

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-394/S001**

**APPROVAL LETTER**

NDA 20-394/S-001

NOV - 9 1998

Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road  
Ridgefield, Connecticut 06877

Attention: C.R. Tamorria, Ph.D.  
Senior Associate Director

Dear Dr. Tamorria:

Please refer to your supplemental new drug application dated December 19, 1997, received December 19, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atrovent (ipratropium bromide) Nasal Spray 0.06%.

We acknowledge receipt of your submissions dated March 11, July 14, September 2, and October 14, 1998. The user fee goal date for this application is December 19, 1998.

This supplemental new drug application provides for use in the symptomatic relief of rhinorrhea associated with the common cold in children age 5 to 11 years.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter with the revisions listed below.

1. The abbreviations TID and QID should be revised to "three times daily and four times daily" in the last sentence of the ADVERSE REACTIONS section and the CLINICAL PHARMACOLOGY, Clinical Trials subsection.
2. In the PRECAUTIONS section, the word "General" should be in bold.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 14, 1998) except for the revisions noted above.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-394/S-001." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or

NDA 20-394/S-001

Page 2

mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Dr. Denise Toyer, Project Manager, at (301) 827-5584.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.  
Director  
Division of Pulmonary Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20-394/S001**

**FINAL PRINTED LABELING**

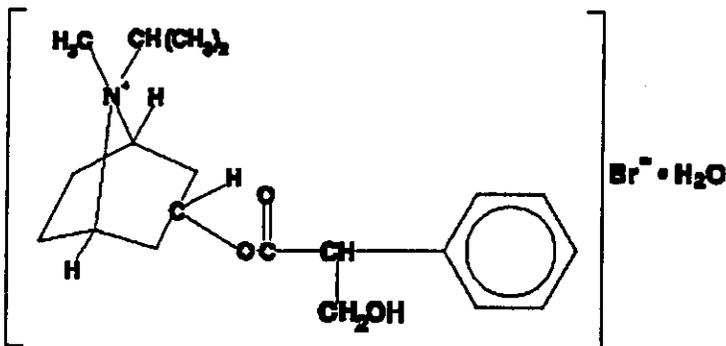
2.0 REVISED ANNOTATED PACKAGE INSERT

**ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with product.**

**Atrovent®  
(ipratropium bromide)  
Nasal Spray 0.06%**

**Prescribing Information**

**DESCRIPTION** The active ingredient in ATROVENT® Nasal Spray is ipratropium bromide monohydrate. It is an anticholinergic agent chemically described as 8-azoniabicyclo (3.2.1) octane,3-(3-hydroxy-1-oxo-2-phenylpropoxy) -8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-, (±) : a synthetic quaternary ammonium compound, chemically related to atropine. Its structural formula is:



ipratropium bromide  
monohydrate

$C_{20}H_{30}BrNO_3 \cdot H_2O$   
Mol. Wt. 430.4

Ipratropium bromide is a white to off-white, crystalline substance. It is freely soluble in lower alcohols and water, existing in an ionized state in aqueous solutions, and relatively insoluble in non-polar media.

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is a metered-dose, manual pump spray unit which delivers 42 mcg ipratropium bromide (on an anhydrous basis) per spray (70  $\mu$ L) in an isotonic, aqueous solution with pH-adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 sprays.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action** Ipratropium bromide is an anticholinergic agent that inhibits vagally-mediated reflexes by antagonizing the action of acetylcholine at the cholinergic receptor. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa. Ipratropium bromide is a quaternary amine that minimally crosses the nasal and gastrointestinal membrane and the blood-brain barrier, resulting in a reduction of the systemic anticholinergic effects (e.g., neurologic, ophthalmic, cardiovascular, and gastrointestinal effects) that are seen with tertiary anticholinergic amines.

**2.0 REVISED ANNOTATED PACKAGE INSERT**

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**Pharmacokinetics**

**Absorption:** Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (2-3%). Less than 20% of an 84 mcg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold adult volunteers, naturally-acquired common cold pediatric patients, or perennial rhinitis adult patients.

**Distribution:** Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and  $\alpha_1$ -acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

**Metabolism:** Ipratropium bromide is partially metabolized to ester hydrolysis products, tropic acid, and tropane. These metabolites appear to be inactive based on *in vitro* receptor affinity studies using rat brain tissue homogenates.

**Elimination:** After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium bromide was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2,505 and 1,019 ml/min respectively. The amount of the total dose excreted unchanged in the urine ( $A_e$ ) within 24 hours was approximately one-half of the administered dose.

**Pediatrics:** Following administration of 84 mcg of ipratropium bromide per nostril three times a day in patients 5-18 years old (n=42) with a naturally-acquired common cold, the mean amount of the total dose excreted unchanged in the urine of 7.8% was comparable to 84 mcg per nostril four times a day in an adult induced common cold population (n=22) of 7.3 to 8.1%. Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.62 ng/mL). No correlation of the amount of the total dose excreted unchanged in the urine ( $A_e$ ) with age or gender was observed in the pediatric population.

**Special Populations:** Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

**Drug-Drug Interactions:** No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

**Pharmacodynamics:** In two single dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate, or systolic/diastolic blood pressure. Similarly, ATROVENT® Nasal Spray 0.06% in adult patients (n=22) with induced-colds, (84 mcg/nostril four times a day) and in pediatric patients (n=45) with naturally acquired common colds (84 mcg/nostril three times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (e.g., sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).

**2.0 REVISED ANNOTATED PACKAGE INSERT**

**Clinical Trials** The clinical trials for ATROVENT® (ipratropium bromide) Nasal Spray 0.06% were conducted in patients with rhinorrhea associated with naturally occurring common colds. In two controlled four-day comparisons of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% (84 mcg per nostril, administered three or four times daily; n=352) with its vehicle (n=351), there was a statistically significant reduction of rhinorrhea, as measured by both nasal discharge weight and the patients' subjective assessment of severity of rhinorrhea using a visual analog scale. These significant differences were evident within one hour following dosing. There was no effect of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% on degree of nasal congestion or sneezing. The response to ATROVENT® (ipratropium bromide) Nasal Spray 0.06% did not appear to be affected by age or gender. No controlled clinical trials directly compared the efficacy of TID versus QID treatment.

**INDICATIONS AND USAGE** ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with the common cold for adults and children age 5 years and older. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% does not relieve nasal congestion or sneezing associated with the common cold.

The safety and effectiveness of the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond four days in patients with the common cold has not been established.

**CONTRAINDICATIONS** ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any of the other ingredients.

**WARNINGS** Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal edema.

**PRECAUTIONS** General ATROVENT® (ipratropium bromide) Nasal Spray 0.06% should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction, particularly if they are receiving an anticholinergic by another route. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported with direct eye contact of ipratropium bromide administered by oral inhalation.

**Information for Patients** Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma, or eye pain may result if ATROVENT® (ipratropium bromide) Nasal Spray 0.06% comes into direct contact with the eyes. Patients should be instructed to avoid spraying ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in or around the eyes. Patients who experience eye pain, blurred vision, excessive nasal dryness or episodes of nasal bleeding should be instructed to contact their doctor. Patients should be reminded to carefully read and follow the accompanying Patient's Instructions for Use.

**Drug Interactions** No controlled clinical trials were conducted to investigate potential drug-drug interactions. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ATROVENT® for oral inhalation.

**2.0 REVISED ANNOTATED PACKAGE INSERT**

**Carcinogenesis, Mutagenesis, Impairment of Fertility** In two-year carcinogenicity studies in rats and mice, ipratropium bromide at oral doses up to 6 mg/kg (approximately 70 and 35 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 45 and 25 times the maximum recommended daily intranasal dose in children, respectively, on a mg/ m<sup>2</sup> basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50mg/kg (approximately 600 times the maximum recommended daily intranasal dose in adults on a mg/ m<sup>2</sup> basis). At an oral dose of 500 mg/kg (approximately 16,000 times the maximum recommended daily intranasal dose in adults on a mg/ m<sup>2</sup> basis), ipratropium bromide produced a decrease in the conception rate.

**Pregnancy TERATOGENIC EFFECTS Pregnancy Category B.** Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond, in each species respectively, to approximately 60, 12,000, and 3,000 times the maximum recommended daily intranasal dose in adults on a mg/ m<sup>2</sup> basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 20 and 45 times, respectively, the maximum recommended daily intranasal dose in adults on a mg/ m<sup>2</sup> basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg in rats (approximately 1,100 times the maximum recommended daily intranasal dose in adults on a mg/ m<sup>2</sup> basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. However, no adequate or well controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide should be used during pregnancy only if clearly needed.

**Nursing Mothers** It is known that some ipratropium bromide is systemically absorbed following nasal administration; however the portion which may be excreted in human milk is unknown. Although lipid-insoluble quaternary bases pass into breast milk, the minimal systemic absorption makes it unlikely that ipratropium bromide would reach the infant in an amount sufficient to cause a clinical effect. However, because many drugs are excreted in human milk, caution should be exercised when ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is administered to a nursing woman.

**Pediatric Use** The safety of ATROVENT (ipratropium bromide) Nasal Spray 0.06% at a dose of two sprays (84 mcg) per nostril three times a day ( total dose 504 mcg/day) for two to four days has been demonstrated in two clinical trials involving 362 pediatric patients 5-11 years of age with naturally acquired common colds. In this pediatric population ATROVENT® (ipratropium bromide) Nasal Spray 0.06% had an adverse event profile similar to that observed in adolescent and adult patients.

