

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

**Atrovent
Ipratropium Bromide**

DK/W/014/pdWS/001

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

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Atrovent
INN (or common name) of the active substance(s):	Ipratropium Bromide
MAH (s):	Boehringer Ingelheim
Pharmaco-therapeutic group (ATC Code):	R03BB01, R01AX03
Pharmaceutical form(s) and strength(s):	Nebuliser solution, unit dose vial, 0,25 mg/2ml and 0,5 mg/2 ml Pressurised inhalation, solution 20 µg/actuation Inhalation powder, capsule 40 µg Nasal spray, solution 0,03%

I. EXECUTIVE SUMMARY

In children, Ipratropium bromide solution for inhalation is approved for the treatment of acute asthma attack or other causes of respiratory distress in adults as well as children from 0 years of age. Ipratropium bromide MDI is approved as a maintenance treatment in asthma as a supplement to treatment with inhaled steroids and beta-2 agonists in children. It is stated in SmPC from several EU countries that Ipratropium MDI should be used under medical advice and supervision of an adult in children under 6 years of age. Ipratropium nasal spray is not approved in children less than 12 years of age in most European countries, though approved to children younger than 12 years in few countries (e.g. Belgium and Greece).

In accordance with Article 45 of the Regulation (EC) No 1901/2006 the pharmaceutical company Boehringer Ingelheim has submitted data from 42 studies of Ipratropium bromide inhalation products and nasal spray.

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

II. RECOMMENDATION¹

No further action required.

III. INTRODUCTION

Boehringer Ingelheim submitted forty two completed paediatric studies for ipratropium bromide inhalation or nasal application, 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 that there is no evidence in support of changes regarding the pediatric patient population.

IV. SCIENTIFIC DISCUSSION

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

The inhalation studies provided involve ipratropium bromide as solution for inhalation, dry powder inhaler (DPI) or pressurised metered dose inhaler (pMDI).

The nasal studies provided involve ipratropium bromide nasal spray.

¹ The recommendation from section V can be copied in this section.

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:

- Therapeutic testing for several weeks in bronchospastic children: daily use of Sch 1000 metered dose aerosol. (U72-0222)
- Therapeutic testing of several days' duration, in bronchospastic children: daily administration of multiple doses of Sch 1000 metered-dose aerosol. Duration of study: 1 - 20 days. (U72-0227)
- Results of a study concerning children with an asthmatic syndrome treated with a parasympatholytic agent, the Sch 1000. (U74-0104)
- Comparison of Ba-253 and Atrovent metered aerosol in exercise-induced asthma. (U78-0018)
- Comparison of the curative effect of IK 6 metered aerosol and its individual constituents in a provocation test with antigen inhalation. (U79-0121)

- Pilot assessment of the effect and tolerability of Th 1165a as a capsule administered with a powder inhaler and assessment of the powder inhaler. (U79-0177)
- Acute and therapeutic dose-response comparison of Th 1165a administered with the CHBS powder inhaler to children. (U80-0167)
- Efficacy and usability of Sch 1000 in capsules with powder inhalator in paediatrics (pilot study). Phase III. (U82-0222)
- Comparison of treatment with IK 6 and SCH 1000 used as capsules by means of a powder inhaler in paediatrics. Phase III. (U82-0226)
- Durban trial of Atrovent: statistical analysis of results. (U83-0398)

