CBG MEB

Public Assessment Report

Scientific discussion

Ipratropiumbromide Newline Pharma 20 microgram per actuation, pressurised inhalation solution

(ipratropium bromide)

NL/H/3507/001/DC

Date: 19 December 2016

This module reflects the scientific discussion for the approval of Ipratropiumbromide Newline Pharma 20 microgram per actuation, pressurised inhalation solution. The procedure was finalised on 24 May 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
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
GINA	Global Strategy for the diagnosis and management of asthma in children 5 years and younger
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
OIP	Orally Inhaled Products
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 Member States have granted a marketing authorisation for Ipratropiumbromide Newline Pharma 20 microgram per actuation, pressurised inhalation solution from NewLine Pharma S.L.

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

- chronic obstructive pulmonary disease (COPD)
- asthma as alternative to short acting β2-agonists when β2-agonists are not tolerated

Ipratropiumbromide Newline Pharma is indicated in children aged 6-12 years, adolescents and adults.

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 proposed product and the reference product contain the same amount of the same active substance and concern the same dosage form (pressurised inhalation, solution).

The concerned member states (CMS) involved in this procedure were Germany, Estonia, Portugal and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Ipratropiumbromide Newline Pharma is a pressurised stainless steel canister containing a transparent and colourless solution, fitted with a 50 µl metering valve with a transparent polypropylene actuator (with mouthpiece) and a green polypropylene dust cap. The metering valve contains aluminium, stainless steel, polyester and EPDM (ethylene propylene diene monomer) polymer. Each pressurised container contains 200 actuations.

One metered dose (ex-valve) contains 21 micrograms of ipratropium bromide monohydrate, corresponding with 20 micrograms of ipratropium bromide. This is equivalent to a delivered dose (ex-actuator) of 17 micrograms ipratropium bromide.

The excipients are: 1,1,1,2-tetrafluorethane, anhydrous ethanol, purified water, anhydrous citric acid.

II.2 Drug Substance

The active substance is ipratropium bromide monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder which is soluble in water, freely soluble in methanol and slightly soluble in ethanol. As the drug product is formulated as a solution, particle size distribution and polymorphism of the active substance are not relevant for the quality of the drug product.

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 drug substance is tested in line with the Ph.Eur. monograph with an additional test for a residual solvent as included on the CEP, and a specification for microbial quality. Sufficient batch analysis data have been provided, demonstrating that the drug substance is of adequate quality.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof The stability data are evaluated by the EDQM as part of granting the CEP.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The test and reference solutions have the same qualitative composition. There are only minor quantitative differences which are not considered clinically relevant.
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'. This abridged application is based on demonstrated *in vitro* equivalence, with and without spacer, and pharmacokinetic studies in adults on safety (without charcoal), also with and without spacer.
Results of *in vitro* equivalence testing of the aerodynamic particle (droplet) size distribution with the next generation impactor have been provided both with and without the use of a spacer (including different patient relevant flow rates with spacer). The HPLC method used for the quantification of the deposit in the different stages of the impactor has been validated over a range of 0.05 to 5.60 µg/ml for solutions of the fractions at the different stages and the limit of quantification has been determined as 0.05 µg/ml. The results at the different stages are above the limit of quantification, and therefore valid. The results were equivalent (within ±15%). Equivalence with and without spacer has been demonstrated by *in vitro* testing.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacture process comprises dissolution, mixture, addition of a propellant, all under stirring and pressure, and subsequent filling of the cans. Manufacture process validation data have been provided of three full-scale batches.

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, identification, assay by weight unit, uniformity and mean delivered dose, fine particle dose, content active ex-valve, related substances, leakage, number of actuations, and microbial quality. The tests and requirements are in line with current guidance in Ph.Eur. 'Preparations for inhalation' and the 'Guideline on the pharmaceutical quality of inhalation and nasal products'. Batch analytical data from the proposed production site have been provided for three full-scale batches demonstrating compliance with the proposed release specification.

Stability of drug product
Stability data on the product has been provided for three production-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Of each batch for each storage condition half of the units 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, upward. All results comply and the only trends observed are an increase in leakage rate (more pronounced at accelerated conditions), a decrease in number of actuations (only at accelerated conditions) and a slight increase in related substances. In downward position there is more decrease in number of actuations at accelerated storage conditions than in upright position. Other differences between the storage positions have not been observed.

The proposed shelf-life (3 years) and storage condition (not above 30°C, do not freeze) are justified based on the provided data and in line with the innovator product. As the storage condition is not considered to change after first use of the product, in-use studies are not required.