**2.0 REVISED ANNOTATED PACKAGE INSERT**

When ATROVENT® was concomitantly administered with an oral decongestant (pseudoephedrine HCl) in 122 children ages 5-12 years, and concomitantly administered with an oral decongestant/antihistamine combination (pseudoephedrine HCl/chlorpheniramine maleate) in 123 children ages 5-12 years, adverse event profiles were similar to ATROVENT® alone. The effectiveness of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% for the treatment of rhinorrhea associated with the common cold in this pediatric age group is based on extrapolation of the demonstrated efficacy of ATROVENT (ipratropium bromide) Nasal Spray 0.06% in adolescents and adults with this condition and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of adults. The recommended dose for the pediatric population is based on cross-study comparisons of the efficacy of ATROVENT (ipratropium bromide) Nasal Spray 0.06% in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of ATROVENT (ipratropium bromide) Nasal Spray 0.06% in pediatric patients under 5 years of age have not been established.

**ADVERSE REACTIONS** Adverse reaction information on ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in patients with the common cold was derived from two multicenter, vehicle-controlled clinical trials involving 1,276 patients (195 patients on ATROVENT®(ipratropium bromide) Nasal Spray 0.03%, 352 patients on ATROVENT®(ipratropium bromide) Nasal Spray 0.06%, 189 patients on ATROVENT®(ipratropium bromide) Nasal Spray 0.12%, 351 patients on vehicle and 189 patients receiving no treatment).

The following table shows adverse events reported for patients who received ATROVENT® (ipratropium bromide) Nasal Spray 0.06% at the recommended dose of 84 mcg per nostril, or vehicle, administered three or four times daily, where the incidence is 1% or greater in the ATROVENT® group and higher in the ATROVENT® group than in the vehicle group.

**% of Patients Reporting Events<sup>1</sup>**

	ATROVENT® Nasal Spray 0.06% (n=352)	Vehicle Control (n=351)
Epistaxis <sup>2</sup>	8.2%	2.3%
Dry Mouth/Throat	1.4%	0.3%
Nasal Congestion	1.1%	0.0%
Nasal Dryness	4.8%	2.8%

<sup>1</sup>This table includes adverse events for which the incidence was 1% or greater in the ATROVENT® group and higher in the ATROVENT® group than in the vehicle group.

<sup>2</sup>Epistaxis reported by 5.4% of ATROVENT® patients and 1.4% of vehicle patients, blood tinged nasal mucus by 2.8% of ATROVENT patients and 0.9% of vehicle patients.

**2.0 REVISED ANNOTATED PACKAGE INSERT**

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% was well tolerated by most patients. The most frequently reported adverse events were transient episodes of nasal dryness or epistaxis. The majority of these adverse events (96%) were mild or moderate in nature, none was considered serious, and none resulted in hospitalization. No patient required treatment for nasal dryness, and only three patients (<1%) required treatment for epistaxis, which consisted of local application of pressure or a moisturizing agent (e.g., petroleum jelly). No patient receiving ATROVENT® (ipratropium bromide) Nasal Spray 0.06% was discontinued from the trial due to either nasal dryness or bleeding.

Adverse events reported by less than 1% of the patients receiving ATROVENT® (ipratropium bromide) Nasal Spray 0.06% during the controlled clinical trials which are potentially related to ATROVENT®'s local effects or systemic anticholinergic effects include: taste perversion, nasal burning, conjunctivitis, coughing, dizziness, hoarseness, palpitation, pharyngitis, tachycardia, thirst, tinnitus, and blurred vision. Additional anticholinergic effects noted with other ATROVENT® dosage forms (ATROVENT® Inhalation Solution, ATROVENT® Inhalation Aerosol and ATROVENT® Nasal Spray 0.03%) include: precipitation or worsening of narrow-angle glaucoma, urinary retention, prostate disorders, constipation, and bowel obstruction.

There were no reports of allergic-type reactions in the controlled clinical trials. Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm, and anaphylactic reactions have been reported with other ipratropium bromide products.

No controlled trial was conducted to address the relative incidence of adverse events for TID versus QID therapy.

**OVERDOSAGE** Acute overdose by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. Following administration of a 20 mg oral dose (equivalent to ingesting more than two bottles of ATROVENT® Nasal Spray 0.06%) to 10 male volunteers, no change in heart rate or blood pressure was noted. Following a 2 mg intravenous infusion over 15 minutes to the same 10 male volunteers, plasma ipratropium concentrations of 22-45 ng/mL were observed (>100 times the concentrations observed following intranasal administration). Following intravenous infusion these 10 volunteers had a mean increase of heart rate of 50 bpm and less than 20 mm Hg change in systolic or diastolic blood pressure at the time of peak ipratropium levels.

Oral median lethal doses of ipratropium bromide were greater than: 1,000 mg/kg in mice (approximately 6,000 and 3,800 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/ m<sup>2</sup> basis) 1,700 mg/kg in rats (approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/ m<sup>2</sup> basis) and 400 mg/kg in dogs (approximately 16,000 and 10,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/ m<sup>2</sup> basis).

**2.0 REVISED ANNOTATED PACKAGE INSERT**

**DOSAGE AND ADMINISTRATION** The recommended dose of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is two sprays (84 mcg) per nostril three or four times daily (total dose 504 to 672 mcg/day) for symptomatic relief of rhinorrhea associated with the common cold in adults and children age 5 years and older. Optimum dosage varies with response of the individual patient. The recommended dose of ATROVENT®(ipratropium bromide) Nasal Spray 0.06% for children age 5-11 years is two sprays (84 mcg) per nostril three times daily (total dose of 504 mcg/day). The safety and effectiveness of the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond four days in patients with the common cold have not been established.

Initial pump priming requires seven sprays of the pump. If used regularly as recommended, no further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than seven days, the pump will require seven sprays to reprime.

**HOW SUPPLIED** ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is supplied in a white high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 16.6 g of product formulation, 165 sprays, each delivering 42 mcg of ipratropium bromide per spray (70 µL), or 10 days of therapy at the maximum recommended dose (two sprays per nostril four times a day).

Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children.

Do not spray in the eyes.

Patients should be reminded to read and follow the accompanying Patient's Instructions for Use, which should be dispensed with the product.

**Rx only.**

Manufactured by  
Boehringer Ingelheim Pharmaceuticals, Inc.  
Ridgefield, CT 06877

Licensed from  
Boehringer Ingelheim  
International GmbH  
U.S. Patent No. 4,385,048  
830922 Printed in U.S.A. 9/95

**2.0 REVISED ANNOTATED PACKAGE INSERT**

**PATIENT'S INSTRUCTIONS  
FOR USE**

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with the common cold for adults and children age 5 years and older. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% does not relieve nasal congestion or sneezing associated with the common cold. Do not use ATROVENT® (ipratropium bromide) Nasal Spray 0.06% for longer than four days unless instructed by your physician. Read complete instructions carefully and use only as directed.

**To Use:**

1. Remove the clear plastic dust cap and the green safety clip from the nasal spray pump (Figure 1). The safety clip prevents the accidental discharge of the spray in your pocket or purse.

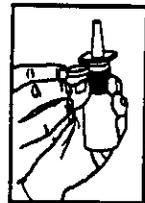


Figure 1

2. The nasal spray pump must be primed before ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times (Figure 2). The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; repriming the pump will only require two sprays. If you have not used your nasal spray for more than seven days, repriming the pump will require seven sprays.



Figure 2

**2.0 REVISED ANNOTATED PACKAGE INSERT**

3. Before using ATROVENT® (ipratropium bromide) Nasal Spray 0.06%, blow your nose gently to clear your nostrils if necessary.

4. Close one nostril by gently placing your finger against the side of your nose, tilt your head slightly forward and, keeping the bottle upright, insert the nasal tip into the other nostril (Figure 3). Point the tip toward the back and outer side of the nose. Press firmly and quickly upwards with the thumb at the base while holding the white shoulder portion of the pump between your index and middle fingers. Following each spray, sniff deeply and breathe out through your mouth.



Figure 3

6. After spraying the nostril and removing the unit, tilt your head backwards for a few seconds to let the spray spread over the back of the nose.

7. Repeat steps 4 through 6 in the same nostril.

8. Repeat steps 4 through 7 in the other nostril (i.e., two sprays per nostril).

9. Replace the clear plastic dust cap and safety clip.

10. You should not take extra doses or stop using ATROVENT® (ipratropium bromide) Nasal Spray 0.06% without consulting your physician.

**To Clean:**

If the nasal tip becomes clogged, remove the clear plastic dust cap and safety clip. Hold the nasal tip under running, warm tap water (Figure 4) for about a minute. Dry the nasal tip, reprime the nasal spray pump (step 2 above), and replace the plastic dust cap and safety clip.



Figure 4

**2.0 REVISED ANNOTATED PACKAGE INSERT**

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**Caution:**

**ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use **ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** as prescribed by your physician. For most patients, some improvement in runny nose is apparent following the first dose of treatment with **ATROVENT® (ipratropium bromide) Nasal Spray 0.06%**. Do not use **ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** for longer than four days unless instructed by your physician.

Do not spray **ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray **ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours. Should eye pain or blurred vision occur, contact your doctor.

Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.

You should not use this drug if you have glaucoma or difficult urination due to an enlargement of the prostate, unless directed by a physician.

**ATROVENT® (ipratropium bromide) Nasal Spray 0.06%** should not be used during pregnancy or breast feeding, unless directed by a physician. It is not known whether ipratropium bromide is excreted in human milk; however, many drugs are excreted in human milk.

**Storage:**

Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children.

