IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Brodilaten 2.5 mg/2.5 ml Nebuliser solution
SALBUTAMOL SULFATE
PA1122/024/002

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6558/001-003/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 11th February 2019 under procedure number IE/H/0713/001-003/DC

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1122/024/001-003
Marketing Authorisation Holder: Noridem Enterprises Ltd

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Brodilaten 1.25 mg/2.5 mL, 2.5 mg/2.5 mL and 5.0 mg/2.5 mL Nebuliser solution (PL 17589/0015-17) could be approved.

Brodilaten 1.25 mg / 2.5 mL Nebuliser solution is indicated for the treatmentof acute severe asthma in children and infants.

Note: Acute severe asthma requires hospital treatment in the intensive care unit.

Brodilaten 2.5 mg/2.5 mL and 5.0 mg/2.5 mL Nebuliser solution are indicated in adults, adolescents and children aged 4 to 11 years. Brodilaten 2.5 mg/2.5 mL and 5.0 mg/2.5 mL Nebuliser solution are not indicated for babies and children under 4 years of age.

Brodilaten 2.5 mg/2.5 mL and 5.0 mg/2.5 mL Nebuliser solution are indicated for treatment of severe acute exacerbations of chronic obstructive pulmonary disease (COPD), and in the treatment of acute severe asthma.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member States (CMS(s) were France, Germany, Greece and Republic of Ireland.

Salbutamol is a selective *$\beta_2$agonist* providing short-acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction. At therapeutic doses it acts on the *$\beta_2$adrenoceptors* of bronchial muscle. With its fast onset of action, it is particularly suitable for the management and prevention of asthma attacks.

These applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be hybrid medicinal products. The reference products with a complete dossier that have been authorised for not less than 10 years in the EEA are Ventoline 1.25mg/2.5ml Solution pour inhalation par nebuliseur en recipient unidose, authorised in France to Laboratoire GlaxoSmithKline on 27 February 2001, Ventolin Nebules 2.5mg/2.5ml Solution for inhalation via a nebuliser (PL 10949/0085), authorised in the UK to Glaxo Wellcome UK Ltd on 01 March 1994 following a change of ownership from PL 00045/0123 authorised on 10 June 1981 and Ventolin Nebules 5mg/2.5ml Solution for inhalation via a nebuliser (PL 10949/0086) authorised in the UK to Glaxo Wellcome UK Ltd on 01 March 1994 following a change of ownership from PL 00045/0133 authorised on 15 May 1987.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being hybrid medicinal products of a reference products that have been licensed for over 10 years.

A biowaiver was submitted with these applications which was accepted. No bioequivalence or therapeutic equivalence studies were required, and none were provided with these applications.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

The RMS and CMSs considered that the applications could be approved at the end of procedure (Day 210) on 10 January 2019. After a subsequent national phase, licences were granted in the UK on 27 February 2019.

II. QUALITY ASPECTS

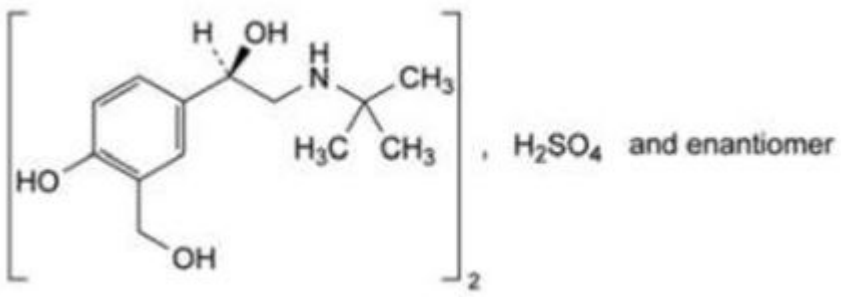
II.1 Introduction
These products consist of a clear and colourless solution.

In addition to salbutamol sulfate, the products also contain the excipients sodium chloride, water for injections and sulfuric acid.

The finished products are supplied as packs of 10, 20, 30, 50 or 60 in low density polyethylene ampoules overwrapped in non-transparent protective aluminium pouches and packed in carton boxes. Each ampoule contains 2.5 mL of solution.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE(S)
rINN: Salbutamol sulfate
Chemical Name: Bis[(lRS)-2-[(l,l-dimethylethyl)amino]-l-[4-hydroxy-3-(hydroxymethyl) phenyl]ethanol] sulfate
Molecular Formula: $C_{26}H_{44}N_2O_{10}S$
Chemical Structure:



IMolecular Weight: 576.7 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Freely soluble in water, practically insoluble or very slightly soluble in ethanol (96 per cent) and in methylene chloride.

Salbutamol sulfate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results.

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years before opening and 3 months after opening the overwrap protective pouch. The storage conditions are "Store below 25°C", "Store the ampoules in the original outer carton and pouch, in order to protect from light" and "The ampoules should be protected from light after opening the overwrap protective pouch". These are acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of salbutamol sulfate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these are hybrid applications of an already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV. CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with these applications.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for these applications and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data have been submitted for these applications and none were required.

Pharmaceutical equivalence was shown between the test and reference products. Therefore, in line with the guidelines, for the purposes of these applications, Brodilaten 1.25 m /2.5 mL, 2.5 mg/2.5 mL and 5.0 mg/2.5 mL Nebuliser solution can be

considered therapeutically equivalent to Ventoline 1.25mg/2.5ml Solution pour inhalation par nebuliseur en recipient unidose, Ventolin Nebules 2.5mg/2.5ml Solution and Ventolin Nebules 5.0mg/2.5ml Solution, for inhalation via a nebuliser.

IV.5 Clinical safety
No new safety data were submitted with these applications and none were required. The safety profile for these products is considered to be the same as Ventoline 1.25mg/2.5ml Solution pour inhalation par nebuliseur en recipient unidose, Ventolin Nebules 2.5mg/2.5ml Solution and Ventolin Nebules 5.0mg/2.5ml Solution, for inhalation via a nebuliser.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V. OVERALL CONCLUSIONS

USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with salbutamol sulfate is considered to have demonstrated the therapeutic value of the products.

The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The following text is the currently approved label text. No label mock-ups have been provided for this/these product(s). In accordance with medicines legislation, this/these product(s) shall not be marketed in the UK until approval of the label mock-ups has been obtained.

VI. REVISION DATE

July 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6558/001-003/DC to IE/H/0713/001-003/DC	N/A	N/A	N/A	Approved 11/02/2019