CBG MEB

Public Assessment Report

Scientific discussion

Ipratropiumbromide Sandoz 20 microgram per actuation, pressurised inhalation solution

(ipratropium bromide)

NL/H/3040/001/DC

Date: 21 October 2015

This module reflects the scientific discussion for the approval of Ipratropiumbromide Sandoz 20 microgram per actuation, pressurised inhalation solution. The procedure was finalised on 19 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ipratropiumbromide Sandoz 20 microgram per actuation, pressurised inhalation solution from Sandoz B.V.

The product 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 can be used as alternative to short acting β2-agonists when β2-agonists are not tolerated.
Ipratropiumbromide Sandoz 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 Czech Republic, Germany 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 Sandoz 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 absolute 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 European Pharmacopoeia.

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 was part of granting the CEP and has been granted by the EDQM.

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'. The delivered dose, ex-actuator, is 17 µg. The 12.5 ml fill includes a global 25% overage of solution in order to assure the 200 declared doses.
This abridged application is based on demonstrated *in-vitro* equivalence, with and without spacer, and PK 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 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 Sandoz 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 Sandoz 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.

According to the Guideline CPMP/EWP/4141/00 Rev.1, “Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease” in abridged dossiers with products containing a known active substance, *in vitro* comparison can be used to establish therapeutic equivalence to a reference drug to waive clinical studies.

Ipratropiumbromide Sandoz 20 mcg/actuation pressurised inhalation solution, the test product, in principle meets the criteria of the guideline to demonstrate therapeutic equivalence by comparing the *in vitro* particle size distribution:

- The product contains the same drug substance as the reference.

- The pharmaceutical dosage form is identical. The two products are pressurized inhalation solutions. The drug substance is in the liquid state (solution) and there are no differences in crystalline structure and/or polymorphic form.
- There are no differences in excipients that may lead to differences from reference in behaviour or in the safety profile of the product.
- The inhaled volume through the device and the resistance to airflow are considered not important as it is a pressurized product.
- Handling of the inhalation device is identical for both products.
- It has been checked that the target delivered dose is similar in both products (within ± 15%).

After confirming the above criteria are satisfied, data on particle size distribution for the test and the reference products were obtained through a 7 stage impactor. Since the product can be used with or without spacer, the *in vitro* equivalence has been performed in the two possible situations: both with and without spacer. The MAH initially applied for a biowaiver based on the above argumentation. However, following comments by the member states, additional *in-vitro* comparison studies were submitted to demonstrate equivalence in which Aerodynamic Particle Size Distribution (APSD) was compared between test and reference product with and without spacer (Aerochamber®) and different patients' breathing patterns.
It was concluded that without spacing device, the *in vitro* data showed that test and originator can be considered therapeutically equivalent by using grouping of the stages. However, equivalence between test and reference product with spacer (Aerochamber®) and different patients' breathing patterns was not yet demonstrated unambiguously. If equivalence with spacer cannot be demonstrated, an additional program in children such as a pharmacokinetic study may be needed. Subsequently the MAH submitted additional study data which sufficiently demonstrate *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 ≥ 6 years are needed.

In addition to the *in vitro* comparisons, a comparative pharmacokinetic study was conducted to evaluate bioavailability between test and reference product. 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 Sandoz 20 mcg/actuation from Sandoz B.V., the Netherlands) versus the reference formulation (Atrovent, Laboratorios Boehringer Ingelheim España, S.A) in healthy volunteers with and without AeroChamber spacer. 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 randomized 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 an 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 PK 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, tmax; median (range)) without spacer (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 (0.91-1.03)	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, tmax; 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 predose 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 events 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.

Children < 6 years
Originally, the MAH also applied for an indication for children < 6 years. In the international guideline GINA (Global Strategy for the diagnosis and management of asthma in children 5 years and younger) and Dutch national clinical guidelines, ipratropium is not indicated for regular treatment in this age population. GINA states "there is no evidence that inhaled ipratropium has an important role in the daily management of asthma in children 5 years and younger". The use of ipratropium is not approved in the Dutch reference SmPC. Therefore, in the SmPC a general comment regarding the use of ipratropium in children < 6 year should be included.

Indication
The originally proposed indication was: 'for the regular treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD) and chronic asthma.'
Following comments of the involved member states, a revised indication was proposed, in line with the current treatment guidelines of asthma (Global Strategy for Asthma Management and Prevention 2014) and COPD (Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, updated 2014).