**Manufactured by  
Boehringer Ingelheim  
Pharmaceuticals, Inc.  
Ridgefield, CT 06877**

**Licensed from  
Boehringer Ingelheim  
International GmbH  
U.S. Patent No. 4,385,048  
830922 Printed in U.S.A. 9/95**

## PROJECT MANAGER LABELING REVIEW

**NDA:** 20-394/SE-01  
**DATE:** 10/22/98  
**DRUG:** Atrovent (ipratropium bromide) Nasal Spray 0.06%  
**SPONSOR:** Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)  
**PROJECT MANAGER:** Denise P. Toyer  
**LAST APPROVED LABELING:** (FA) February 23, 1996  
**SUBMISSION DATE(S):** October 14, 1998

### Background

An efficacy supplement was submitted on December 19, 1997. Attached to this review is the October 12, 1998, facsimile which contains BIPI's response to the September 30, 1998, telecon in which BIPI and the Division discussed labeling for this supplement. The first section of this review will pertain to the attached facsimile. The second section of the review will pertain to the final draft labeling submitted on October 14, 1998.

### October 12, 1998 Facsimile

#### **CLINICAL PHARMACOLOGY, Pharmacokinetics, Distribution section**

BIPI labeling: Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and  $\alpha_1$ -acid glycoprotein.

BIPI changed  $\alpha_1$ -acid to  $\alpha_1$ -acid. This is acceptable.

#### **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions section.**

BIPI labeling: . . . (n=45) with naturally acquired common colds (84 mcg/nostril three times a day) had no significant. . .

BIPI added an "s" to the word cold. This is acceptable.

#### **PRECAUTIONS, Pregnancy, TERATOGENIC EFFECTS Pregnancy Category B section.**

BIPI labeling: . . . Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg respectively, (approximately 20 and 45 times, respectively, the maximum recommended daily intranasal dose in adults, **respectively**, on a mg/m<sup>2</sup> basis).

BIPI added the word "respectively." This should be removed.

**PATIENT'S INSTRUCTIONS FOR USE**

Figure #3 immediately follows narrative instruction #3 and figure #4 immediately follows narrative instruction #4.

This is inaccurate. Figure #3 should follow narrative instruction #4 and figure #4 should immediately follow the section entitled, "To Clean:"

October 14, 1998 submission

BIPI indicated that the draft labeling contained in this submission is identical to the labeling submitted in the October 12, 1998 facsimile except the following changes have been made.

**PRECAUTIONS, Pregnancy, TERATOGENIC EFFECTS** Pregnancy Category B section.

The word "respectively" was removed from the following sentence. . . . and rabbits at doses of 1.5 and 1.8 mg/kg respectively, (approximately 20 and 45 times, respectively, the maximum recommended daily intranasal dose in adults, on a mg/m<sup>2</sup> basis).

**PATIENT'S INSTRUCTIONS FOR USE**

Figures #3 and #4 were moved and follow the appropriate narrative sections.

**RECOMMENDATIONS**

1. This draft labeling should be approved.

          / S /          

          10/23/98          

Denise P. Toyer, R.Ph., Pharm.D.  
Project Manager

Date

cc: Orig NDA # 20-394  
HFD-570 Division File  
HFD-570/Chowdhury/Poochikian/Sun/Chen/Toyoy  
R/D: TOYERD/10-22-98  
Initialed by: SCHUMAKER/

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10/23/98

AUG 11 1998

## PROJECT MANAGER LABELING REVIEW

**NDA:** 20-394/SE-01  
**DATE:** 08/10/98  
**DRUG:** Atrovent (ipratropium bromide) Nasal Spray 0.06%  
**SPONSOR:** Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)  
**PROJECT MANAGER:** Denise P. Toyer  
**LAST APPROVED LABELING:** (FA) February 23, 1996  
**SUBMISSION DATE(S):** December 19, 1997, July 14, 1998

### Background

An efficacy supplement was submitted on December 19, 1997. This will be a review of the last approved labeling and the labeling which was submitted by the sponsor. An efficacy supplement for Atrovent Nasal Spray 0.03% was approved on April 1, 1998. This review will also include any recommendations to maintain consistency between the Atrovent Nasal Spray 0.06% and the Atrovent Nasal Spray 0.03% labeling.

### DESCRIPTION

The sponsor's submission is identical to the last approved labeling. The Division recommends the following changes for consistency with the Atrovent Nasal Spray 0.03% labeling.

**Third Paragraph should be changed to the following.**

- Atrovent (ipratropium bromide) Nasal Spray 0.06% is a metered-dose, manual pump spray unit which delivers 42 mcg (70 $\mu$ L) ipratropium bromide per spray on an anhydrous basis in an isotonic, aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 sprays.

### CLINICAL PHARMACOLOGY

**Mechanism of Action:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

**Pharmacokinetics:** The sponsor's submission is identical to the last approved labeling. The Division has revised this section for easier reading and for consistency with the Atrovent Nasal Spray 0.03% labeling.

**This section should be revised to the following.**

**Absorption:** Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (2-3%). Less than 20% of an 84 mcg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold patients, or perennial rhinitis patients.

**Distribution:** Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and  $\alpha_1$ -acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

**Metabolism:** Ipratropium bromide is partially metabolized to ester hydrolysis products, tropic acid, and tropane. These metabolites appear to be inactive based on *in vitro* receptor affinity studies using rat brain tissue homogenates.

**Elimination:** After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2,505 and 1,019 ml/min, respectively. The amount of the total dose excreted unchanged in the urine ( $A_e$ ) within 24 hours was approximately one-half of the administered dose.

**Pediatrics:** Following administration of 84 mcg of ipratropium bromide per nostril three times a day in patients 5-18 years, the mean amount of the total dose excreted unchanged in the urine (7.8%)

Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.62 ng/ml). No correlation of the amount of the total dose excreted unchanged in the urine ( $A_e$ ) with age or gender was observed in the pediatric population.

**Special Populations:** Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

**Drug-Drug Interaction:** No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

**Pharmacodynamics:** In two single-dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate, or systolic/diastolic blood pressure. Similarly, in patients with induced-colds, ATROVENT

(ipratropium bromide) Nasal Spray 0.06% 84 mcg/nostril four times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

**The last paragraph should remain the same as listed below.**  
"Controlled clinical trials demonstrated . . . or the air conditioning capacity of the nose).

**Clinical Trials:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

#### **INDICATIONS AND USAGE**

No changes were made by the sponsor. The Division does not recommend any changes to this section.

#### **CONTRAINDICATIONS**

No changes were made by the sponsor. The Division does not recommend any changes to this section.

#### **WARNINGS**

No changes were made by the sponsor. The Division does not recommend any changes to this section.

#### **PRECAUTIONS**

**General:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

**Information for Patients:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

**Drug Interactions:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The sponsor's submission is identical to the last approved labeling. The Division has revised this section for easier reading and for consistency with the Atrovent Nasal Spray 0.03% labeling.

**This section should read as follows.**

In two-year carcinogenicity studies in rats and mice, ipratropium bromide at oral doses up to 6 mg/kg (approximately 70 and 35 times the maximum recommended daily intranasal dose in adults, respectively, and 45 and 25 times the maximum recommended daily intranasal dose in children, respectively, on a mg/m<sup>2</sup> basis) showed no carcinogenic activity. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats was unaffected by ipratropium bromide at oral doses up to 50 mg/kg (approximately 600 times the maximum recommended daily intranasal dose in adults on a mg/m<sup>2</sup> basis). At an oral dose of 500 mg/kg (approximately times the maximum recommended daily intranasal dose in adults on a mg/m<sup>2</sup> basis), ipratropium bromide produced a decrease in the conception rate.

**Pregnancy:** The sponsor's submission is identical to the last approved labeling. The Division has revised this section for easier reading and for consistency with the Atrovent Nasal Spray 0.03% labeling.

**This section should read as follows.**

**Pregnancy:** TERATOGENIC EFFECTS Pregnancy Category B. Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 mg/kg in rats, and 125 mg/kg in rabbits. These doses correspond, in each species respectively, to approximately 60, 12,000, and 3,000 times the maximum recommended daily intranasal dose in adults on a mg/m<sup>2</sup> basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 20 and 45 times, respectively, the maximum recommended daily intranasal dose in adults on a mg/m<sup>2</sup> basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses above 90 mg/kg (approximately 1,100 times the maximum recommended daily intranasal dose in adults on a mg/m<sup>2</sup> basis) embryotoxicity was observed as increased resorption.

**The last three sentences should remain the same as listed below.**  
"This effect is not considered relevant to human use due to the . . . should be used during pregnancy only if clearly needed.

**Nursing Mothers:** No changes were made by the sponsor. The Division does not recommend any changes to this section.

**Pediatric Use:** The sponsor's submission includes a modification which indicates that Atrovent may be used in pediatric patients five years and above. The Division has revised this section to reflect the data reviewed to support the change dosing age.

**This section should read as follows.**

The safety of ATROVENT (ipratropium bromide) Nasal Spray 0.06% at a dose of two sprays (84 mcg) per nostril three times daily (total dose 504 mcg/day) for two to four days has been demonstrated in two clinical trials involving pediatric patients 5-11 years of age with naturally acquired common cold (362 patients were on ATROVENT). The effectiveness of ATROVENT Nasal Spray 0.06% for the treatment of rhinorrhea associated with the common cold in this pediatric age group is based on an extrapolation of the demonstrated efficacy of ATROVENT Nasal Spray 0.06% in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparisons of the efficacy of ATROVENT Nasal Spray 0.06% in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of ATROVENT Nasal Spray 0.06% in pediatric patients under 5 years of age have not been established.

#### ADVERSE REACTIONS

No changes were made by the sponsor. The Division does not recommend any changes to this section. Lines 245-246 appear to be duplicates of Lines 259-260.

#### OVERDOSAGE

**The first paragraph should remain the same as listed below.**

"Acute overdosage by intranasal administration is unlikely. . . change in systolic or diastolic blood pressure at the time of peak ipratropium levels.

