

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml,
nebuliser solution
Pharma Stulln GmbH, Germany**

ipratropium bromide (as monohydrate)/salbutamol (as sulphate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2736/001/DC
Registration number in the Netherlands: RVG 112344**

12 March 2014

Pharmacotherapeutic group:	adrenergics and other drugs for obstructive airway diseases
ATC code:	R03AK04
Route of administration:	inhalation
Therapeutic indication:	management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol
Prescription status:	prescription only
Date of authorisation in NL:	6 December 2013
Concerned Member States:	Decentralised procedure with DE, IE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution from Pharma Stulln GmbH. The date of authorisation was on 6 December 2013 in the Netherlands.

The product is indicated for management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

A comprehensive description of the indications and posology is given in the SPC.

Ipratropium bromide is an anticholinergic agent, which inhibits vagally-mediated reflexes by antagonising the muscarinic action of acetylcholine. 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 muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

Ipratropiumbromide Salbutamol Stulln 0.5/2.5 mg per 2.5 ml 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Combivent UDVs, which has been marketed in the UK by Boehringer Ingelheim Limited since 1995. In the Netherlands, the reference product Combivent Unit Dose, nebuliser solution (NL License RVG 20233) has been registered by Boehringer Ingelheim B.V. since 1997 (original product). In addition, reference is made to Combivent authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, hybrid application, as bioequivalence cannot be demonstrated through bioavailability studies.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Ipratropiumbromide Salbutamol Stulln 0.5/2.5 mg per 2.5 ml, nebuliser solution is a product for inhalation use, it is exempted for bioequivalence study. Essential similarity is demonstrated by comparative *in vitro* data only. This is acceptable and in line with the NfG CPMP/EWP/4151/00Rev.1. The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for hybrid medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances

The active substances are ipratropium bromide monohydrate and salbutamol sulphate, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Ipratropium bromide is a white or almost white, crystalline powder, which is soluble in water. Salbutamol sulphate is a white or almost white, crystalline powder, which is free soluble in water, practically insoluble or very slightly soluble in methylene chloride and alcohol, slightly soluble in chloroform and ether. As the active substances are dissolved in the drug product, particle size and polymorphism are not critical.

The CEP procedure is used for ipratropium bromide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

For salbutamol sulphate, the Active Substance Master File (ASMF) procedure is used. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

For ipratropium bromide a CEP has been submitted; therefore no details on the manufacturing process have been included.

For salbutamol a description of the process has been provided. Sufficient information on the starting material, solvents and reagents was included. The process has been adequately validated.

Quality control of drug substances

The drug substances are tested in line with their Ph.Eur. monograph with additional tests as included on the CEP and in the ASMF, and for microbiological quality. Sufficient batch analysis data has been provided for both drug substances, demonstrating that the drug substances are of adequate quality.

Stability of drug substances

The active substance ipratropium bromide is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

For salbutamol sulphate stability testing was conducted during storage at 25 °C/60% RH (60 months) and 40°C/75% RH (6 months). No out of specifications were measured at either the long term or accelerated conditions. The presented stability data justify the claimed retest period of 5 years. No special storage conditions are deemed necessary.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition

Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml is formulated as a clear, colourless solution with pH approx. 3.5 and osmolality approx. 300 mOsm/kg.

The nebuliser solution is packed in LDPE single-dose containers containing 2.5 ml of solution.

The excipients are sodium chloride, sulphuric acid 10% (for pH adjustment) and water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation of the proposed drug product is very similar to the innovator. No bioequivalence studies or clinical trials have been performed as it concerns a nebuliser solution with comparative physicochemical parameters as the innovator product. The development of the manufacturing process and the choice of container closure system have been adequately discussed. The choice of aseptic processing and sterilisation by filtration is justified. For avoiding microbial contamination of non-preserved inhalation solutions, the solution is filled in unit dose containers which are designed for single use only. No overages of the active ingredients or excipients are required. In order to guarantee the nominal declared amount in the single-dose containers, an overfill of about 0.05 ml per container is applied. All physico-chemical characteristics tested (appearance, pH value, relative density, osmolality, viscosity, surface tension, assay and impurity profile) are comparable between Ipratropiumbromide Salbutamol Sulln and Combivent UDVs, nebuliser solutions. The proposed primary packaging materials are considered to be suitable for the intended use. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by dissolution of sodium chloride and salbutamol sulphate in nitrogen purged water, followed by pH adjustment and subsequent addition of ipratropium bromide. The pH is adjusted once more. The bulk solution is filtered and filled into freshly formed LDPE ampoules by the Form-Fill-Seal (FFS) route in a continuous process. The manufacturing process has been adequately validated.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance of solution, identification, relative density, pH, osmolality, sterility, particulate contamination, extractable volume, uniformity of dosage units (mass variation), assay and related substances. The release and shelf-life specifications are identical and are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided three production-scale batches stored at 25°C/60%RH (24 months), 30°C/65%RH (12 months) and 40°C/75%RH (6 months), both pouched and unpouched. The conditions used in the stability studies are according to the ICH stability guideline. The product outside the pouch is found to be sensitive for light and evaporation of water. Due to the aluminium pouches, evaporation of water from the containers no longer occurred.

Out of specification results were observed for unknown impurities under intermediate and accelerated storage conditions. For the other parameters no clear trends could be observed. A photostability study in accordance with the ICH Q1B Note for Guidance showed that the product is sensitive to light. Based on the stability data provided, the claimed shelf life of 24 months and storage conditions 'Do not store above 25°C, Do not freeze, Store in the original packaging to protect from light and evaporation' are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a hybrid formulation of Combivent, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ipratropium bromide or salbutamol sulphate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ipratropium bromide and salbutamol sulphate are well-known active substances with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

The application does not include clinical demonstration of therapeutic equivalence versus Combivent® UDV® nebuliser solution. According to the Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev. 1) the requirement for clinical studies may be waived when solutions for nebulisation have the same qualitative and quantitative composition as the reference product. This applies to the product at issue. As Ipratropiumbromide Salbutamol Stulln is an aqueous solution for nebulisation with a practically identical composition as compared to the reference product, the product will also perform in the same way as the reference product. No nebuliser device is included in the application nor in the SmPC of the reference product. Based on the pharmaceutical form and the identical composition of the proposed product compared to the reference product, the biowaiver is accepted.

Risk management plan

The combination of ipratropium bromide and salbutamol sulphate was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ipratropium bromide and salbutamol sulphate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. Submission of a Risk Management Plan was not required at the time of this application.

Product information

SmPC

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for Combivent UDV nebuliser solution.

Readability test

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both rounds of testing at least 90% of participants were able to trace the requested information and at least 90% were able to show they comprehend it. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution has a proven chemical-pharmaceutical quality and is a hybrid form of Combivent UDVs. Combivent is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are aqueous solutions intended for inhalation use, no bioequivalence study is deemed necessary. See SmPC and package leaflet for recommended nebulisers for use with Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution.

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

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other ipratropium bromide and salbutamol containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 September 2013. Ipratropiumbromide Salbutamol Stulln 0.5 mg/2.5 mg per 2.5 ml, nebuliser solution was authorised in the Netherlands on 6 December 2013.

The date for the first renewal will be: 23 September 2018.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/non approval	Assessment report attached