CBG MEB

Public Assessment Report

Scientific discussion

Ipratropiumbromide 20 microgram/dose Vincion, aerosol, solution

(ipratropium bromide monohydrate)

NL License RVG: 117347

Date: 26 February 2019

This module reflects the scientific discussion for the approval of ipratropiumbromide 20 microgram/dose Vincion, aerosol, solution. The marketing authorisation was granted on 21 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COPD	Chronic Obstructive Pulmonary Disease
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
pMDI	pressured Metered Dose Inhaler
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ipratropiumbromide 20 microgram/dose Vincion, aerosol, solution from Vincion BV.

The product is a bronchodilator indicated in adults for the symptomatic treatment of reversible bronchospasm in:

- chronic obstructive pulmonary disease (COPD) according to the patients needs or on regular basis to prevent or reduce symptoms
- asthma as alternative to short acting β2-agonists when β2-agonists are not tolerated

There are insufficient data available with regard to the use of Ipratropiumbromide 20 microgram/dose Vincion in adolescents and children.

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

This decentralised procedure concerns a hybrid application with reference to the innovator product Atrovent 20 µg pressurised inhalation solution (NL License RVG 26834), which has been registered in the Netherlands by Boehringer Ingelheim B.V. since 14 November 2001.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

Indication
The MAH applied for a broad target population, including also children and adolescents. However, no *in vitro* equivalence has been demonstrated with the reference product (with and without spacer. Bioequivalence was shown by means of pharmacokinetic data obtained in healthy volunteers aged >18 years (with and without spacer) which precludes the extrapolation to adolescents and children. Therefore, the product did not meet the criteria given in the OIP guideline for showing equivalence and therefore the indication is limited to adults only.

II. QUALITY ASPECTS

II.1 Introduction

Ipratropiumbromide Vincion is a colourless solution, filled in an aluminum container fitted with a suitable 50 mcl metering valve and a plastic actuator. One metered dose (ex-valve) contains 20 micrograms ipratropium bromide monohydrate, which corresponds to 18 microgram ipratropiumbromide. Each container is filled to deliver 200 metered doses.

The excipients are norflurane (HFA-134a), citric acid, ethanol and purified water.

II.2 Drug Substance

The active substance is ipratropiumbromide monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ipratropiumbromide monohydrate is a white or almost white crystalline powder. It is very soluble in methanol, soluble in water and slightly soluble in ethanol.

The CEP procedure is used for the active substance. 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 Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The specification includes an additional test for a residual solvent and a specification for microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

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

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The development of the drug product has been performed in line with the 'Guideline on the pharmaceutical quality of inhalation and nasal products' and the Ph.Eur. monograph 'Preparations for inhalation'. The manufacturer has demonstrated extensive experience with the development and manufacture of this kind of drug products.

This abridged application is based two pharmacokinetic studies, one with charcoal and one without charcoal, both without spacer. And in addition one pharmacokinetic study to show equivalence with a spacer.

Manufacturing process
The manufacture process comprises dissolution of the ipratropium bromide and citric acid in water and ethanol mixture and subsequent the addition of a propellant, all under stirring and pressure, and subsequent filling of the cans. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, assay (can), uniformity and mean delivered dose, average weight of metered dose, fine particle dose, related substances, leakage, number of actuations, alcohol content, water content, particulate matter and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided three production scaled batches stored at 25°C/60% RH and 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Half of the units of each batch for each storage condition have been put in inverted position with the product in contact with the materials of the closure and the other half have been put in normal position, upwards. Yet for delivered dose only results in inverted positions have been provided. That needs to be clarified. The tested parameters are sufficiently stability indicating. All results comply and the only trends observed are increase in leakage rate and related substances. No differences are observed between the storage positions.
In view of the submitted stability data a shelf-life of 24 months is acceptable. Also the storage condition on temperature (do not store above 50°C) is 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Ipratropiumbromide Vincion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ipratropiumbromide Vincion is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Atrovent 20 µg pressurised inhalation solution which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ipratropiumbromide monohydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

For this hybrid application, evaluation of the test product has been done in a stepwise approach according to the guideline of orally inhaled products CPMP/EWP/4151/00 Rev1. As *in vitro* equivalence was not met, two pharmacokinetic studies (with and without concurrent charcoal blockade) were conducted in healthy adults. The MAH submitted an additional pharmacokinetic study conducted in healthy volunteers to show bioequivalence with a spacer.