- Ipratropium bromide (Atrovent) maintenance therapy of bronchial asthma and spastic bronchitis: results of a multicenter study on 2557 cases. (U84-0774)
- Report to Boehringer-Ingelheim, Australia on clinical trial to determine the optimum dose of nebulised ipratropium bromide (Atrovent) solution (0.020 %) in children with chronic asthma. (U84-0885)
- Comparative study with Ipratropium bromide versus Salbutamol in 30 asymptomatic asthmatic children. (U84-0911)
- Effect of ipratropium bromide on the diurnal variation of asthma in children. (U85-0252)
- Comparison of the bronchospasmolytic action of Berotec and Atrovent inhalation solution in infants. (U86-0413)
- Mechanisms of bronchial hyper-reactivity in cystic fibrosis. (U86-0564)
- Statistical report: Atrovent by inhalation in asthmatic children, a dose response study. (U86-0925)
- Comparison of the bronchodilatory effect of nebulised ipratropium bromide and fenoterol in children with acute crisis of asthma. (U86-0985)
- Clinical and spirometric evaluation of ipratropium bromide and salbutamol in children with bronchitis and preceding asthma. (U87-0035)
- Comparative study of ipratropium bromide and salbutamol in children with chronic bronchitis and / or asthmatic bronchitis. (U87-0397)
- Study of bronchospasmolytic action of ipratropium bromide in asthmatic children in intercritical period: dose action curve. (U87-0945)
- Long term safety of ipratropium bromide in children with reversible obstructive pulmonary disease in stable period. (U88-0151)

- Comparison of the efficacy of preservative free ipratropium bromide and Atrovent nebuliser solution in children with asthma (Should ipratropium bromide be preservative free ?). (U88-0553)
- Atrovent or Berotec mite in children with recurrent obstructive bronchitis. (U89-0249)
- Evaluation of optimal effective dose and action duration of ipratropium bromide in reducing bronchospasm in children with reversible chronic obstructive airway disease. (U90-0054)
- Study of the efficacy and tolerance of ipratropium bromide solution administered by nebulisation in children during an asthma attack and with a theophylline infusion. (U90-0055)
- A retrospective study of Atrovent nebuliser solution in wheezy infants. (U91-0623)
- Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. (U92-0221)
- Efficacy and tolerability of Ipratropium bromide solution in the prevention of exercise-induced bronchospasm in children. (U92-0573)
- Tolerability and acceptability of Ipratropium bromide - Dry powder form in children with asthma. (U92-0812)
- To evaluate, in an open pilot study, the effect on lungfunction of Ipratropium bromide inhalation solution and the additional effect of a beta 2-agonist (Salbutamol inhalation solution) in children with an acute attack of asthma. (U93-0136)
- A four-way, single-dose crossover, dose-ranging study of inhaled Atrovent and placebo in children with chronic asthma. (U93-0304)

- A study of the Efficacy and Safety of repeated nebulized therapy combining ipratropium bromide 0.25mg plus salbutamol sulphate 3.0mg versus salbutamol sulphate 3.0mg alone in children with acute asthma. (U94-0664)
- Randomized, Double-Blind, Parallel Comparison of Atrovent Nasal Spray 0.03% vs. Placebo Administered Twice a Day in Pediatric Patients with Allergic or Nonallergic Perennial Rhinitis with an Optional 6-month Treatment Comparison of ATROVENT Nasal Spray 0.03% vs. Beconase AQ. (U95-3002)
- Randomized, Double-Blind, Parallel Comparison of Atrovent Nasal Spray 0.03% vs. Placebo Administered Twice a Day in Pediatric Patients with Allergic or Nonallergic Perennial Rhinitis with an Optional 6-month Treatment Comparison of Atrovent Nasal Spray vs. Beconase. (U96-3125)
- Comparative double-blind study of the bronchodilating effect of ipratropium bromide administered as inhalation powder with two different powder inhalators in children with bronchial asthma. (U97-0051)
- A double-blind, vehicle controlled pharmacokinetic study of ATROVENT Nasal Spray 0.06% in children with naturally acquired common colds. (U97-3023)
- A single-blind, placebo-controlled safety evaluation of ATROVENT Nasal Spray 0.06% administered alone or in combination with over-the-counter cold therapies in children with naturally acquired common colds. (U97-3216)
- Efficacy of inhaled ipratropium bromide in acute bronchiolitis. (U98-0091)