**The second paragraph should read as follows.**

Oral median lethal doses of ipratropium bromide were greater than: 1,000 mg/kg in mice (approximately 6,000 and 3,800 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m<sup>2</sup> basis), 1,700 mg/kg in rats

(approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m<sup>2</sup> basis), and 400 mg/kg in dogs (approximately 16,000 and 10,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m<sup>2</sup> basis).

#### **DOSAGE AND ADMINISTRATION**

The sponsor changed the age from 12 years and older to 5 years and older.

**The following sentence was added to this section.**

"The recommended dose of ATROVENT Nasal Spray 0.06% for children age 5-11 years is two sprays (84 mcg) per nostril three times daily (total dose of 504 mcg/day).

**The following change should be made to the last paragraph.**

The word actuations should be changed to "sprays."

#### **HOW SUPPLIED**

The sponsor's submission is identical to the last approved labeling. The Division recommends the following changes for consistency with the Atrovent Nasal Spray 0.03% labeling.

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is supplied in a white high density polyethylene (HDPE) bottle fitted with a metered nasal spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 16.6 g of product formulation, 165 sprays, each delivering 42 mcg (70 µL) of ipratropium bromide per spray, or 10 days of therapy at the maximum recommended dose (two sprays per nostril four times a day). Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children.

Do not spray in the eyes.

#### **PATIENT'S INSTRUCTIONS FOR USE**

The sponsor changed the age from 12 years and older to 5 years and older.

The color of the safety clip was added to Step 1.

**Caution Section:** The sentence "Avoid spraying ATROVENT (ipratropium bromide) Nasal Spray 0.06% in or around your eyes." should be changed to "Do not spray ATROVENT (ipratropium bromide) Nasal Spray 0.06% in your eyes."

**REFERENCES**

All references should be deleted from the labeling.

**RECOMMENDATIONS**

1. A marked-up copy which includes the above changes, should be sent to the sponsor. BIPI should submit a revised version of the labeling to the Division by August 21, 1998.
2. Once the revised labeling is received an approval letter should be sent to the sponsor.

*ISI*

Denise P. Toyer, R.Ph., Pharm.D.  
Project Manager

*11 August 98*  
Date

cc:

Orig NDA # 20-394  
HFD-570 Division File  
HFD-570/Chowdhury  
HFD-570/Poochikian  
HFD-570/Sun  
HFD-570/Chen  
HFD-570/Toyler

R/D: TOYERD/7-29-98  
Initialed by: SCHUMAKER/8-10-98

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-394/S001**

**MEDICAL REVIEW(S)**

JUN 24 1998

I. Summary

<b>MEDICAL OFFICER REVIEW</b>			
<b>Division of Pulmonary Drug Products (HFD-570)</b>			
<b>Application #:</b>	20-394 Supplement for pediatric use	<b>Application Type:</b>	NDA Supplement
<b>Sponsor:</b>	Boehringer Ingelheim	<b>Proprietary Name:</b>	Atrovent nasal spray
<b>Investigator:</b>	Multiple	<b>USAN Name:</b>	Ipratropium bromide
<b>Category:</b>	Anticholinergic	<b>Route of Administration:</b>	Topical intranasal
<b>Reviewer:</b>	Badrul A. Chowdhury, MD	<b>Review Date:</b>	6/23/98
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Document Date</b>	<b>CDER Stamp Date</b>	<b>Submission Type</b>	<b>Comments</b>
December 19, 1997	December 19, 1997	NDA supplement	Submission has 13 volumes
<b>RELATED APPLICATIONS (If applicable)</b>			
<b>Document Date</b>	<b>Application Type</b>	<b>Comments</b>	
<b>REVIEW SUMMARY:</b>			
<p>The purpose of this supplemental NDA is to obtain approval for a labeling change of Atrovent nasal spray 0.06% for relief of rhinorrhea in common cold from the currently approved age of 12 years and older to 5 years and older. In support of the application, results of two studies (244.2448 and 244.2465) are submitted. In the studies, children between the ages of 5 and 18 years with naturally acquired common cold were treated with Atrovent nasal spray 0.06% tid for 2 or 4 days. Total number of patients enrolled in the two studies were 637 of which 565 were between the ages of 5 and 11 years. Study 244.2448 was designed to compare the pharmacokinetics of ipratropium bromide in children to the pharmacokinetics already established by the sponsor in adults. There were no efficacy measures in this study. In study 244.2465, Atrovent was used alone or in combination with decongestant/antihistamine to assess safety of the drug combinations. Efficacy was assessed secondarily from patient recording of symptom severity on a visual analog scale and from the opinion of parents and guardians on the effectiveness of the nasal spray. Both the studies support safety of Atrovent nasal spray 0.06%. Efficacy was extrapolated from the adult efficacy data of Atrovent nasal spray 0.06% for common cold, and from the pediatric efficacy data of Atrovent nasal spray 0.03% for control of rhinorrhea associated with perennial rhinitis. The safety and efficacy data from this submission taken in the context that the pathophysiology of common cold disease is the same in adults and children support the use of Atrovent nasal spray 0.06% in children up to the age of 5 years for control of rhinorrhea in common cold.</p>			
<b>OUTSTANDING ISSUES:</b>			
None.			
<b>RECOMMENDED REGULATORY ACTION:</b>			
New clinical studies	<input type="checkbox"/>	Clinical Hold	<input type="checkbox"/>
NDA, Efficacy/Label supplement:	<input checked="" type="checkbox"/>	Approvable	<input type="checkbox"/>
		Study May Proceed	<input type="checkbox"/>
		Not Approvable	<input type="checkbox"/>
<b>SIGNATURES:</b>			
<b>Medical Reviewer:</b>		<b>Date:</b>	6/23/98
<b>Medical Team Leader:</b>		<b>Date:</b>	6/24/98

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### III. Materials reviewed and conduct of the review

This supplemental NDA comprises 13 volumes, which includes a revised label, non-clinical information, and clinical data. Results of 2 studies are submitted in support of the application. The studies were primarily designed to establish the safety of Atrovent (ipratropium bromide) nasal spray 0.06% in children with naturally acquired common cold. In the first study (244.2448) the pharmacokinetics of ipratropium bromide was investigated in children with common cold, and in the second study (244.2465) the safety of Atrovent nasal spray 0.06% used either alone or with other over-the-counter decongestants/antihistamines was investigated in children with common cold. Both the studies and all volumes of the submission are reviewed. Throughout the review, references to the original NDA (as v for volume and p for page numbers) are made to indicate the source of information.

### IV. Chemistry/manufacturing and controls

Atrovent nasal spray 0.06% was developed as an isotonic solution with a pH of 4.5 to 6 which is consistent with the normal physiology of the nasal mucosa. Ipratropium bromide (the active ingredient) is a synthetic quaternary ammonium compound, chemically related to atropine. It is a white crystalline substance, freely soluble in water and alcohol, and insoluble in ether and chloroform. In addition to the active ingredient, ipratropium bromide, Atrovent Nasal Spray 0.06% contains the excipients benzalkonium chloride (BAC) and disodium at  
concentrations of respectively. The excipients are not of additional safety concern, as both BAC and disodium are widely used in pediatric formulations for nasal application, both are listed in the FDA inactive ingredients guide, and disodium is listed (v 1, p 32).

### V. Animal pharmacology/toxicology

Ipratropium bromide demonstrates a wide margin of safety in rodent and non-rodent studies. In rat studies, ipratropium nasal spray at a dose of 252 µg/kg/day (about 10 times the maximum pediatric dose based on 20 kg body weight) for 26 weeks caused no adverse events. The maximum tolerated dose at the 26-week rat study, as evidenced by mortality, was 2016 mg/kg/day. In dog studies, ipratropium applied locally to the nose at a dosage up to 201.6 µg/kg/day (about 8 times the maximum pediatric dose based on 20 kg body weight) for 13 or 26 weeks produced no toxic effects or irritative changes in nasal tissues. Systemic absorption was also minimal (v 1, p 32). These animal studies support the safety of Atrovent nasal spray both from a systemic toxicity and local irritation perspective. No additional toxicity concerns are anticipated in pediatric patients that was not observed in adults.

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## VI. Clinical background

### A. Rhinitis in common cold

Human nasal mucosa consists of a lining of pseudostratified ciliated columnar epithelial cells and nonciliated goblet cells over a lamina propria rich in seromucus acinar glands, blood vessels, and nerves (parasympathetic, adrenergic, and sensory), and a deeper tissue containing venous sinusoids. The serous and submucous glands supply the mucosal surface with a viscous seromucus acidic fluid of pH 5.5-6.5. During rhinitis from the common cold, the nasal mucosa is inflamed resulting in mucus hypersecretion, congestion, sneezing, and altered mucociliary clearance. Common cold is caused by viruses, such as, rhinovirus, influenza virus, parainfluenza virus, coronavirus, adenovirus, and respiratory syncytial virus. The disease is self limiting, and treatment is primarily symptomatic in nature. The viral agents that are responsible for the common cold and the pathophysiology of the disease is same in adults and in children (v 1, p 86-89, 116-118).

Common cold is usually a self-limiting non life-threatening disease. There is no curative treatment for the common cold, therefore, usually the most bothersome symptoms are treated. Symptoms that often prompt patients to seek treatment include rhinorrhea, nasal congestion, fever, headache, and cough. Typical categories of drugs used for treating common cold include decongestants, antihistamines, cough suppressants and/or expectorants, and analgesic/anti-inflammatory agents. Since rhinorrhea is a common symptom, specific agents to control rhinorrhea may have a role in symptomatic treatment of the common cold. The nasal submucosal glands have abundant parasympathetic innervation, therefore, the rhinorrhea associated with the common cold is amenable to treatment with topical anticholinergic drugs. With that premise, the sponsor has developed Atrovent nasal spray 0.06% for symptomatic treatment of rhinorrhea in the common cold.