IV.2 Pharmacokinetics

The MAH has submitted three pharmacokinetic studies, one with charcoal and one without charcoal, both without spacer, and a third study with spacer in adults.

The reference product was Atrovent inhaler CFC-free 20 mcg/actuation (Boehringer Ingelheim, UK). The choice of the reference product in the bioequivalence studies has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Inter-subject variability is higher during concurrent administration of oral charcoal with inhaled products regardless of the class of molecule. The study with concurrent charcoal blockade was planned as a replicate design study with a sample size that was adequate to account for such high CV that is expected to be ≥30%.

Bioequivalence studies

Bioequivalence study between Ipratropium Vincion and Atrovent under fasting conditions without concurrent charcoal blockade

Design

A randomised, single dose, open label, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21 - 41. Each subject received a single dose of four actuations (4x 20 mcg) without aid of a spacer of one of the two ipratropiumbromide formulations. Dosing was done under the supervision of an investigator and trained personnel after at least ten hours of fasting. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected at pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 9.00, 12.00, 18.00 and 24.00 hours after administration of the products.

The design of the study is acceptable.

Results

All 24 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ipratropiumbromide under fasted conditions.

Treatment N=24	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h
Test	363.39 ± 169.02	398.73 ± 173.14	80.08 ± 39.24	0.17 (0.08 - 3.00)
Reference	344.14 ± 121.98	375.77 ± 121.08	77.54 ± 33.07	0.17 (0.17 - 2.00)
***Ratio (90% CI)**	0.93 (0.89 - 1.20)	--	1.03 (0.87 - 1.21)	--
CV (%)	31	--	34	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Safety

No adverse events as well as serious adverse events were reported during the conduct of this bioequivalence study.

Bioequivalence study between Ipratropium Vincion and Atrovent under fasting conditions with concurrent charcoal blockade

Design

A randomised, single dose, open label, four-period, crossover, replicate bioequivalence study was carried out under fasted conditions with concurrent oral charcoal blockade in 90 healthy male subjects, aged 18 - 45 years. The study was conducted in three cohorts (Cohort A (n=42), Cohort (n=18), Cohort C (n=30)). Each subject received a single dose of four actuations (4x 20 mcg) without aid of a spacer of one of the two ipratropiumbromide formulations. Dosing was done under the supervision of

an investigator and trained personnel after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of seven to 14 days between two consecutive treatments.
On each of the treatment days, 50 ml (approximately 5 g) of activated charcoal suspension was given to the subjects two minutes prior to the inhalation of the first puff and immediately after dosing followed by at 1.00, 2.00 and 4.00 hours post-dose.

Blood samples were collected at pre-dose and at 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 6.00, 9.00, 12.00, 18.00 and 24.00 hours after administration of the products.

The design of the study is acceptable.

Results
Three subjects discontinued the study and five subjects dropped out. 81 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ipratropiumbromide under fasted conditions.

Treatment N=81	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h
Test	251.12	283.59	63.76	0.17 (0.08 - 3.00)
Reference	267.08	299.18	66.76	0.17 (0.17 - 2.00)
***Ratio (90% CI)**	0.94 (0.90 - 0.98)	0.95 (0.91 - 0.98)	0.96 (0.91 - 1.00)	--
CV (%)	21	19	24	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Safety
A total of 25 adverse events (13 events with the test product and 12 events with the reference product) were reported in the study by 21 subjects. All AEs were of mild to moderate severity. There were a total of four drug related AEs (three events of headache and one event of cough with the reference product).
One subject experienced a serious adverse event (SAE) (hospitalisation due to convulsion) in period 1. The SAE was of moderate severity and not related to the study drug or study related procedures. The SAE resolved completely without any sequalae.