- A multiple dose comparison of ipratropium bromide HFA-MDI and Atrovent MDI in a 12-week, double-blind, parallel group study in paediatric patients with bronchial asthma. (U98-0129)
- Double-blind, controlled trial to assess the efficacy of ipratropium bromide associated with high dose salbutamol by repeated nebulisation versus repeated nebulisation of salbutamol alone, for 120 minutes, in acute asthmatic attacks in young children. (U00-0090)
- A Phase IV Safety Trial in Pediatric Patients (Ages 2-5) with Rhinorrhea Associated with a Common Cold or Allergy. (U03-3585)

The company's expert statement included 19 of the above studies. The remaining 23 studies were performed prior to 1990, they were judged to have limitations, e.g. mostly included less than 40 study subjects, and were not considered in the company's expert statement. In the following review, the summary of the 19 studies is followed by a short assessor's comment. In addition I have summarised the remaining 23 studies and added a short comment to each summary. These studies are marked by an asterisk in the beginning.

2. Clinical studies

Oral Inhaled Products

- U87-0397 reports a study that was performed in 1987 with the objective to evaluate the efficacy of ipratropium bromide vs. salbutamol in children with bronchitis. A total of 60 children between the ages of 6 and 15 years were randomized. The conclusion from this study was that ipratropium bromide is a very effective bronchodilator in the treatment of chronic bronchitis and bronchial reactivity in children. No side effects were reported.

Assessor's comments: The text of the study is in Spanish, but an English summary is provided. In an open cross over design, patients received either inhaled salbutamol 100 mcg t.i.d. or inhaled ipratropium 40 mcg t.i.d for 2 weeks. The primary endpoint is symptoms; therefore the open design of the study is questionable. Atrovent is approved for the treatment of asthma in children > 6 years old in most European countries.

- Study 244.2317 (U88-0151) was performed during 1986 and 1987 with the objective to evaluate the long term safety of ipratropium bromide in children with reversible obstructive pulmonary disease in stable period. Overall, 147 children with stable asthma between 8 and 15 years were included in a multi-centre non-controlled design. Ipratropium bromide 40 mcg t.i.d was given via pMDI. The conclusion from this study was that treatment with ipratropium bromide was well tolerated and showed no tachyphylaxis after 3 months of treatment.

Assessor's comments: the findings of this study suggest that ipratropium bromide given for 3 months is well tolerated in children older than 8 years.

- Study 244.601 (U89-0249) was performed during 1987 and 1988 with the objective to determine which substance, Atrovent or Berotec, is of greater therapeutical benefit in children with recurrent obstructive bronchitis aged between 4 to 12 years. A total of 163 children participated. The conclusion from this study was that Berotec and Atrovent are both effective in the treatment of recurrent obstructive bronchitis in children. No relevant safety information was reported.

Assessor's comments: both interventions improved lung function by approximately 20% and only one patient in the Atrovent group experience side effects, which is not specified by the report.

- Study 244.2310 (U90-0055) was performed in 1987 with the objective to evaluate the efficacy and tolerance of ipratropium bromide 0.025% solution in asthma attacks in children with an infusion of theophylline. A total of 52 children between the ages of 5 and 15 years were randomized. The conclusion from study was that there was no statistically significant difference between the 2 groups, though there was a trend in favour of ipratropium bromide (success rate: 66.7% as compared with 60%). There were no trial discontinuations. No adverse events were reported.

Assessor's comments: the design of this study is certainly outdated by the current treatments of asthma in stable phase and under exacerbations.

- Study 244.2395 (U92-0221) was performed from 1988 to 1989 with the objective to determine the efficacy of inhaled bronchodilators, salbutamol and ipratropium, compared with placebo in the treatment of bronchiolitis. A total of 62 children between the ages of 2 months to 2 years of age were randomized. Patients received one drug or placebo followed one hour later by the other drug or placebo. The change in oxygen saturation of recipients of both drugs, salbutamol and ipratropium, was significantly better than either drug alone. This change however, was not statistically better from that of the control group. No difference was observed in the clinical score or hospital duration. Inhaled bronchodilators did not improve the condition of hospitalized mild bronchiolitics. The use of either salbutamol or ipratropium bromide in the treatment of patients hospitalized with mild bronchiolitis cannot be recommended.

