Public Assessment Report
Scientific discussion

Ipravent
(ipratropium bromide (as monohydrate))

SE/H/1361/01/DC

This module reflects the scientific discussion for the approval of Ipravent. The procedure was finalised on 2015-10-01. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Ipravent, 20 micrograms per actuation pressurised inhalation, solution, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, ELC GROUP s.r.o applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, BG, CZ, DE, EL, HR, HU, NO, PL, SI and SK as concerned member states (CMS). PT was withdrawn as CMS in clock stop.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atrovent, 20 micrograms per actuation pressurised inhalation, solution authorised in SE since 1978, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Drug Substance
The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.
III. NON-CLINICAL ASPECTS
III.1 Discussion on the non-clinical aspects
Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS
IV.1 Pharmacokinetics
According to the Guideline for Orally Inhaled Products (OIP) (CPMP/EWP/4151/00 Rev.1, 2009), a step-wise approach should be considered when demonstrating therapeutic equivalence. The first step consists of pharmaceutical data, the second step of pharmacokinetic data and the third step is represented by pharmacodynamic/clinical efficacy and safety data. In the current application, equivalence has not been demonstrated based on pharmaceutical data alone and the demonstration of therapeutic equivalence is based on pharmacokinetic data.

According to the Guideline for Orally Inhaled Products (OIP), pharmacokinetic data may be used to support efficacy and safety. A pharmacokinetic study designed to assess pulmonary deposition (efficacy), has to be able to exclude absorption of the active moiety from the gastrointestinal tract (for example by using charcoal blockade). In the investigation of systemic safety total systemic exposure has to be measured. However it may be possible for substances with negligible gastrointestinal absorption that the pharmacokinetic study designed to assess pulmonary deposition may be sufficient in the assessment of therapeutic equivalence.

Depending on formulation and inhalation technique, 10-30 % of an inhaled dose of ipratropium bromide reaches the lungs. The majority of the dose is swallowed. Cumulative renal excretion (0-24 hours) of parent substance is estimated to 46% of an intravenous dose, less than 1% of an oral dose and 3-13% of an inhaled dose. Based on these data the total systemic bioavailability of oral and inhaled doses is estimated to 2% and 7-28% respectively. Following intravenous administration, the terminal half-life has been assessed as approximately 1.6 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers without activated charcoal blockade, comparing Ipratropium bromide HFA pMDI, 20 microgram/actuation, manufactured by Cipla Limited, India with Atrovent CFC-free, 20 microgram/actuation, pressurised inhalation, solution by Boehringer-Ingelheim Limited, UK under fasting conditions. Since the product is a pressurised metered dose inhaler there is no flow dependency of the product. Hence, a study in healthy volunteers is acceptable. The study was conducted at Sitec Labs Pvt Ltd, Mumbai, India between 7th and 22nd December 2011. A dose of 4 actuations (80 microgram) was used. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of ipratropium bromide were determined with an adequately validated LC/MS/MS method. For AUC$_{0-t}$ and C$_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Bioequivalence was also evaluated in one single-dose, four-way crossover replicated study conducted in 90 healthy volunteers with activated charcoal blockade, comparing Ipratropium bromide HFA pMDI, 20 microgram/actuation, manufactured by Cipla Limited, India with Atrovent CFC-free, 20 microgram/actuation, pressurised inhalation, solution by Boehringer-Ingelheim Limited, UK under fasting conditions. Since the product is a pressurised metered
dose inhaler there is no flow dependency of the product. Hence, a study in healthy volunteers is acceptable. The study was conducted at Sitec Labs Pvt Ltd, Navi Mumbai, India between 16th October and 4th December 2014. A dose of 4 actuations (80 microgram) was used. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of ipratropium bromide were determined with an adequately validated LC/MS/MS method. For $AUC_{0-t}$ and $C_{\text{max}}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Thus, bioequivalence with and without charcoal has been demonstrated, supporting equivalence in efficacy and safety compared to the reference product.

**IV.2 Discussion on the clinical aspects**

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

**IV.3 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 Ipravent.

<table>
<thead>
<tr>
<th>Summary of safety concerns as approved in RMP</th>
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<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
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<tr>
<td>• Hypersensitivity reactions including anaphylactic reactions;</td>
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<tr>
<td>• Cardiac events (palpitations, supraventricular tachycardia, atrial fibrillation);</td>
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<tr>
<td>• Ocular complications (intraocular pressure increase, acute narrow-angle glaucoma, corneal oedema).</td>
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<tr>
<td>• Paroxysmal bronchospasm</td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<td>• Acute narrow-angle glaucoma</td>
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<tr>
<td>• Disturbance in gastrointestinal motility in cystic fibrosis patients</td>
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<tr>
<td>• Off-label use in children</td>
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<tr>
<td><strong>Missing information</strong></td>
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<td>• The effect of Ipratropium bromide on fertility The effect in pregnancy and during lactation.</td>
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</tbody>
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Routine pharmacovigilance and risk minimization activities are proposed by the Applicant. This is endorsed.

**Summary of the RMP**

The RMP is approved.
V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
This application concerns Ipravent, pressurised inhalation, solution formulated as 20 microgram/actuation. The product is applied as a hybrid application and evaluated in a step-wise approach according to the guideline CPMP/EWP/4151/00 Rev.1.

The base in the evaluation is the pharmaceutical properties. Comparative in vitro studies of the applied product and the reference product have been performed and statistical analysis is provided for grouped stages of the aerodynamic particle size distribution. The data do not comply with all pharmaceutical criteria of the guideline. Therefore, the application cannot be based solely on in vitro data and in vivo studies are needed for demonstration of therapeutic equivalence.

Since equivalence has not been demonstrated based on pharmaceutical data alone the demonstration of therapeutic equivalence is based on pharmacokinetic data. The applicant has submitted two single-dose bioequivalence studies in the fasted state, one with and one without activated charcoal blockade. Bioequivalence in the study without activated charcoal is concluded, thus indicating equivalence regarding systemic safety. Bioequivalence has also been demonstrated in the study with activated charcoal blockade, which supports equivalent efficacy compared to the reference product.

The benefit/risk ratio is considered positive and Ipravent, 20 micrograms per actuation pressurised inhalation, solution, is recommended for approval.

VII. APPROVAL
The Mutual recognition/Decentralised procedure for Ipravent, 20 micrograms per actuation pressurised inhalation, solution, was positively finalised on 20151001.
## Public Assessment Report – Update

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<th>Scope</th>
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<th>Product Information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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Y/N (version)