### B. Relevant human experience with Atrovent

Atrovent nasal spray 0.06% was approved in the US on October 1995 (NDA 20-394) for adults and children aged 12 years and older for the symptomatic relief of rhinorrhea associated with the common cold (v 1, p 24, PDR 1998).

### C. Foreign experience

In addition to the USA, Atrovent nasal spray 0.06% has been approved and marketed in Canada. The indications, formulations, and container system of the product marketed in Canada are the same as in the USA. As for other countries, the sponsor is planning to obtain approval for marketing in Australia at this time.

The sponsor has carried out postmarketing surveillance of Atrovent nasal spray 0.06% for the USA and Canada. The amount of exposure is estimated to be about patient-years. This calculation is based on the recommended dose of 2 sprays qid for 4 days, units sold since marketing and the cut-off data of August 1, 1997 ( in USA, in Canada), and the assumption that each unit represents one unique patient  
 ( ) x 4 days/365 days per year = On the spontaneous adverse event

reporting system, no death or serious adverse event related to Atrovent nasal spray 0.06% has been reported (v 1, p 166-179).

#### **D. Human pharmacokinetics, and pharmacodynamics**

Ipratropium bromide is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. Less than 20% of an 84 µg per nostril dose is absorbed from the nasal mucosa of adult normal volunteers or adult rhinitis patients, but the amount absorbed from nasal administration exceeds the amount absorbed from an inhalation solution or inhalation aerosol. The half-life of elimination of ipratropium is about 1.6 hours after intravenous administration. Ipratropium bromide is minimally bound (0 to 9% in vitro) to plasma albumin and  $\alpha_1$ -acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, about one-half of the dose is excreted unchanged in the urine. The pharmacokinetics of ipratropium has not been studied in patients with hepatic or renal insufficiency or in the extremes of life (PDR 1998).

Ipratropium bromide is an anticholinergic agent that inhibits vagally mediated reflexes by antagonizing the action of acetylcholine at the cholinergic receptor. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa.

#### **E. Directions for use**

Atrovent nasal spray 0.06% is for local administration to the nasal mucosa. It is supplied in a high density polyethylene bottle fitted with a metered nasal spray pump. Each spray delivers 70 µL containing 42 µg of ipratropium bromide. A new bottle or one that has not been used for 7 days requires initial priming. Priming is done by seven actuations of the pump. On regular daily use, no further priming is necessary. The dose used in the clinical trials were 2 sprays (84 µg) per nostril 3 or 4 times a day.

### **VII. Description of clinical studies**

Atrovent nasal spray 0.06% was approved on October 1995 (NDA 20-394) for the symptomatic relief of rhinorrhea associated with common cold in adults and children 12 years of age and older. The purpose of this supplemental NDA is to obtain approval for a labeling extension of Atrovent nasal spray 0.06% for relief of rhinorrhea in the common cold in children down to the age of 5 years (v 1, p 15). Results of 2 studies (244.2448 and 244.2465) are submitted in this supplemental NDA. Both the studies were designed to study the safety of Atrovent nasal spray 0.06% in children with naturally acquired common colds. Study 244.2448 was designed to compare the pharmacokinetics (urinary excretion and plasma levels) of ipratropium bromide in children and adolescents with naturally acquired common colds to the pharmacokinetics already established by the sponsor in adults with an induced cold. Results of the study showed that the pharmacokinetic profile of ipratropium bromide was comparable between the pediatric patients and adults. Study 244.2465 was designed to obtain safety information on Atrovent nasal spray 0.06% administered either alone or in combination with an over-the-counter decongestant or a decongestant and antihistamine combination in children with a

naturally acquired common cold. Efficacy information was obtained as secondary endpoints. Results of the study showed that Atrovent nasal spray 0.06% was safe and well tolerated when given to children with common cold with or without over-the-counter antihistamines and/or decongestants. In subsequent sections, the 2 studies are reviewed.

**A. 244.2448: Pharmacokinetic study of Atrovent nasal spray 0.06% in children with common cold**

**1. Title**

A double-blind, vehicle-controlled pharmacokinetic study of Atrovent nasal spray 0.06% in children with naturally acquired common colds.

**2. Investigators and centers**

The study was conducted in 2 centers in US. The principal investigators and the center locations are as follows.

Robert J. Dockhorn, MD, Laxena, Kansas

Jeffrey Adelglass, MD, Dallas, Texas

**3. Objective**

The objective of the study was to obtain pharmacokinetic (plasma ipratropium concentration and 24-hour urinary ipratropium amounts) and pharmacodynamic (pulse rate, blood pressure, and pupil diameters) data in children with naturally acquired common cold following Atrovent nasal spray 0.06% administration (v 3, p 81).

**4. Study population**

Patients were required to have active cold with rhinorrhea present for not more than 36 hours. On nasal examination patients were required to have swollen erythematous nasal membranes. To avoid onset of allergy season, the study was completed during winter season between the months of October and March (v 3, p 82).

Inclusion criteria were as follows (v 3, p 82):

1. Males and premenarchal females between the ages of 5 and 18 years inclusive.
2. The presence of common cold with rhinorrhea for no more than 36 hours.
3. The presence of swollen erythematous nasal membranes.
4. Ability to provide consent by the patient and/or patient's legal guardian.

Exclusion criteria were as follows (v 3, p 82):

1. Significant cardiovascular, renal, hepatic, endocrine, metabolic, neurologic, pulmonary or other systemic disease. History of asthma or chronic respiratory disease, allergic rhinitis, perennial rhinitis, or nasal polyps.
2. History of seasonal allergic rhinitis with allergen in season.

3. A positive Strep test, presence of physical findings suggestive of lower respiratory tract infection, or an oral temperature higher than 102°F.
4. A history of frequent complications associated with upper respiratory tract infections (e.g., sinusitis, bronchitis, etc.).
5. Known intolerance to anticholinergics or hypersensitivity to benzalkonium chloride.
6. Use of any investigational drug within the past 30 days.
7. Previous participation in this trial

### 5. Study design

This was a double blind, randomized, vehicle-controlled (saline), parallel group study (v 3, p 81).

### 6. Study procedures

A total of 90 patients were enrolled and randomized equally to the two treatment groups - Atrovent nasal spray 0.06% or vehicle nasal spray. Study procedure is summarized in Table 1 and described below under the heading of the visits. For 24 hours prior to entry into the study, and during the study, patients were not allowed to use any prescription or over-the-counter medications for relief of their symptoms, except for over-the-counter analgesics such as aspirin, acetaminophen, and ibuprofen. Patients received the study medications for 2 days, 2 doses were given on day 1, and 3 doses were given on day 2. Each dose consisted of 2 sprays in each nostril. The total dose of Atrovent was 336 µg on day 1 and 504 µg on day 2 (v 3, p 29).

Table 1. Flow chart of the study

	Visit 1, Day 1	Visit 2, Day 2	Visit 3, Day 3
Medical history	x		
Physical and nasal exam	x		
Informed consent	x		x
Strep test	x		
Randomization	x		
Administer trial medication	x		
Vital signs	15 min post-dose 60 min post-dose	5 min pre-dose 15 min post-dose 60 min post-dose	x
Pupillary diameters		5 min pre-dose 15 min post-dose 60 min post-dose	x
Obtain blood sample		5 min pre-dose 15 min post-dose 60 min post-dose	x
Dispense trial medication	x		
Urine collection	From 3 PM on day 1 to 7 AM on day 2		
Return trial medication			x
Record adverse events and concomitant therapy	x	x	x

Source: v 3, p 94

**a) Visit 1 (Day 1 in the afternoon)**

Patients were asked to empty his/her bladder and then 2 sprays of the study medication (Atrovent 0.06% or saline) were given in each nostril by the study site personnel. Patients were observed in the clinic for one hour post-dosing. Adverse events were recorded and pulse rate and blood pressure were recorded at 15 and 60 minutes. Patients were then discharged from the clinic with the instruction to collect all urine until 7 AM the following morning and bring it to the clinic on the next visit. They were also instructed to administer 2 sprays of the study medication in each nostril at 8 PM on day 1 and at 7 AM on day 2 (v 3, p 83).

**b) Visit 2 (Day 2 in the afternoon)**

The overnight urine sample was collected, and patients were given 2 sprays of the study medication in each nostril and observed in the clinic for one hour. About 5 minutes prior to the dosing and at 15 and 60 minutes after dosing, vitals and pupillary diameter were recorded and blood samples were drawn. The pupillary diameter was measured by photographing the patient's pupil and scanning the image into a computer. On discharge from the clinic the patients were instructed to administer 2 sprays of the study medication in each nostril at 8 PM (v 3, p 84).

**c) Visit 3 (Day 3 in the morning)**

At this visit, pulse rate, blood pressure, and pupillary diameters were measured. A blood sample was drawn and final physical examination including a nasal examination was done and adverse events recorded (v 3, p 84).

**7. Efficacy parameters**

There were no efficacy measurements in this study. The objective of the study was to obtain pharmacokinetic and pharmacodynamic information on the use of Atrovent nasal spray. The pharmacokinetic endpoints were plasma ipratropium concentrations and urinary ipratropium excretion, and the pharmacodynamic endpoints were pulse rate, blood pressure, and pupillary diameters (v 3, p 85).

**8. Safety analysis**

The safety measures in this study were the reporting of adverse events, vitals, physical and nasal examinations. No routine laboratory tests were performed (v 3, p 85).