Assessor's comments: In this study patients with bronchiolitis aged 2 months to 2 years did not benefit from nebulised ipratropium.

- Study 244.2371 (U92-0573) was performed from 1989 to 1990 with the objective to compare the preventive efficacy and the tolerance of ipratropium bromide as a nebulized solution in exercise-induced bronchospasm in children. A total of 22 children between the ages of 8 and 15 years participated. Efficacy of ipratropium was limited and only significant 1 minute after exercise. The three treatments (placebo, sodium cromoglycate and ipratropium bromide) were comparable in terms of tolerability. No severe adverse events were reported.

Assessor's comments: This study suffers serious limitations including small sample size, suboptimal design and outdated treatment options for the included patients, yet no convincing evidence of efficacy is documented.

- Study 244.2355 (U92-0812) was performed from 1990 to 1991 with the objective of evaluating the tolerance and acceptability of ipratropium bromide in children with asthma. A total of 59 children between the ages of 5 and 15 years were evaluated. The conclusion from the study was that this study confirms the excellent tolerability in children of ipratropium bromide in inhaled powder form. The adverse events reported by the parents were infrequent and amongst those attributable to the product, limited to dry mouth and thirst, a bitter taste, cough or nausea. One serious adverse event was reported (convulsions 3 days after treatment end). Drug acceptability was also very good since the use of the device was judged as easy in 98 per cent of cases and easier than the metered-dose inhaler form in 70 per cent of cases.

Assessor's comments: The mean age of asthma patients in this trial is 10 years. Ipratropium DPI was well tolerated in 89% of patients and the device was easy to handle. No efficacy issues are discussed in this study.

- Study 244.2366 (U93-0304) was performed from 1989 to 1990 with the objective to assess the safety, bronchodilator efficacy and the relationship between dosage of drug and the extent of bronchodilation following single administrations of 18 mcg, 36 mcg and 72 mcg of Atrovent Inhalation Aerosol or placebo inhalation aerosol in 20 children between the ages of 6 and 12 years with bronchial asthma. The conclusion from study was that the use of Atrovent Inhalation aerosol for the treatment of asthma in children was safe; however, Atrovent Inhalation aerosol did not uniformly demonstrate bronchodilator efficacy and no definite dose-response relationship was seen between the dose of Atrovent and the extent of bronchodilation.

Assessor's comments: The efficacy of ipratropium is questioned in this study of patients with stable asthma 6-12 year-old; however no safety concerns are raised by the study. Atrovent is approved for the treatment of stable asthma in this age group in most European countries.

- Study 244.2430 (U94-0664) was performed from 1993 to 1994 with the objective to evaluate whether combination treatment of nebulized ipratropium bromide 0.25 mg plus salbutamol sulphate 3.0 mg provided significant additional bronchodilating effects over nebulized salbutamol sulphate 3.0 mg alone given repeatedly in children with acute severe bronchial asthma presenting to a hospital emergency room. A total of 163 children between the age of 5 and 12 years were randomized. The conclusion was that both treatment regimens were efficacious in the patient population in this study; however, the combination of ipratropium bromide and salbutamol sulphate did not provide additional bronchodilation as compared with salbutamol sulphate given repeatedly in children with acute asthma. The safety profiles of the two regimens used in the treatment of acute asthma in children were similar. Although not significant, there were slightly more exacerbations of asthma resulting in admission to hospital in the salbutamol group. The observed changes in vital signs were small and similar in the two treatment groups. Arterial oxygen saturation levels rose and were maintained above 90% during the study in both treatment groups.

Assessor's comments: Again, questionable efficacy of ipratropium in acute asthma children 5-12 year-old.

- Study 244.2372 (U97-0051) was performed in 1988 with the objective to compare the bronchodilating effect of 40 mcg of ipratropium bromide administered by a conventional Ingelheim powder inhaler (IPI) and by a metered dose inhaler (MDI) in children and

adolescents with stable bronchial asthma. A total of 70 patients aged 7 to 16 years participated. No significant differences in the bronchodilating effect were found. No adverse effects were observed following inhalation of ipratropium bromide.