Bioequivalence study between Ipratropiumbromide Vincion and Atrovent under fasting conditions using a spacer
Design
A randomised, single dose, open label, two-way crossover bioequivalence study was carried out under fasted conditions in 64 healthy male subjects (mean age 28 years). Each subject received a singe dose of two actuations (2x 20 mcg) of one of the two ipratropium formulations. The actuations were orally administered at least 60 seconds between each puff. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose and at 0.017, 0.05, 0.08, 0.17, 0.25, 0.33, 0.42, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 18 and 24 hours after administration of the products.

The design of the study is acceptable. The wash-out between periods is long enough and the sampling scheme is adequate.

Results
One subject withdrew in the first period because of a sore throat and five subjects did not arrive for the second period. Therefore 58 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ipratropiumbromide under fasted conditions.

Treatment N=58	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h
Test	272.82	255.81	68.44	0.08 (0.02 - 0.42)
Reference	287.42	270.00	73.55	0.08 (0.02 - 0.50)
***Ratio (90% CI)**	0.95 (0.92 - 0.98)	0.95 (0.92 - 0.98)	0.93 (0.87 - 1.00)	0.95 (0.92 - 0.98)
CV (%)	11	10	22	11

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Ipratropiumbromide Vincion is considered bioequivalent with Atrovent.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Clinical efficacy and safety

No new clinical study data have been submitted for this procedure. Ipratropium bromide has been on the market for several decades, and its efficacy and safety haves been well established.

Children
The originator Atrovent is licensed for children. The MAH applied for a broad target population, including also children and adolescents.

In order to obtain an indication in children for a hybrid orally inhaled product, the development of the product may need an additional program. The request for an additional program depends on the base on which equivalence is established. If *in vitro* equivalence is demonstrated, then under special conditions no children studies are needed (OIP guideline). For example, no clinical studies are needed in children if *in vitro* equivalence is demonstrated and the test product is a pressured metered dose inhaler (pMDI) with the same spacer as recommended for use with the reference product when administered via a pMDI. The spacer must be approved in the paediatric population (situation 1 of the OIP guideline).

However, no *in vitro* equivalence was demonstrated with the reference product (with and without spacer. Bioequivalence was only shown by means of pharmacokinetic data obtained in healthy volunteers aged >18 years (with and without spacer) which precludes the extrapolation to adolescents and children. Therefore, the product did not meet the criteria given in the OIP guideline for showing equivalence and therefore the indication is limited to adults only.

IV.4 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 Ipratropiumbromide Vincion.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions (i.e. urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis) • Ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) • Inhalation-induced bronchoconstriction/paradoxical bronchospasm • Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, tachycardia and palpitation)
Important potential risks	• Myocardial infarction • Stroke • Acute narrow-angle glaucoma • Disturbance in gastrointestinal motility in cystic fibrosis patients
Missing information	• Pregnancy and lactation • Effect of ipratropiumbromide on fertility

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Atrovent. No new clinical studies were conducted. The MAH demonstrated therapeutic equivalence in adults based on bioequivalence studies. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ipratropiumbromide Vincion has a proven chemical-pharmaceutical quality and is a generic form of Atrovent. Atrovent is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence between Ipratropiumbromide Vincion and the reference formulation has been established in adults.

In the Board meetings of 16 September 2015 and 18 May 2016, the following was discussed: One quality concern regarding fine particle mass, and the absence of pharmacokinetic equivalence between test and reference product in adults, adolescents, and children. In response, the MAH adequately provided the results of an additional study in adults with a spacer and without charcoal

blockade. In addition the indication has been brought in line with the Global Initiative for chronic obstructive Lung Disease (GOLD) guidelines.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ipratropiumbromide Vincion with the reference product, and have therefore granted a marketing authorisation. Ipratropiumbromide Vincion was authorised in the Netherlands on 21 September 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update product information	IA	24-7-2017	31-8-2017	Approval	N
Update product information	IA	24-8-2017	14-9-2017	Approval	N
Update manufacturing process	IB	6-11-2017	21-11-2017	Approval	N
Batch size increase	IB	6-11-2017	29-11-2017	Approval	N