**9. Statistical considerations**

No formal sample size calculation based on power consideration was done. The statistical analysis was primarily descriptive in nature. A t-test was performed for the vitals and pupillary size measurement (v 3, p 38, 87).

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## 10. Results

### a) Population enrolled/analyzed

The study was conducted between November 1995 and March 1996. A total of 90 patients were enrolled and 45 each were randomized into the Atrovent and vehicle group. For pharmacokinetic analysis, 42 patients out of the 45 patients from the Atrovent group provided urine samples. The protocol requested 180 blood samples from patients of the Atrovent group, of these 31 samples were missing or duplicates were non-replicating. Therefore, 149 samples were used for plasma concentration analysis. For pharmacodynamic analysis, the number of patients with measurable pupillary diameter ranged from 31 to 35 patients for each group because of technical problems such as photographic recording problems, variable measures between the two eyes for a specific patient, and patient refusal of being photographed. All patients were included in the safety measurements (v 3, p 44, 50).

### b) Subject demographics

Demographics of study subjects are shown in Table 2. The groups were comparable with the exception that the Atrovent group had more males as compared to the vehicle group (v 3, p 43).

Table 2. Demographics of randomized patients

		Atrovent	Vehicle	Total
Number of patients		45	45	90
Sex	Male	32	23	55
	Female	13	22	35
Age in years	5-12	33	35	68
	13-18	12	10	22
	Mean $\pm$ SD	9.8 $\pm$ 3.7	9.6 $\pm$ 3.3	9.7 $\pm$ 3.5
Race	White	38	37	75
	Black	3	2	5
	Other	4	6	10
Weight (lbs)	Mean $\pm$ SD	86.5 $\pm$ 43.5	89.3 $\pm$ 45.6	87.9 $\pm$ 44.3
Source: volume 11, page 39				

### c) Protocol deviations

Of the 90 patients enrolled in the study, there were a total of 42 protocol violations associated with 36 patients (Table 3). All were minor and none of these patients were excluded from any analysis (v 3, p 41).

Table 3. Summary of protocol violations

	Atrovent	Vehicle	Total
Missing value, examination, or visit	10	6	16
Incorrect timing of value, examination, or visit	4	9	13

	Atrovent	Vehicle	Total
Entrance criteria not met	5	2	7
Incorrect trial medication use	3	0	3
Trial medication non compliance	1	1	2
Prohibited medication use	1	0	1
Total	24	18	42

Source: volume 11, page 37

#### d) Pharmacodynamic results

Pulse and blood pressure were recorded on day 1, 2 and 3 and pupillary diameter was measured on day 2 and 3 at time points shown in Table 1. None of these measures changed significantly at any time point. On day 3, the pulse and blood pressure were noted to be outside normal ranges in a number of patients (16 in the Atrovent group and 17 in the vehicle group). There was no consistent pattern in the changes and the changes were considered to represent day-to-day variation of the measures and the differences in the recording by different personnel. Plasma ipratropium concentration was determined as part of the pharmacokinetic assessments. A total of 16 patients had detectable (> 0.10 ng/mL) plasma levels. There were no trends in detectable plasma levels and the pulse rate (v 3, p 44-52). Overall the use of Atrovent nasal spray 0.06% was not seen to cause any pharmacodynamic changes in the study population.

#### e) Pharmacokinetic results

All patients receiving Atrovent nasal spray 0.06% excreted the drug in the urine. The amount of dose excreted varied among patients with a range of 0.4-19.6% and a mean  $\pm$  SD of  $7.8 \pm 4.4\%$  of the intranasal dose. This was comparable to the sponsor's data on adults where 0-20.8% excretion of the nasal dose in urine were seen. Plasma ipratropium was detected in 22 samples (15 patients) out of the 149 samples analyzed. The concentrations ranged from ng/mL to ng/mL. The detectable plasma levels were transients, as only 4 out of the 15 patients who had detectable plasma levels had detectable levels at two consecutive timepoints (v 3, p 53, 54, 71-74).

### 11. Safety outcomes

#### a) Total drug exposure

Of the 45 patients randomized to Atrovent, 41 received Atrovent for the planned 2 days of the study. One patient refused to return after day 1 of the study, and 3 patients took extra doses on day 3 of the study due to misunderstanding of the directions. All patients were included for safety analysis (v 3, p 55).

#### b) Adverse events

The incidence of adverse events is summarized in Table 4. None of the adverse events were severe and no patient was discontinued due to adverse events. Pharyngitis and dry mouth was reported more frequently by patients randomized to the Atrovent group and these events were considered to be study drug related by the investigators. One

patient in the vehicle group experienced mild nasal bleed that was considered to be study drug related by the investigator. Another patient in the vehicle group developed peri-orbital cellulitis that was not study drug related (v 3, p 56-58).

**Table 4. Adverse events reported by study subjects**

	Atrovent (n=45)		Vehicle (n=45)	
	Total*	Related†	Total*	Related†
<b>Total with any adverse event</b>	8 (17.8%)	4 (8.9%)	4 (8.9%)	1 (2.2%)
Pharyngitis	3 (6.7%)	3 (6.7%)	1 (2.2%)	0
Dry mouth	2 (4.4%)	2 (4.4%)	0	0
Hyperkinesia	1 (2.2%)	0	0	0
Nasal bleeding	1 (2.2%)	0	1 (2.2%)	1 (2.2%)
Nose congestion	1 (2.2%)	0	0	0
Fatigue	1 (2.2%)	0	0	0
Fever	1 (2.2%)	0	0	0
Headache	0	0	1 (2.2%)	0
Tooth disorder	0	0	1 (2.2%)	0
Cellulitis	0	0	1 (2.2%)	0

\* Number (percentage) of patients reporting adverse events  
† Adverse events thought to be related to the treatment  
Source: volume 11, page 53.

**c) Premature withdrawals**

A total of 8 patients were withdrawn from the study prior to completing all scheduled visits. Seven out of the 8 patients were withdrawn due to refusal to have blood drawn one was withdrawn due to incorrect drug dosing. Of the discontinued patients, 4 were from the Atrovent group and 4 were from the vehicle group (v 3, p 27).

**d) Physical examination**

In addition to vitals (described above in pharmacodynamic results section) all patients had nasal examination and general physical examination on day 1 and 3 of the study. All patients had nasal findings consistent with the entry diagnosis of common cold. Most had rhinorrhea with erythematous and edematous mucosa. The majority of the patients showed some improvements of the nasal findings over the 3 days of the study, which is consistent with the time elapsed between the two examinations. There were no differences between the two treatment groups. On general physical examination also no differences between the groups were seen (v 3, p 59-63).

**e) Laboratory measures**

There were no safety laboratory measures done in this study.

**12. Conclusion from study results**

The relevance of this study to the application is the safety assessment of Atrovent nasal spray 0.06% used for 2 days in children 5 to 18 years of age with common cold.

Overall, Atrovent was well tolerated by the patients in this study. A total of 45 patients received Atrovent and none discontinued from the study due to adverse events. Potential local anticholinergic effects were pharyngitis reported by 3 patients and dry throat reported by 2 patients. Although the drug was systemically absorbed in some patients (ipratropium was detected in the blood in 15 patients) and excreted unchanged in the urine in all patients, none had any potential systemic anticholinergic effects. Therefore, this study supports the safety of Atrovent nasal spray 0.06% in children 5-18 years of age.

**B. 244.2465: Safety study of Atrovent nasal spray 0.06% in children with common cold**

**1. Title**

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.

**2. Investigators and centers**

The study was conducted in 18 sites in US. The principal investigators and site locations are listed below (v 5, p 16).

Jeffrey L. Blumer, MD, Cleveland, Ohio  
B. Lauren Charous, MD, Milwaukee, Wisconsin  
Timothy J. Fiorillo, DO, Harleysville, Pennsylvania  
Willis M. Gooch, MD, Salt Lake City, Utah  
Jay Grosman, MD, Tucson, Arizona  
Kirk Kinberg, MD, Lincoln, Nebraska  
Michael Karemer, MD, Spokane, Washington  
Zev Munk, MD, Houston, Texas  
David Pearlman, MD, Aurora, Colorado  
Michael Pichichero, MD, Rochester, New York  
Eugene Shapiro, MD, New Haven, Connecticut  
Nathan Schultz, MD, Danville, California  
Richard Schwartz, MD, Vienna, Virginia  
Ellen Wald, MD, Pittsburgh, Pennsylvania  
Martha White, MD, Washington, District of Columbia  
David Dobratz, MD, Overland Park, Kansas  
Robert Hippert, DO, Fleetwood, Pennsylvania  
Jack S.C. Fong, MD, Danbury, Connecticut

**3. Objective**

The objective of this study was to evaluate the safety of Atrovent nasal spray 0.06% in children with naturally acquired common cold, administered both as a monotherapy and in combination with a decongestant (Decofed liquid) and a

decongestant/antihistamine preparation (Ryna liquid). Atrovent nasal spray 0.06% was compared, in a single blinded fashion, to an oral placebo suspension administered with the same concomitant therapies (v 5, p 20, 130).

#### 4. Study population

Patients with common cold with onset of rhinorrhea within 48 hours were enrolled in the study. On nasal examination, patients were required to have swollen nasal membranes characteristic of common cold. To avoid onset of allergy seasons, the study was completed between the months of October and March (v 3, p 131).

Inclusion criteria were as follows (v 5, p 132):

1. Males and premenarchal females between the ages of 6 and 12 years inclusive.
2. The presence of common cold with rhinorrhea for no more than 48 hours.
3. The presence of swollen erythematous nasal membranes.
4. Ability to provide consent by the patient and/or patient's legal guardian.