Assessor's comments: Only 15 patients (21%) showed significant increase (>15%) in FEV1 30 minutes after inhaling ipratropium. Those "responders" were then randomised to either ipratropium powder inhaler or pMDI. This study raises questions regarding the efficacy of ipratropium in this population of patients with stable asthma.

- Study 244.2429 (U98-0091) was performed from 1991 to 1992 with the objective to determine the effective dose of inhaled ipratropium bromide and the least adverse way of delivering the drug in bronchiolitis. Twenty-six children under the age of 12 months were entered into the study. In general, the results showed that ipratropium bromide is safe and well-tolerated. Ipratropium bromide treated infants were noted to have elevated heart rates. The conclusion from study 244.2429 was that inhaled ipratropium bromide administered as a single 500µg dose via a nebuliser or an 80µg dose via a metered dose inhaler is a useful adjunctive therapy in the treatment of acute bronchiolitis. Dosing by metered dose aerosol is a satisfactory alternative to administration by nebuliser, the former method being associated with less infant distress and less time to administer.

Assessor's comments: Neither the primary endpoint (change in oxygen saturation) nor the calculation of sample size are clearly accounted for in this study.

- Study 244.1409 (U98-0129) was performed between 1995 and 1996 with the objective to compare the safety of ipratropium bromide HFA-MDI with the established Atrovent MDI (containing CFC) in paediatric patients with bronchial asthma. A total of 191 children between the ages of 6 and 15 years were randomized. The conclusion from study was that the safety and efficacy profile of ipratropium bromide formulated in an MDI using the propellant HFA134a is comparable to that of the currently marketed CFC-formulated Atrovent MDI. This was demonstrated in three months regular treatment (2 puffs tds) in paediatric patients with bronchial asthma. There were no significant changes in laboratory results, physical examination and vital signs. The formulation of ipratropium bromide using the new hydrofluoroalkane HFA134a propellant is therefore considered to be a satisfactory alternative to the conventional marketed CFC-Propelled Atrovent MDI. Study 244.1409 (U98-0129) was previously submitted to regulatory agencies.

Assessor's comments: The propellant containing CFC is no longer in use in pMDI and this study confirms that inhaled sprays with HFA are as safe and as effective as those containing CFC.

- Study 244.2413 (U00-0090) was performed in 1998 with the objective to determine whether addition of ipratropium bromide to salbutamol nebulisations produces significantly greater bronchodilation in young children presenting to an emergency department with an acute attack of asthma. The study was discontinued due to lack of recruitment. Three children (ages 3 to 6 years) were randomized. No adverse events related to the study drug were reported. There is insufficient information from the study that could lead to relevant conclusions.

Assessor's comments: with this sample size (3 children) no conclusions can be drawn from this study.

