LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ipratropium/Salbutamol Neutec (ipratropium bromide monohydrate, salbutamol sulfate)

SE/H/2103/01/DC

This module reflects the scientific discussion for the approval of Ipratropium/Salbutamol Neutec. The procedure was finalised on 2023-05-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Ipratropium/Salbutamol Neutec, 0,5 mg/2,5 mg, nebuliser solution.

The active substances are ipratropium bromide monohydrate and salbutamol sulphate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Ipratropium/Salbutamol Neutec, 0,5 mg/2,5 mg, nebuliser solution, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Neutec lnhaler Ireland Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, DE, DK, ES, FI, IE, IS, NL, NO and UK(NI) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Combivent, 0,5 mg/2,5 mg/ml, nebuliser solution, single dose containers, authorised in SE since 1998, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS DE, IS, IE, NO, ES: Combivent 0,5 mg/2,5 mg/ml, nebuliser solution, authorised in SE since 1998 with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The justification to use this product is based on RMS's own files.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substances (ipratropium bromide / salbutamol sulphate) are well known. As the active substances are widely used and well-known, no further studies are required, and the applicant provides none. A non-clinical overview based on literature review has been provided. The proposed product has the same dose strength, composition and indication as the reference product. There are no differences in SmPC 4.6 and 5.3 text as compared to the SmPC of the reference product. As such, there are no differences to the reference product that require specific non-clinical discussion.

Shortly (based on a literature overview), ipratropium bromide is a short acting muscarinic-antagonist (SAMA) that blocks the muscarinic cholinergic receptors (M3) leading to a decrease in the production of cyclic guanosine monophosphate (cGMP) and a decreased contraction of the smooth muscles. Salbutamol sulphate is a short acting β2-adrenergic agonist (SABA) that promotes the intracellular adenyl cyclase that generates cyclic 3´,5´- adenosine monophosphate (cAMP) and activates effector molecules such as cAMP-dependent protein kinase A (PKA). High cAMP levels are associated with relaxation of bronchial smooth muscle. Administration is via inhalation. Non-clinical pharmacokinetics and toxicology data are largely superseded by clinical data for ipratropium bromide and salbutamol sulphate - both as individual and combined compounds.

There are no indication of genotoxicity or carcinogenicity for ipratropium bromide. Salbutamol sulphate has no indications of genotoxicity but in a two-year study in rat, it caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111x, 555x, and 2,800x the maximum human inhalation dose. The relevance of these findings to humans is not known.

With regard to reproductive toxicity, ipratropium bromide exposure of rat (oral doses of 5, 50 and 500mg/kg given 60 days prior to and during early gestation) caused a fertility delay in 8 of 20 couples at 500mg/kg, spurious pregnancy in 5 of 20 females, and a decreased conception rate in 75% of females. No teratogenic outcomes were detected in rat or rabbit from inhalation exposure (maternal toxicity and embryotoxicity was observed after oral exposure at 1000mg/kg). For salbutamol sulphate, there are no indications of reproductive toxicity in rat. Teratological studies show that it is teratogenic in mice (s.c. exposure 0.025mg/kg generated cleft palate, corresponding to 1.4x maximum the human aerosol dose) but less so in rats (oral exposure, at 50mg/kg, there was an increase in neonatal mortality but no malformations). It is also teratogenic (findings of cranioschisis) in rabbit at 50mg/kg (oral, corresponding to 2800x the human exposure).

Environmental Risk Assessment (ERA)
Since Ipratropium/Salbutamol Neutec is a generic product, and based on principle of generic substitution, it is unlikely that this product will lead to an increased exposure to the environment. A full environmental risk assessment is therefore not deemed necessary.

Conclusion
There are no objections to approval of product name from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has not submitted any clinical studies.

Pharmacokinetic properties of the active substance
Absorption: Ipratropium has a bioavailability following oral and inhaled doses of 2 % and 7-28% respectively. For salbutamol the oral bioavailability is approximately 50%. Following an inhalation of salbutamol maximal plasma concentrations occur within 3 hours.

Elimination: The terminal half-life is approximately 1.6 hours for ipratropium bromide and 4 hours for salbutamol.

Discussion and overall conclusion
The applied product has the same qualitative and quantitative composition in terms of active substances (ipratropium bromide and salbutamol sulphate) and the same qualitative and similar quantitative composition in excipients as the reference medicinal product. In vitro data with jet nebulisers have been provided by the applicant in support of therapeutic equivalence compared to the reference product. Therapeutic equivalence when using jet nebulisers, PARI LC Plus Nebuliser and PARI BOY® SX, can be concluded based on Quality data and thus the absence of clinical studies is accepted in line with the OIP guideline. The applicant also provided additional in vitro data using Mesh Nebuliser which do not comply with acceptance criteria. Therefore, that nebuliser is not included as an option in the product information.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 relating to Ipratropium/Salbutamol Neutec.

Safety specification
Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

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

Summary of the RMP
The submitted Risk Management Plan, version 0.3 signed 26 April 2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to COMBIPRASAL 0.5 mg / 2.5 mg per 2.5 ml nebuliser solution, NL/H/2736/001 regarding content and Neuair Airmaster 50 microgram/100 microgram/dose inhalation powder, pre-dispensed, SE/H/1891/001-003 regarding the layout. The bridging report regarding content and layout submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Ipratropium/Salbutamol Neutec, is found adequate. There are no objections to approval of Ipratropium/Salbutamol Neutec, from a non-clinical and clinical point of view. Therapeutic equivalence is sufficiently demonstrated by in vitro data for use with jet nebulisers, PARI LC Plus Nebuliser and PARI BOY® SX. The product information is acceptable. The benefit/risk ratio is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Ipratropium/Salbutamol Neutec, 0,5 mg/2,5 mg, nebuliser solution was positively finalised on 2023-05-11.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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