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 member states consider that Ipratropiumbromide Newline Pharma 20 microgram per actuation, pressurised inhalation solution 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 Newline Pharma is intended for substitution of comparable products, 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

Equivalence with and without spacer has been demonstrated by *in-vitro* testing. In addition to the *in vitro* comparisons, a comparative pharmacokinetic study was conducted to evaluate bioavailability between test and reference product, both with and without spacer. The results are briefly discussed below.

IV.2 Pharmacokinetics

Comparative bioavailability study
Design
A partial four-way cross-over study with and without spacing device was conducted. The study was designed to compare the systemic availability of test formulation (Ipratropiumbromide Newline Pharma 20 mcg/actuation from Newline Pharma S.L., Spain) versus the reference formulation (Atrovent, Laboratorios Boehringer Ingelheim España, S.A) in healthy volunteers with and without Aerochamber

spacer. Safety and clinical tolerability of both formulations were evaluated as a secondary objective. Eighty-one healthy volunteers, aged 18-45 years, were included in the study.
This trial involved the administration of a single dose of two formulations of ipratropium bromide 120 mcg. It was a sequential clinical trial, single dose, crossover, with randomised assignment and balanced carry-over effect. The trial was developed in two stages: the first with a small number of subjects (18) to obtain data for calculating the total number of subjects which were added in a second stage (60). Patients received test and reference product both with and without spacer.
Eighteen sequenced blood samples were obtained: at baseline, +2min, +5min, +10min, +15min, +30min, +45min, +1h, +1h30min, +2h, +2.5h, +3h, +4h, +6h, +8h, +10h, +12h and +24h post-administration of the medication. A wash-out period of at least one week was established between the four doses.

For a pMDI, the guideline for orally inhaled products not only recommends evaluation with and without spacer, but also evaluation in the presence of charcoal to eliminate the contribution of intestinal absorption. However, the contribution of ingested ipratropium to the systemic exposure is considered negligible following inhalation using pMDI and no pharmacokinetic studies with charcoal are needed for ipratropium pMDI.
As the first stage of the study was not used to evaluate bioequivalence but to determine the sample size of the study, it is acceptable to determine bioequivalence in the second stage. The statistical methods used were standard.

Results
The 81 volunteers who participated in this trial received any dose of ipratropium bromide. All 18 subjects that initiated the first stage completed it. Of the 60 subjects that initiated the second stage of the trial, three did not finish the trial: two dropped out, one for work reasons and one for health reasons, and another volunteer was withdrawn for taking medication that was not allowed. These three subjects were replaced by three reserves with the same sequence of treatments. At the end, 60 volunteers completed this stage.
A total of 78 subjects were included in the bioanalysis; of those, 24 subjects were exposed to 12 administrations of ipratropium bromide and 54 subjects were exposed to 24 administrations.
Seventy-seven subjects were included in the statistical analysis because one of the subjects showed a concentration higher than 5% of his C_{max} in the baseline sample during the second experimental period. All volunteers received both treatments (test and reference with and without spacer).

Table 1 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max}; median (range)) without Aerochamber (N=77)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h
Test	599 ± 258	764 ± 997	124 ± 79	0.17 (0.03 - 2.50)
Reference	615 ± 245	702 ± 307	121 ± 61	0.17 (0.03 - 2.00)
***Ratio (90% CI)**	0.97 (0.9 1- 1.03)	0.97 (0.90 - 1.04)	0.99 (0.90 - 1.07)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached
**ln-transformed values*

Table 2 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max}; median (range)) with Aerochamber (N=54)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h
Test	920 ± 258	1073 ± 425	230 ± 106	0.17 (0.03 - 1.00)
Reference	915 ± 221	1064 ± 347	228 ± 98	0.16 (0.03 - 2.50)
***Ratio (90% CI)**	1.00 (0.95 - 1.04)	0.99 (0.93 - 1.06)	0.99 (0.91 - 1.08)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

Table 3 Statistical analysis of pharmacokinetic parameters of the second stage of the study with and without Aerochamber.

With Chamber

n= 36 Ipratropium bromide	TEST Geometric mean	REFERENCE Geometric mean	T/R %	90% CI (Classical)
Ln C_{max} (pg/mL)	181.06	186.40	97.13	87.62-107-69
Ln AUC_{0-t} (h*pg/mL)	792.25	819.21	96.71	92.37-101.26
Ln $AUC_{(0-\infty)}$ (h*pg/mL)	853.12	903.56	94.42	89.67-99.41

Without Chamber

n= 59 Ipratropium bromide	TEST Geometric mean	REFERENCE Geometric mean	T/R %	90% CI (Classical)
Ln C_{max} (pg/mL)	87.51	93.30	93.79	85.59-102.78
Ln AUC_{0-t} (h*pg/mL)	479.35	502.39	95.41	89.39-101.85
Ln $AUC_{(0-\infty)}$ (h*pg/mL)	525.48	554.34	94.79	89.28-100.65

After logarithmic transformation of C_{max} and $AUC_{(0-t)}$ parameters, the confidence intervals for both formulations were found to be within the acceptance range (80-125%) with (Table 2) and without (Table 1) spacer, thus indicating bioequivalence between the test and reference formulations with and without spacer. However, the conduct of the study seemed to be less robust in the first stage of the study (positive pre-dose values, extrapolation of AUC>20% and C_{max} at first time point) compared to the second stage of the study. Bioequivalence was also demonstrated using data from the second stage only (see Table 3).