- *Study U72-0222 the text provided is German and I cannot comment on it.
- *Study U72-0227 from 1972 included 12 children with asthma age 2-13 years. The design and the choice of outcome variables in this study are unclear.
- *Study U74-0104 from 1974 included 11 children 8-16 year-old with asthma. Children received aerosolized ipratropium. The study is described as experiment without randomisation or blinding. Better described as a pilot study with no conclusions of efficacy or safety derived from it.
- *Study U78-0018 the text provided is in German and I cannot comment on it.
- *Study U79-0121 included 24 patients 12-18 year-old who received the active substance SCH 1000 (Atrovent) over 2 days. The conclusion was that Atrovent alone had no bronchodilator effect.
- *Study U79-177 included 10 patients with the age range 5-73 years and the design and the objective of the study are not evident from the submitted report.
- *Study U80-0167 included 10 children 7-13 year-old treated with single inhalation of Atrovent dry powder inhaler over 5 days without placebo arm. The authors conclude that a bronchodilator effect was achieved. Questionable design.
- *Study U82-0222 is a pilot study of Atrovent dry powder inhaler in 7 patients aged 8-15 years with "recurrent spastic bronchitis". No side effects were observed and the treatment had good efficacy, though it is unclear what kind of efficacy parameters are measured in this pilot study. Unclear target population and outcome variables.
- Study U82-0226 from 1982 included children with asthma aged 5-14 years. Children were randomized into either fenoterol 100 mcg + ipratropium 40 mcg or 200 mcg ipratropium three times daily for 14 days. No difference was seen between the 2 arms.
- *Study U84-0774 the text provided is in Portuguese and I cannot comment on it.
- *Study U84-0885 included 13 children aged 6-13 years with asthma. The response to inhaled ipratropium was studied. Data from 3 children were not included, and the analysis of the remaining suggested a dose of 250 mcg. The authors suggested that a double blind trial be carried out.
- *Study U84-0911 the text provided is in Spanish and I cannot comment on it.
- *Study U85-0252 is a randomized placebo-controlled double-blind trial of the effect of Ipratropium 40 mcg 3 times a day on diurnal variation of airways in 31 asthmatic children aged 8-17 years. The conclusion of this study was that ipratropium did not diminish the diurnal variation in airway calibre or in bronchial reactivity in asthmatic children.
- *Study U86-0413 was an open randomized trial to compare the bronchodilator effect of ipratropium 250 mcg and fenoterol 150 mcg in children aged 0-3 years with recurrent obstructive airways disease. After single dose of the study medications lung function was measured and the statistical analysis showed no difference between the 2 groups. A slight clinical improvement was seen with both medications.

- *Study U86-0564 included 14 children with cystic fibrosis and bronchial hyper-reactivity. Treatment with Fenoterol or Ipratropium reduced histamine-induced bronchial hyper-reactivity.
- *Study U86-0925 was a randomised double-blind cross over study to measure and compare pulmonary and cardiovascular responses to ipratropium and placebo. 13 children with asthma aged 9-14 years were included in the final analysis. Treatment with ipratropium resulted in effective bronchodilation, yet failed to show a clear dose response.
- *Study U86-0985 was a randomized open trial to compare the bronchodilatory effect of inhaled ipratropium bromide and inhaled fenoterol in children with acute asthma attack. 18 children aged 6-12 years were included. Both treatments had significant bronchodilator effect probably larger effect in the ipratropium group.
- *Study U87-0035 the text is in Spanish, but an English summary is provided. The authors included 30 children with bronchitis with and without prior history of asthma. They were treated with salbutamol for 2 weeks then ipratropium for further 2 weeks. Both treatments resulted in lung function improvement. The purpose of this study is unclear and the design is questionable.
- *Study U87-0945 is a placebo controlled randomized double-blind study of one day duration. 12 children with asthma aged between 5-17 years (mean 11 years) were included. The number of patients was determined according to the recruitment possibilities of the study centre. The optimal response was obtained using a dose of 40 mcg. The inhalation was safe.
- *Study U88-0553 was a randomised double-blind cross over trial to compare the efficacy of preservative-free ipratropium bromide and Atrovent nebuliser solution in a group of children with asthma. The study duration was one day. 33 children with asthma aged 6-15 years were included. Both formulations produced bronchodilation and were well tolerated. There was no difference in the degree of bronchodilation between the 2 formulations. Atrovent solution for nebulisation is currently approved and marketed without preservatives.
- *Study U90-0054 is a randomized double blind study of 10 children with stable asthma, mean age 9.5 years. The duration of study was 5 days. Atrovent achieved maximal bronchodilation at doses of 500 mcg and 750 mcg, with no difference between the 2 doses. Tolerability of the drug was judged to be perfect. A small study with short duration.
- *Study U91-0623 is a retrospective study of Atrovent nebulised solution in infants. Records of 39 infants treated with Atrovent 125 mcg or 250 mcg for wheeze due to asthma or bronchiolitis were analyzed. The mean age of the infants was 346 days (range 15-1237 days). Adverse events were reported in 16 cases and the investigator was unable to relate any event to treatment with Atrovent nebulised solution. Particularly, no anticholinergic side effects were reported. Efficacy outcomes were not evaluated. As stated above this was a retrospective study.
- *Study U93-0136 is an open pilot study from 1985. The aim was to study the effect of ipratropium inhalation solution and the additive effect of salbutamol solution in 13 children with asthma (aged 5-15 years), who arrived at the emergency ward with acute

