

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Combivent/Berovent  
Ipratropium Bromide + Salbutamol**

**DK/W/015/pdWS/001**

<b>Rapporteur:</b>	Denmark
<b>Finalisation procedure (day 90):</b>	03-05-2011
<b>Date of finalisation of PAR</b>	17-05-2011

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Combivent/Berovent
INN (or common name) of the active substance(s):	Ipratropium Bromide + Salbutamol
MAH (s):	Boehringer Ingelheim
Pharmaco-therapeutic group (ATC Code):	R03AK04
Pharmaceutical form(s) and strength(s):	Nebuliser solution, unit dose vial, 0,5 mg+2,5 mg/2,5 ml Pressurised inhalation, 20 µg+100 µg/actuation

## **I. EXECUTIVE SUMMARY**

In accordance with Article 45 of the Regulation (EC) No 1901/2006 the pharmaceutical company Boehringer Ingelheim has submitted data from five studies of Ipratropium bromide and Salbutamol.

None of the studies submitted contribute new safety or efficacy information to warrant any changes to SmPC and PL.

## **II. RECOMMENDATION<sup>1</sup>**

No further action is required.

## **III. INTRODUCTION**

The combination of ipratropium bromide and salbutamol (Combivent) as inhalation solution is indicated in the treatment of chronic obstructive lung diseases in adults and children more than 12 years old, when monotherapy is considered to be insufficient.

The MAHs has submitted five completed pediatric studies for ipratropium bromide and salbutamol, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for ipratropium bromide and salbutamol and that there is no consequential regulatory action.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical studies**

In the studies U88-0360, U87-0758 and U91-0747 nebulised solution of ipratropium bromide 0.25 mg and salbutamol 5 mg was given. In the study U00-0040 fixed combinations of aerosolized ipratropium bromide 20 mcg + salbutamol 100 mcg was used. And in the study U85-0434 aerosolized ipratropium bromide and aerosolized salbutamol were given separately.

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<sup>1</sup> The recommendation from section V can be copied in this section.  
Ipratropium bromide/Salbutamol  
DK/W/015/pdWS/001

## **IV.2 Non-clinical aspects**

The MAH did not submit Non-clinical studies.

## **IV.3 Clinical aspects**

### **1. Introduction**

The following studies were submitted by the MAH:

- Study U85-0434: Loennerholm G, Foucard T, Bratteby LE. Combined treatment with ipratropium bromide and beta-2 adrenoceptor stimulating agents in chronic childhood asthma. 1 July 1985.
- Study U87-0758: Kazim F. Statistical report: Comparison of the use of salbutamol solution and the combination of salbutamol and ipratropium solution in the treatment of acute asthma attacks in children. 2 July 1986.
- Study U88-0360: Storr J, Lenney W. A study of nebulised Ventolin versus nebulised Ventolin plus Atrovent in acute childhood asthma. 16 May 1988.
- Study U91-0747: Skene PC. A comparison of a combination of Ipratropium bromide and Salbutamol with Salbutamol alone in acute severe asthma. 10 April 1991.
- Study U00-0040: Glanczspigel R. Combivent vs. salbutamol in patients with metacholine induced bronchospasm. 29 December 1998.

The MAH submitted reports for all the above mentioned studies.

### **2. Clinical studies**

U88-0360 reports a randomized study from 1984-1985 with a total of 138 asthmatic children between the ages of 11 months and 15 years. Patient demographics were not provided by the report. The objective of the study was to discover whether the addition of ipratropium to salbutamol improves therapeutic response apparently defined as the length of hospital stay and the number of nebulisers needed. Children admitted with asthma were randomized to be treated with either nebulised salbutamol (5mg) or a mixture of salbutamol (5mg) and ipratropium (0.25mg). There was no difference in the length of hospital stay or the number of nebulisations required. In addition, there was no difference in the number of patients requiring treatment with steroids. The authors conclude that they cannot recommend the addition of ipratropium to the treatment of severe childhood asthma. The report included no information about undesirable effects.

U91-0747 reports a double-blind parallel group study to determine whether nebulised ipratropium bromide used with salbutamol is more effective than salbutamol alone in children with acute severe asthma. In particular, whether this combination reduces the need for other therapy, especially i.v. theophylline. A total of 20 children between the ages of 3 and 12 years were randomized to either salbutamol 2.5 mg for children

between 3-9 years or 5 mg for children over 9 years or a combination of nebulised salbutamol and ipratropium bromide (patients 3-9 years receiving 2.5 mg salbutamol and 250 mcg ipratropium, whereas children over 9 years receiving 5 mg salbutamol and 500 mcg ipratropium). A single nebulised dose was given. The authors state that the volume of missing data is such that no statistical calculations can be drawn. However, the addition of ipratropium bromide to nebulised salbutamol did not appear to benefit this group, since there was no evidence of a reduced need for other therapy. Neither group showed any significant change in heart rate during the study period. The increase in peak flow was larger in the salbutamol group, but this was not statistically significant. The report included no information about undesirable effects.