Results

A total of 90 adverse events (45 adverse events and 45 laboratory abnormalities) were reported in 45 volunteers. The clinical adverse events by treatment:

- 15 occurred with the test formulation.
- 30 occurred with the reference formulation.
- 45 were unrelated to any formulation.

The most common clinical adverse event reported for both formulations was headache (21). The most

common analytical alterations were low haemoglobin (8) and haematocrit (12). All of the analytical alterations were considered to be unrelated to administration of the trial formulations. Both formulations displayed an acceptable tolerance profile.

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. However, in the involved member states the age range and dose recommendations differ.

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 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).
The MAH submitted study data showing *in vitro* equivalence with and without the Aerochamber spacer. The reference pMDI and spacer combination are approved in the UK (Atrovent + Spacer Aerochamber Plus). Therefore no additional clinical studies in children are needed.

Indication
The MAH proposed the following indication: *'Ipratropiumbromide Newline Pharma is a bronchodilator indicated for the treatment of reversible bronchospasm. In chronic obstructive pulmonary disease (COPD) it is indicated on an as-needed basis or on regular basis to prevent or reduce symptoms. In asthma, it is indicated as alternative to short acting β2-agonists for relief of asthma symptoms or as a supplement to β2-agonists in an acute asthma attack.'*

During the procedure, following comments of the member states, the indication was adapted to *'Ipratropiumbromide Newline Pharma is a bronchodilator indicated for the symptomatic treatment of reversible bronchospasm in: chronic obstructive pulmonary disease (COPD); asthma as alternative to short acting β2-agonists when β2-agonists are not tolerated.*

Ipratropiumbromide Newline Pharma is indicated in children aged 6-12 years, adolescents and adults.'

This indication is in general in line with the reference SmPC and is supported by Dutch treatment guidelines.

In section 4.2 the following statement is included: *'Ipratropium bromide administered by spacer can be added to inhaled short acting bronchodilators in the treatment of an acute severe asthma exacerbation in the home situation. Both bronchodilators should be administered by spacer. For further conditions and further treatment recommendations, please refer to the national guidelines.'*

The reference SmPC does not include a statement regarding the use of ipratropium pMDI in the treatment of acute severe asthma. Support for the use of ipratropium pMDI as supplement to β2 agonists in the treatment of acute severe asthma exacerbations can be found in the GINA guidelines. The GINA 2014 guideline provides support for the use of ipratropium nebulisation in addition to nebulised β2 agonists in the treatment of acute severe asthma exacerbations. However, the GINA guideline fails to provide direct support for the use of ipratropium pMDI in the treatment of an acute severe asthma exacerbation. The included references in the GINA guideline provide some evidence for the use of ipratropium pMDI + spacer in an emergency setting for the treatment of an acute severe asthma. The GINA pocket guideline supports only the use of ipratropium pMDI in the treatment of an acute severe asthma exacerbation to those patients who will be transferred to an emergency setting or to those patients who are in an emergency setting.
In patients with an acute severe asthma exacerbation, bronchodilation should be provided by nebulisation or by pMDI and spacer. The GINA guidelines are international guidelines made based on consensus between member states, but at national level other guidelines may apply. Therefore, the

inclusion of a general statement in section 4.2, with a reference to the national guidelines, is agreed.

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 Newline Pharma 20 microgram per actuation, pressurised inhalation solution.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions (i.e. urticarial, 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
Missing information	• Pregnancy and lactation

The member states 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 20 µg pressurised inhalation solution. No new clinical studies were conducted. The MAH demonstrated therapeutic equivalence based on *in vitro* data and a pharmacokinetic study. 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 3 participants, followed by two rounds with 10 participants each. The 15 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 Newline Pharma 20 microgram per actuation, pressurised inhalation solution has a proven chemical-pharmaceutical quality and is a hybrid form of Atrovent 20 µg pressurised inhalation solution. Atrovent is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence between Ipratropiumbromide Newline Pharma and the reference formulation Atrovent has been established. In addition the indication is in line with the revised GINA guidelines and with the approved indication of the reference products in the RMS and CMS.

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 therapeutic equivalence has been demonstrated for Ipratropiumbromide Newline Pharma 20 microgram per actuation, pressurised inhalation solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 May 2016.

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