bronchospasm. A significant increase in peak flow was measured 15 minutes after Atrovent with additional bronchodilation achieved with salbutamol inhalation. No serious side effects were observed. Three of the 13 children dropped out and one child felt vomiting and 2 felt dizzy. The study design is weak and number of patients is small.

Nasal Spray Products

- U83-0398 reports a study that was performed in 1983 with the objective to demonstrate the efficacy of ipratropium bromide in reducing the secretion in the nose in all forms of rhinitis. A total of 60 patients between the ages of 6 and 56 years were included in the study with an unknown number of pediatric patients. The conclusion from this study was that the total patient group contained a mixed set of symptomatology and showed no overall benefit of the use of Atrovent. The allergic subgroup of subjects however did show a marked improvement, and the trial strongly indicates the use of Atrovent for such sufferers.

Assessor's comments: The number of pediatric patients in this study was unknown.

- Study 244.2440 (U95-3002) was performed from 1993 to 1994 with the objective to compare efficacy and safety of Atrovent Nasal Spray 0.03% administered twice a day for four weeks vs. placebo in Pediatric Perennial Rhinitis. A total of 206 children between the ages of 6 and 17 years were randomized. The conclusion from study was that Atrovent Nasal Spray 0.03% is well tolerated and effective in pediatric patients with non-allergic perennial rhinitis. Twice-a-day administration is adequate for non-allergic perennial rhinitis patients, however, allergic perennial rhinitis patients might benefit from a more frequent administration (t.i.d.).

Assessor's comments: in this study Atrovent nasal spray reduced rhinitis symptoms in patients with non-allergic rhinitis but not patients with allergic rhinitis; however, both groups were insufficiently treated prior to enrolment according to current guidelines. The drug was well tolerated. Approximately one third of patients were older than 12 years. In my opinion this study does not provide sufficient evidence for the use of Atrovent nasal spray for the treatment of non-allergic perennial rhinitis in children aged less than 12 years.

- Study 244.2441 (U96-3125) was performed from 1993 to 1995 with the objective to evaluate the pharmacokinetics, safety and long term benefit of Atrovent Nasal Spray 0.03% administered twice a day for six months in pediatric perennial rhinitis patients. A total of 146 children between the ages of 8 and 16 years were randomized. The conclusion from study was that Atrovent Nasal Spray 0.03% at a dose of 42 mcg/nostril b.i.d is a safe and effective new therapy for control of rhinorrhea in pediatric perennial rhinitis. There were no significant systemic or anticholinergic effects. There were no changes in vital signs or laboratory parameters.

Assessor's comments: In this study patients were randomised to either Atrovent nasal spray 0.03% (42 mcg) or beclomethasone 84 mcg twice a day for 6 months. While Atrovent nasal spray provides symptomatic relief in rhinorrhea, nasal steroids are the main treatment of the underlying inflammation in this condition. The design of this study should have been that of add on to treatment with nasal steroids and not that of comparison. One third of the included children were older than 12 years. No safety issues were encountered.

- Study 244.2448 (U97-3023) was performed from 1995 to 1996 with the objective to obtain pharmacokinetic and pharmacodynamic data in children with naturally acquired common colds following Atrovent Nasal Spray 0.06% administration. A total of 90 children between the ages of 5 and 18 years were randomized. The conclusion from study 244.2448 was that Atrovent Nasal Spray 0.06%, when administered as two sprays per nostril three times daily to children and young adults ages 5-18 years with the common cold, is safe and well tolerated. The pediatric population yields a comparable distribution range (0.4 to 19.6%) of percent ipratropium excreted unchanged in a 24 hour steady state urine sample to an adult population (0 to 20.8%).

