CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ipratropiumbromide/Salbutamol Sandoz 0.5/2.5 mg per 2.5 ml, nebuliser solution Sandoz B.V., the Netherlands

ipratropium bromide/salbutamol 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/2221/001/DC
Registration number in the Netherlands: RVG 109136

26 March 2013

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:	17 October 2012
Concerned Member States:	Decentralised procedure with DE, DK, SE, 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 (SPC), 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 Sandoz 0.5/2.5 mg per 2.5 ml, nebuliser solution from Sandoz B.V. The date of authorisation was on 17 October 2012 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 Sandoz 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 beta$_2$-adrenergic receptors in the lung. This provides enhanced bronchodilation over that provided by each agent singly.

This decentralised procedure concerns a hybrid 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 Sandoz 0.5/2.5 mg per 2.5 ml, nebuliser solution is a product for inhalation use, it is exempted for biostudy. 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, freely soluble in methanol, slightly soluble in alcohol. Salbutamol sulphate is a white or almost white, crystalline powder, which is freely soluble in water, slightly soluble in alcohol and in ether, very slightly soluble in methylene chloride.

The CEP procedure is used for both active substances. 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.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substances are tested in line with their Ph.Eur. monographs with additional tests for residual solvents as included on the CEP. As the drug product concerns a solution, no tests on particle size or polymorphism are deemed necessary. Sufficient batch analysis data has been provided for both drug substances, demonstrating that the drug substances are of adequate quality.

Stability of drug substance
The CEP of ipratropium bromide states a retest period of 5 years when stored under the stated conditions. For salbutamol sulphate, stability data have been provided on three commercial-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The results justify the claimed retest period of two years and no 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 Sandoz 0.5/2.5 mg per 2.5 ml is formulated as a clear, colourless solution filled in 2.5 mL FFS (form-fill-seal) ampoules.

The excipients are sodium chloride, sulphuric acid (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 compositions of the test and reference solutions are considered as identical; the only minor difference is the very low amount of diluted sulphuric acid instead of diluted hydrochloric acid for pH adjustment. It is not expected that this minor difference affects the behaviour of the solution. No

bioequivalence studies or clinical trials have been performed. As the proposed product 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. Based on the pharmaceutical form and the identical composition of the proposed product compared to the reference product, the biowaiver is accepted.
The applicant performed the characterisation method as described in Pharmeuropa monograph 2.9.44 *Preparations for Nebulisation: Characterisation* concerning aerodynamic assessment of nebulised aerosols. As nebuliser the commercially available apparatus Pari LC Plus Reusable Nebuliser was used, and as impactor apparatus Apparatus E (as described in Pharmeuropa monograph 2.9.18). The parameters studied are deemed suitable for characterisation of the aerosol generated with the nebulisation solution. The data generated using the NGI (next generation impactor) are comparable for both solutions (generic and reference product), as expected based on their practically identical composition.
The product under consideration is a respule used for inhalation and is manufactured by the FFS (Form Fill Seal) route wherein the container is formed, filled, and sealed in a continuous process without human intervention, in a sterile enclosed area inside a machine. Thus this technology can be used to aseptically manufacture sterile pharmaceutical liquid dosage forms. Since the FFS technology is used to fill this product, which employs an aseptic route and PE granules to form the base of the container, terminal sterilisation is not a suitable method for this product.
The development of the manufacturing process and the choice of container closure system have been adequately discussed. In general, the pharmaceutical development of the product has been adequately performed. The MAH has included information on the nebulizer apparatus used in the Pharmeuropa 2.9.44 characterisation test (PARI LC PLUS Nebuliser, jet nebulizer) in the product information.

Manufacturing process
The manufacturing process has been sufficiently described. The pH is adjusted by using sulphuric acid. The bulk solution is sterile filtered and filled intro freshly formed LDPE ampoules in the Form-Fill-Seal (FFS) manner. The filled and sealed ampoules are deflashed, leak tested and wrapped in triple laminated Alu pouches. The MAH validated the holding times of the bulk solutions before and after filtration. 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 description, identification, pH, fill volume (net content of respule), clarity of solution, colour, osmolality, uniformity of dosage units, water loss (only shelf-life), related substances, sterility, particulate contamination – sub-visible particles, droplet size distribution, assay for both active substances and packaging materials inspection.
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 (36 months) and 40°C/75%RH (6 months). Water loss testing was also performed under dry long-term (25°C/40%RH) and accelerated (40°C/20%RH) storage conditions. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in LDPE FFS ampoules wrapped in a protective triple laminated polyester/aluminium/polythene pouch.
The photosensitivity of the drug product in the ampoules has been demonstrated. The light-protecting effect of the pouch and carton without pouch has been demonstrated. With secondary packaging no significant changes were observed.
The results of the in-use study demonstrate stability of the ampoules for 3 months after opening of the pouch, provided that the ampoules are placed back in the pouch to protect from light.

Some trends were observed, but all results stayed within the specifications. A shelf-life of 24 months was granted with the storage condition “do not store above 25°C; do not refrigerate or freeze; keep ampoules in the outer pouch or carton in order to protect from light”, which is justified based on the stability data.
The MAH committed to place the first two commercial batches and thereafter one batch annually on stability under long-term conditions.

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 orsalbutamol 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® UDVs® 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 Sandoz 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. 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 and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for Ipramol (IE/H/0163/001/R/001), a medicinal product with an identical composition. This is acceptable.

Readability test

The package leaflet has not been evaluated via a user consultation study. The MAH applied the package insert text approved in procedure IE/H/0163 into its house style (format, layout and design). The MAH's house style was successfully tested in the user tests of more than 50 user package leaflets. inserts. This demonstrates that the format, design and layout are extremely clear and the information provided is located particularly well. The MAH provided a detailed comparison of key elements and messages between the two package leaflets. The MAH's justification for not providing user testing results is acceptable and no further readability testing is considered necessary.

It is sufficiently proven that the package leaflet is of sufficient quality to ensure that the relevant information including the key safety messages can be easily found and understood by patients.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ipratropiumbromide/Salbutamol Sandoz 0.5/2.5 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. As with the innovator product any of the available nebulisers currently available on the market can be used.

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

The SPC, 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 October 2012. Ipratropiumbromide/Salbutamol Sandoz 0.5/2.5 mg per 2.5 ml, nebuliser solution was authorised in the Netherlands on 17 October 2012.

The date for the first renewal will be: 9 October 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to place the first two commercial batches and thereafter one batch annually on stability under long-term conditions.

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
SPC	Summary of Product Characteristics
$t_{½}$	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