The MAH proposed the following indication:
'Ipratropiumbromide Sandoz is a bronchodilator indicated for the treatment of reversible bronchospasm. In 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.'

However, the RMS disagreed with this proposal, because it is insufficiently supported by the GINA guidelines:

- GINA guidelines consider that "the benefits of ipratropium bromide in the long term management of asthma have not been established, although it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from β_2 agonists (GINA guideline 2014)."
- The proposed indication: "during an acute asthma attack" is too broad as it might also include an acute bronchoconstriction. This indication lacks support in the GINA guidelines.
- The GINA Pocket guideline supports the use of inhaled ipratropium added to short acting β_2 agonists for the treatment of an acute severe asthma exacerbation in a home situation, for those patients who will be referred to an emergency department. However, no posology is provided.

The RMS considered that the use of ipratropium inhaled added to a short acting β_2 agonist can be of value in the treatment of an acute severe exacerbation of asthma in a home situation. Both bronchodilators should be administered by spacer. Although this recommendation is not strongly supported by the international GINA guidelines, this is supported by Dutch treatment guidelines.

The MAH argued that the GINA guidelines support the use of ipratropium pMDI as supplement to β_2 agonists in the treatment of acute severe asthma exacerbations (instead of asthma attacks) and proposed to add this comment in the indication.
Indeed, the GINA 2014 guideline provides support for the use of ipratropium nebulization in addition to nebulized β_2 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. The RMS considers, that in these patients, bronchodilation should be provided by nebulization or by pMDI and spacer. In addition, the MAH did not provide other evidence to support the use of ipratropium pMDI in the acute treatment of a severe asthma exacerbation, although the use of a pMDI + spacer for the treatment of acute severe asthma exacerbations is recommended in the Dutch national guideline.

The Dutch reference SmPC does not include a statement regarding the use of ipratropium pMDI for the treatment of acute severe asthma, although the use of pMDI + spacer is included in the Dutch national guideline.
The GINA guidelines are international guidelines made based on consensus between member states, but at national level other guidelines may apply. Therefore, the RMS proposed a general statement for this indication in section 4.2, with a reference to the national guidelines. This proposal was agreed by the CMS.

Section 4.1 'Therapeutic indications'
'Ipratropiumbromide Sandoz is a bronchodilator indicated for the treatment of reversible bronchospasm. In COPD, it is indicated on an as-needed basis or on regular basis to prevent or reduce symptoms. In asthma, it can be used as is indicated as alternative to short acting β2-agonists for relief of asthma symptoms when β2 agonists are not tolerated.
Ipratropiumbromide Sandoz is indicated in children aged 6-12 years, adolescents and adults.'

The following text to be included in section 4.2, 'Posology and method of administration':
Treatment of acute severe exacerbations
'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 other conditions and further treatment recommendations, please refer to the national guidelines.'

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 Sandoz 20 microgram per actuation, pressurised inhalation solution.

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Hypersensitivity reactions (i.e. urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis)	SmPC sections 4.4 and 4.8	None
Ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain)	SmPC sections 4.4 and 4.8	None
Inhalation-induced bronchoconstriction/ paradoxical bronchospasm	SmPC sections 4.4 and 4.8	None
Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, tachycardia and palpitation)	SmPC sections 4.8 and 4.9	None
Important potential risk		
Myocardial infarction		None
Stroke		None
Missing information		
Pregnancy and Lactation	SmPC section 4.6	None

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 PK study. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

No user test was provided. Adequate justification is provided for bridging of proposed package leaflet with the package leaflet of the reference product Atrovent Inhaler CFC-Free 20 micrograms per metered dose pressurised inhalation, solution authorised in Ireland (parent leaflet). With regard to content the leaflets are sufficiently similar. Also the provided evidence of a successful user test for the parent leaflet is acceptable. Regarding the design and layout of the package leaflet adequate bridging has been performed. Therefore all criteria for bridging are met, and the bridging report can be accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ipratropiumbromide Sandoz 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 Sandoz 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.

On 15 October 2014, the application was discussed in the Board meeting of the RMS. The Board came to a positive conclusion for the indication in adults. An indication in children < 6 years was not considered approvable.

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 Sandoz 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 19 January 2015.

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