Exclusion criteria were as follows (v 5, p 132):

1. Significant cardiovascular, renal, hepatic, endocrine, metabolic, neurologic, pulmonary or other systemic disease.
2. History of perennial or seasonal allergic rhinitis with allergen in season.
3. A positive Strep test, presence of physical findings suggestive of lower respiratory tract infection, or an oral temperature higher than 102°F.
4. Known intolerance to anticholinergics, pseudoephedrine, chlorpheniramine maleate or hypersensitivity to benzalkonium chloride.
5. Use of any investigational drug within the past 30 days.
6. Previous participation in this trial or trial 244.2448.

Concomitant medications (v 5, p 135):

The following medications were not allowed during the study:

1. Over the counter antihistamines and/or decongestants (other than the study medications as described below) for 24 hours prior to screening and during the study.
2. All prescription antihistamines, decongestants, nasal or ocular cromolyns for 24 hours prior to screening and during the study.
3. Atarax for 1 week prior to screening and during the study.
4. Hismanal for 12 weeks prior to screening and during the study.
5. Robitussin AC, Robitussin CF, Robitussin cold and cough, Robitussin DAC, Robitussin maximum strength cold and cough, Robitussin pediatric cold and cough, Robitussin PE.

The following medication were allowed during the study:

1. Acetaminophen, and ibuprofen.
2. Robitussin cough syrup, Robitussin DM, Robitussin maximum strength cough suppressant, Robitussin pediatric cough suppressant

#### 5. Study design

This was a single-blinded, randomized, placebo-controlled study (v 5, p 143).

## 6. Study procedures

The study was conducted over 15 days and required 3 clinic visits. There were 2 periods in the study, a treatment period (days 1 through 4) and a follow-up period (days 5 through 15). Procedures done on each study day and during the 3 clinic visits are shown in Table 5. On visit 1 patients were screened for participation in the study and randomized to one of the 6 treatment groups (Table 6). The patients with the help of their parents or guardians recorded the severity of 4 common cold symptoms (rhinorrhea, nasal congestion, sneezing, and middle ear discomfort) on a visual analog scale (VAS). The VAS was a 10-cm long horizontal line which had the statement "did not bother me at all" at one end, and "worst it could be" at the other end, with cartoon figures of "happy face" - "sad face" gradation in between. Patients placed a vertical line on the scale that they thought correspond best to their symptom severity. This recording was the baseline symptom assessment. The patients were then given the study medications according to the randomization schedule and observed in the clinic for 30 minutes for adverse events. To maintain blinding, the placebo oral suspension was called a "study medication" and the patients and parents or guardians were unaware that the placebo was not an active medication. The rationale for using oral suspension as a placebo was the suspicion that saline nasal spray (corresponding placebo for Atrovent nasal spray) may provide a palliative effect on the nasal mucosa and give a benefit on its own in this study, and the observation that the commonly used over-the-counter medications for common cold are in an oral form, such as suspension, syrups, or tablets (v 5, p 133, 139, 143).

The study medications were given on a tid schedule during the 4 days of treatment (upon awakening at about 8 AM, at mid-afternoon at about 3 PM, and before bedtime at about 8 PM). On the first study day (visit 1) patients received 1, 2, or 3 doses of the medications, depending on the time of the day patients came to the clinic. Concomitant medication restriction followed during the study are listed above (section VII.B.4). On study days 2 through 14, patients were asked to record the severity of each symptom using the VAS (as described above) daily at bedtime (approximately 8 PM). During visit 2 (study day 5) parents or guardians completed a global questionnaire. In the questionnaire they were asked to record the child's cold frequency for the previous year (1 to >10), give the reason for seeking medical advice (visit already scheduled, cold was long than usual, child was in discomfort, concern of ear infection, not sleeping at night, etc.), and comment on the usefulness of the study medication (very useful, somewhat useful, not very useful, not at all useful), ease of use of the study medication (extremely easy, very easy, neither easy nor difficult, somewhat difficult, very difficult), and whether they will use the nasal spray again for another cold (definitely will use, probably will use, may or may not use, probably will use, definitely will not use) (v 5, p 20, 133, 140-145).

**Table 5. Flow chart of the study**

	Treatment		Follow-up		
	Visit 1		Visit 2		Visit 3
	Day 1	Days 2 - 4	Day 5	Days 6 - 14	Day 15
Informed consent, medical history	x				
Physical exam including ENT exam	x		x		x
Strep test	x				

	Treatment		Follow-up		
	Visit 1		Visit 2		Visit 3
	Day 1	Days 2 - 4	Day 5	Days 6 - 14	Day 15
Randomization	x				
Baseline symptom assessment	x				
Dispense trial medication	x				
Administer trial medication	x	x			
Dispense symptom assessment card	x		x		
Symptom assessment at home	x	x	x	x	
Return trial medication			x		
Global safety questionnaire			x		
Telephone contact for adverse event				day 10	
Record adverse events and therapy	x	x	x	x	x
Return symptom assessment card			x		x

Source: v 5, p 124

**Table 6. Treatment groups**

	No additional treatment	Decofed <sup>†</sup> liquid	Ryna <sup>†</sup> liquid
Atrovent nasal spray 0.06%	2 sprays in each nostril, tid (8 AM, 3 PM, 8 PM)	2 sprays in each nostril, tid (8 AM, 3 PM, 8 PM) + 1 teaspoon <sup>‡</sup> of syrup tid (8 AM, 3 PM, 8 PM)	2 sprays in each nostril, tid (8 AM, 3 PM, 8 PM) + 1 teaspoon <sup>‡</sup> of syrup tid (8 AM, 3 PM, 8 PM)
Oral placebo suspension	1 teaspoon tid (8 AM, 3 PM, 8 PM)	1 teaspoon tid (8 AM, 3 PM, 8 PM) + 1 teaspoon <sup>‡</sup> of syrup tid (8 AM, 3 PM, 8 PM)	1 teaspoon tid (8 AM, 3 PM, 8 PM) + 1 teaspoon <sup>‡</sup> of syrup tid (8 AM, 3 PM, 8 PM)

<sup>\*</sup> Pseudoephedrine HCl 30 mg per teaspoon  
<sup>†</sup> Pseudoephedrine HCl 30 mg + chlorpheniramine maleate 2 mg per teaspoon  
<sup>‡</sup> For patients 12 years old, 2 teaspoons of syrup was administered

Source: v 5, p 21, 28, 29, 131, 134, 135

## 7. Efficacy parameters

The study was not designed to measure efficacy. Efficacy was secondarily assessed from the patients recording of the symptoms (rhinorrhea, nasal congestion, sneezing, and middle ear discomfort) on the VAS. A score of 0 represented no symptoms ("does not bother me at all") and a score of 10 represented unbearable symptoms ("worst it could be"). Two question from the global questionnaire (comment on the usefulness of the study medication, and whether the parent or guardian will use the nasal spray again for another cold) were also used to evaluate efficacy (v 3, p 20, 50, 52 130, 138).

## 8. Safety analysis

Safety analysis was the primary objective of the study. Safety was determined by adverse event reporting. The primary comparison groups for safety were the Atrovent nasal spray 0.06% group to the placebo group when Atrovent was used alone or in combination with concomitant medications (v 5, p 20, 130).

## 9. Statistical considerations

Sample size of 360 patients for the Atrovent groups and 180 for the oral placebo groups was calculated to detect a 5% difference in epistaxis at 80% power at a 5% significance level using Fisher's exact test. Epistaxis was chosen as the primary safety variable because of the seriousness of the adverse event. In the adult studies, epistaxis was reported by about 5% of the patients. The adverse events, symptom scores, and global questionnaire answers were summarized using descriptive statistics (v 5, p 147).

## 10. Efficacy results

### a) Population enrolled/analyzed

The study was conducted between October 1996 and March 1997. A total of 547 patients were enrolled of which 534 completed the study. Disposition of the randomized patients is shown in Table 7, and the patients withdrawn from the study are listed in Table 8. A total of 4 patients were withdrawn due to adverse events, which are described in the footnote of Table 8. For safety analysis, all patients enrolled in the study were included. For efficacy analysis, patient who had baseline symptom scores and scores on at least one other day was included. Of the 547 patients enrolled, 4 patients (3655, 3656, 3747, and 3765) with baseline scores only were excluded from efficacy analysis (v 5, p 46-47, 52).

Table 7. Disposition of study patients

	ANS	ANS + Decofed	ANS + Ryna liq	Pbo	Pbo + Decofed	Pbo + Ryna liq	Total
Enrolled	119	122	123	63	60	60	547
Completed	115	121	121	63	56	58	534
Discontinued	4	1	2	0	4	2	13
Reasons for discontinuation:							
Adverse event	1	1	0	0	1	1	4
Protocol deviation	3	0	0	0	1	0	4
Consent withdrawal	0	0	1	0	0	0	1
Lost to follow-up	0	0	1	0	2	1	4

Source: v 5, p 46

Table 8. Patient withdrawals

Treatment group	Patient number	Study period when withdrawal occurred	Reason for withdrawal
Atrovent	3557	Treatment	Adverse event*
	3656	Treatment	Non compliant with protocol
	3747	Treatment	Non compliant with protocol
	3963	Follow-up	Non compliant with protocol
Atrovent + Decofed	3671	Treatment	Adverse event†
Atrovent + Ryna liquid	3408	Treatment	Consent withdrawn
	3869	Follow-up	Lost to follow-up
Placebo + Decofed	3655	Treatment	Non compliant with protocol
	3680	Follow-up	Lost to follow-up

Treatment group	Patient number	Study period when withdrawal occurred	Reason for withdrawal
	3751 3953	Follow-up Treatment	Lost to follow-up Adverse event <sup>†</sup>
Placebo + Ryna liquid	3765 3827	Treatment Follow-up	Lost to follow-up Adverse event <sup>‡</sup>
<sup>*</sup> Influenza on day 2. Not considered related to treatment. <sup>†</sup> Red eye on day 1. Considered to be related to treatment. No indication of drug being sprayed to eyes. <sup>‡</sup> Mild hyperkinesia (jumpy) on day 1. Considered related to treatment. <sup>§</sup> Headache, diarrhea, earache, stomach aches on days 1-7. Study medication discontinued on day 3.			
Source: v 5, p 25, 26, 81			

**b) Subject demographics**

Baseline demographics were comparable among the 6 treatment groups. The majority of the study subjects were caucasian (83%), and there was no predominant gender in the study (54% males, 46% females). The average age of the subjects was 8.7 years and patients were similarly distributed across the age category of 6 to 11 years (ranged from 12.6% for 8 years, 17.2% for 6 years). Only 0.5% was 5 years of age and 8% of patients were 12 years of age (v 5, p 49).