Study U00-0040 was a randomized double-blind cross over study performed in 1998 with the objective to evaluate whether 2 puffs of fixed combination of aerosolized 120 mcg salbutamol sulphate (equivalent to 100 mcg of the base) + 20 mcg ipratropium bromide (Combivent pMDI) confers significant additional protection against metacholine induced bronchoconstriction in asthmatic atopic patients when compared to 2 puffs of aerosolized 100 mcg salbutamol alone. A total of 30 asthmatic atopic children between the ages of 7 and 13 years were randomized. The Combivent PD20 (provocative dose of methacholine that reduces FEV1 by 20%) mean value was 8 times greater than the Salbutamol PD20 mean value ( $p < 0.01$ ). During metacholine challenge test after Combivent, 66.7% of the patients were asymptomatic while after the salbutamol treatment, 13.3% were asymptomatic ( $p < 0.01$ ). Only one patient under Combivent treatment showed dry mouth judged by the investigator not to be drug related, yet without further elaboration on this point. It was concluded that Combivent confers significant additional protection against metacholine induced bronchoconstriction in asthmatic pediatric patients compared to salbutamol. Children in this study had mild asthma and were excluded if they were on inhaled corticosteroids in the last month. The primary endpoint cannot be directly related to improved control of asthma symptoms and lung function.

The aim of the study U85-0434 from 1985 was to investigate whether addition of ipratropium bromide to oral and inhaled salbutamol resulted in improvement in children with asthma. Study design was double-blind cross over study. Thirteen children (8 boys and 5 girls) aged 9-16 years with stable moderate to severe asthma were enrolled. In the acute phase, three children were excluded from further analysis because of 25% increase in FEV1 at day 2. Analysis of the remaining children showed that the addition of ipratropim to salbutamol improved lung function parameters significantly. In the maintenance phase inhalation of ipratropium 40 mcg four times daily did not improve lung function or alleviate asthma symptoms. None of the included patients received inhaled steroids. The report included no information about undesirable effects.

U87-0758 is a double-blind, randomized single-day study of 25 children known with asthma between 6-17 years of age (16 boys and 9 girls). Upon admission with acute asthma exacerbation, patients were randomized to either nebulized solution of salbutamol every 20 minutes for 2 hours or nebulized solution of salbutamol given every 20 minutes for 2 hours and ipratropium bromide given at 0, 40 and 80 minutes. The primary variables were change in FEV1 and FVC. Only three patients were on treatment

with inhaled steroids. Both treatments resulted in significant increase in lung function parameters; however, the combination therapy resulted in a significantly greater bronchodilation than salbutamol alone. The change in FEV1 after 150 minutes was 0.687 L in the combination group and 0.413 L in the salbutamol group (p=0.006). Similar pattern was seen with FVC. Tremor was a frequent side effect in both groups. Other undesirable effects were vomiting, dry mouth and cough. No serious undesirable effects were reported.

### **3. Discussion on clinical aspects**

The company has provided an expert statement concluding that: “the results of the above studies and their conclusions are not thought to support a change in the combination ipratropium bromide and salbutamol sulphate (Combivent) Company Core Data Sheet”. I certainly agree with this statement and have to conclude that these data warrant no change to SmPC or PL.

The bronchodilator treatment of choice in asthma exacerbation is short acting beta-2 agonist, which can be supplied with anti-cholinergic drug if needed (GINA guidelines). Ipratropium bromide can be used for children from 0 years of age, if treatment with inhaled beta-2 agonist is insufficient. The question is whether the provided studies justify the use of combination of ipratropium and salbutamol in children younger than 12 years. In my opinion the answer is no. The first 2 studies (U88-0360 & U91-0747) are negative studies. The largest study with 138 children showed no significant efficacy of the combination of Ipratropium bromide compared to Salbutamol. Efficacy was being defined as the length of hospital stay. Otherwise, the number of patients enrolled is small, and the target population of children below 12 years is still smaller. The justification for the sample size calculation in all studies is unclear. All included patients are considered today as undertreated, as the majority did not receive optimal asthma treatment with inhaled corticosteroids, which is probably due to the old dates of these studies. Therefore, it is hard to accept any changes in the treatment recommendations of stable asthma and acute asthma exacerbations in children below the age of 12 years based on the mentioned data. The reporting of undesirable effects in these studies is unsatisfactory or absent which makes the risk benefit ration unfavourable in this population.

## **V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The summarised studies do not add any relevant clinical efficacy or safety information that justifies changes to SPC or patient leaflets.

➤ **Recommendation**

No further action required

**VI. REQUEST FOR SUPPLEMENTARY INFORMATION**

Not applicable

**VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

*The list can be taken from the spreadsheet compiled from the EMEA*