5% of the plasma level of salbutamol are found in the brain. However, this amount probably represents the distribution of the substance in the extracellular water of the brain.

Biotransformation and Elimination
Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291mL/min.
Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulfate. The R(-)- enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+) –enantiomer. Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64.2%) and 12.0% were excreted as sulfate conjugate. After oral administration urinary excretion of unchanged drug and sulfate conjugate were 31.8% and 48.2 of the dose, respectively.

IV.3 Pharmacodynamics

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca++ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilation following inhalation of ipratropium bromide is primarily local and specific to the lung and not systemic in nature.

Salbutamol is a beta2-adrenergic agonist, which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscles from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

Ipratropium bromide/salbutamol Azure provides the simultaneous delivery of ipratropium bromide and salbutamol sulphate producing effects on both muscarinic and beta2-adrenergic receptors in the lung. This provides enhanced bronchodilation over that provided by each agent singly.

IV.4 Clinical Efficacy
No new efficacy studies have been performed. The Applicant has adequately reviewed and discussed the clinical studies and literature data in support of the efficacy of that Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution.

IV.5 Clinical Safety

No new safety studies have been performed.

The summary of safety concerns is empty. Routine pharmacovigilance and routine risk minimisation measures are accepted.

Active substance is currently listed in the published EURD list
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This Marketing Authorisation Application (MAA) for Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution a prescription medicine for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) was submitted in accordance with Article 10(3) of Directive 2001/83/EC. The reference medicinal product is Combivent Unidose registered since 26/05/2000.

V. OVERALL CONCLUSIONS

The HPRA, on the basis of the data submitted considered that Ipratropium bromide/salbutamol Azure 0.5 mg/2.5 mg per 2.5 ml Nebuliser Solution was the same as the reference product Combivent Unidose and therefore granted a marketing authorisation.

VI. REVISION DATE

05.02.2031