Assessor's comments: the duration of this study was 2 days and conclusions concerning safety issues with long-term use cannot be drawn.

- Study 244.2465 (U97-3216) was performed from 1996 to 1997 with the objective to evaluate the safety evaluation of Atrovent Nasal Spray 0.06% in children with a naturally acquired cold, administered as a monotherapy or in combination with a decongestant (Decofed) or a decongestant/antihistamine preparation (Ryna Liquid). A total of 547 children between the ages of 6 and 12 years were randomized. The conclusion from study 244.2465 was that Atrovent Nasal Spray 0.06% administered to 5-12 year old patients with a naturally acquired common cold is well tolerated and the addition of a decongestant or a decongestant/antihistamine medication does not change the safety profile of the drug.

Assessor's comments: this large study lasted four days with a ten days follow-up. The number of patients experiencing adverse events was larger in the Atrovent group than the placebo group. However, Atrovent was well tolerated. Efficacy analysis showed that rhinorrhea symptoms did not differ between the active and the placebo group. This large study suggests that the indication of nasal Atrovent is at the best doubtful in the pediatric population with common cold.

- Study 244.2503 (U03-3585) was performed from 2002 to 2003 with the objective to determine the safety of Atrovent Nasal Spray 0.06% in pediatric patients with symptoms of rhinorrhea associated with a naturally occurring common cold, or from symptoms of rhinorrhea associated with allergies. A total of 268 children between the ages of 2 and 5 years were enrolled into the study. The conclusion from study 244.2503 was that Atrovent Nasal Spray was useful, easy to use, and provided relief for symptoms of runny, stuffy nose, and sneezing in children 2-5 years of age with a common cold or allergies. Atrovent had no detrimental effect on nasal mucosa. The incidence of nasal adverse events was low with six patients in the Common Cold Group and 11 patients in the Allergy Group reporting nasal AEs. The incidence of AEs leading to trial withdrawal was very low with one patient in the Common Cold Group and five patients in the Allergy Group discontinuing because of adverse events. None of these adverse events were considered to represent previous unsuspected or important adverse events of Atrovent. Atrovent did not cause any changes in vital signs.

Assessor's comments: This was an open label trial with no placebo arm. No formal sample size calculations were conducted. The primary efficacy variable was patient's parents' global assessment with no statistical test being performed. The design and objective of this study is questionable.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The studies provided are of varying quality. Some of them are outdated and of poor quality. Ipratropium bromide inhalation solution is approved for the treatment of acute attacks of bronchospasm not sufficiently treated with inhaled beta-2 agonists in children from 0 years of age. The studies submitted provided do not raise safety issues that justify any changes to this indication, although evidence of efficacy in younger children is debatable (Study 244.2395 and Study 244.2430). Ipratropium bromide inhalation via MDI is approved in some European countries for the maintenance treatment of asthma in children of all ages (e.g. Germany), children older than 6 years (e.g. Portugal), or older than 7 years (Denmark). There is indeed no sufficient evidence to recommend the use of ipratropium bromide MDI for the maintenance treatment of asthma in children younger than 6 years. The studies summarised above raise no worrying safety issues of ipratropium bromide in children of all ages; however, proof of efficacy in children younger than 6 years is missing. Finally Ipratropium bromide nasal spray for the treatment of allergic and non-allergic rhinitis and common cold in children younger than 12 years is only approved in few European countries (e.g. Spain, Belgium). The studies summarised above show that ipratropium bromide is well tolerated and probably have a place in the treatment of perennial rhinitis in children above 12 years of age, whose main symptom is rhinorrhea.

Generally speaking, the studies provided do not add to our knowledge of the anti-cholinergic ipratropium bromide for the treatment of stable asthma (DPI and MDI), acute respiratory distress in different lung conditions (solution for inhalation) and rhinorrhea (nasal spray); and do not justify a change in the indication for pediatric population.

➤ 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