**c) Protocol deviations**

A total of 186 protocol deviations occurred during the study (Table 9). The deviations were minor in nature and included protocol noncompliance (sporadic missed doses), incorrect timing of visit, use of prohibited medications, entrance criteria not being met, and sporadic missing of examinations. None of the protocol violations caused patients to be excluded from the safety analyses (v 5, p 47).

**Table 9. Summary of protocol violations**

	ANS	ANS + Decofed	ANS + Ryna liq	Pbo	Pbo + Decofed	Pbo + Ryna liq	Total
Protocol deviation	21	20	17	16	13	8	95
Incorrect visit timing	14	12	11	4	10	9	60
Prohibited medication	4	4	1	2	3	1	15
Entrance criteria	4	4	2	0	1	0	11
Missing examination	1	3	1	0	0	0	5
Total	44	43	32	22	27	18	186

Source: v 5, p 46

**d) Efficacy endpoint outcome**

Mean symptom score generally improved over the treatment period and during the follow-up period for patients in all groups. Nasal symptom scores for the baseline, 4 days of treatment, and 3 follow-up days (out of 10) are shown in Table 10. Although the overall symptoms scores were similar across the treatment groups, patients on Atrovent showed a greater relief of rhinorrhea than those on placebo, and patients on placebo fared better for nasal congestion and sneezing. Symptom scores for ear pain were comparable

between the treatment groups (data not shown). Parents and guardians rated Atrovent nasal spray favorably (Table 11), with a greater percentage indicated that the product was more useful than placebo and a greater percentage indicated that they would use Atrovent nasal spray again for treatment of cold in their child (v 5, p 12, 53-67).

**Table 10. Mean symptom scores\* during the treatment and follow-up period**

		ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
<b>Rhinorrhea:</b>							
Baseline	Day 0	5.139	4.496	4.867	5.139	4.996	4.867
Treatment	Day 1	4.917	4.945	4.735	4.850	5.014	5.070
	Day 2	4.185	3.964	3.702	4.052	4.364	3.885
	Day 3	3.783	3.556	3.261	3.250	3.805	3.582
	Day 4	3.041	2.819	2.665	3.187	3.701	3.287
Follow-up	Day 5	3.430	2.951	2.946	2.934	2.894	3.250
	Day 10	2.596	2.306	2.749	2.363	1.565	2.058
	Day 14	1.588	1.785	2.094	1.740	1.584	1.704
<b>Nasal congestion:</b>							
Baseline	Day 0	5.044	5.044	5.044	5.354	5.354	5.354
Treatment	Day 1	5.176	5.210	5.105	5.592	5.564	4.912
	Day 2	5.136	4.602	5.077	4.394	4.914	4.146
	Day 3	4.727	4.825	4.667	3.902	4.120	4.200
	Day 4	4.242	4.207	3.970	3.508	3.849	4.182
Follow-up	Day 5	3.786	4.090	3.431	2.979	3.427	3.732
	Day 10	2.882	2.449	2.796	2.246	1.750	2.483
	Day 14	1.764	1.997	2.196	2.012	1.721	1.701
<b>Sneezing:</b>							
Baseline	Day 0	2.938	2.938	2.938	2.480	2.480	2.480
Treatment	Day 1	2.600	3.201	2.948	2.353	2.537	1.988
	Day 2	2.377	2.789	2.175	2.135	2.627	1.585
	Day 3	2.036	2.087	1.861	1.762	1.900	1.783
	Day 4	1.633	1.833	1.834	1.468	1.957	1.334
Follow-up	Day 5	1.888	1.568	1.333	1.559	1.453	1.493
	Day 10	1.591	1.335	1.672	1.327	0.749	1.442
	Day 14	1.367	1.131	1.229	1.243	0.839	1.158
* Scored from visual analog scale, ranged from 0 (does not bother at all) to 10 (worst it could be)							
Source: v 5, p 54-61 figures; table created from data in v 6, p 152-160							

**Table 11. Frequency distribution of parents or guardians response to questionnaire**

	ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
<b>Comment on the usefulness of the study medication (n and %):</b>						
Very useful	37 (32 %)	41 (34 %)	54 (45 %)	17 (27 %)	18 (31 %)	22 (37 %)
Somewhat useful	68 (59 %)	64 (52 %)	58 (49 %)	24 (38 %)	28 (48 %)	20 (34 %)
Not very useful	9 (7.8 %)	15 (12 %)	6 (5.0 %)	15 (24 %)	11 (19 %)	13 (22 %)
Not at all useful	2 (1.7 %)	2 (1.6 %)	1 (0.8 %)	7 (11 %)	1 (1.7 %)	4 (6.8 %)
Total	116 (100)	122 (100)	119 (100)	63 (100)	58 (100)	59 (100)
<b>Whether the parent/guardian will use the nasal spray medication again for another cold (n and %):</b>						
Definitely will use	40 (35 %)	34 (28 %)	44 (37 %)	NA	NA	NA
Probably will use	43 (37 %)	44 (37 %)	51 (42 %)	NA	NA	NA

	ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
May/may not use	22 (19 %)	28 (23 %)	17 (14 %)	NA	NA	NA
Probably will not use	6 (5.2 %)	12 (10 %)	7 (5.8 %)	NA	NA	NA
Definitely will not use	4 (3.5 %)	2 (1.7 %)	1 (0.8 %)	NA	NA	NA
Total	115 (100)	120 (100)	120 (100)			
<b>Whether the parent/guardian will use the liquid medication again for another cold (n and %):</b>						
Definitely will use	NA	23 (20 %)	37 (34 %)	10 (16 %)	17 (29 %)	15 (25 %)
Probably will use	NA	49 (43 %)	40 (37 %)	16 (25 %)	18 (31 %)	17 (29 %)
May/may not use	NA	24 (21 %)	27 (25 %)	19 (30 %)	11 (19 %)	12 (20 %)
Probably will not use	NA	15 (13 %)	2 (1.8 %)	7 (11 %)	8 (14 %)	10 (17 %)
Definitely will not use	NA	4 (3.5 %)	3 (2.8 %)	11 (17 %)	4 (6.9 %)	5 (8.5 %)
Total		115 (100)	109 (100)	63 (100)	58 (100)	59 (100)

Source: v 5, p 62-63

## 11. Safety outcomes

### a) Total drug exposure

A total of 547 patients were exposed to the study medication. All were included in safety analysis (v 5, p 68).

### b) Adverse events

Adverse events reported by at least 1% of patients in any of the Atrovent nasal spray treatment groups during the treatment period are shown in Table 12, and the respiratory system adverse events during the follow-up period is shown in Table 13. Most of the adverse events reported during the study were of mild or moderate intensity. A summary of severe adverse events are provided in Table 14. The number of patients experiencing adverse events was higher in the Atrovent groups than in the corresponding placebo groups, however, the incidence was similar between the Atrovent groups. Most of the adverse events were nasal in nature. Epistaxis and blood tinged nasal mucous was more common in patients who received Atrovent, both during the treatment and during the follow-up period. The potential anticholinergic events in the Atrovent treated groups were dry mouth and dry throat (v 5, p 12, 69-83).

Table 12. Common\* adverse events reported during active treatment period

	ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
Total treated	119	122	123	63	60	60
Total with any adverse event	30 (25 %)	27 (22 %)	35 (28 %)	10 (16 %)	7 (12 %)	14 (23 %)
Body as a whole						
Fever	1 (0.8 %)	2 (1.6 %)	1 (0.8 %)	0	0	0
Headache	3 (2.5 %)	3 (2.5 %)	6 (4.9 %)	2 (3.2 %)	1 (1.7 %)	3 (5.0 %)
Nervous system						
Dizziness	0	1 (0.8 %)	1 (0.8 %)	0	0	1 (1.7 %)
Hyperkinesia	2 (1.7 %)	1 (0.8 %)	0	0	1 (1.7 %)	0

	ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
Nervousness	0	0	0	0	1 (1.7 %)	0
Somnolence	0	4 (3.3 %)	11 (9 %)	1 (1.6 %)	1 (1.7 %)	4 (6.7 %)
Gastrointestinal system						
Abdominal pain	0	0	3 (2.4 %)	0	0	3 (5.0 %)
Diarrhea	0	0	1 (0.8 %)	1 (1.6 %)	0	1 (1.7 %)
Dry mouth	2 (1.7 %)	0	0	0	0	0
Dry throat	1 (0.8 %)	2 (1.6 %)	0	0	0	0
Hearing and vestibular						
Earache	1 (0.8 %)	0	2 (1.6 %)	0	1 (1.7 %)	3 (5.0 %)
Resistance disorders						
Otitis media	2 (1.7 %)	0	0	0	1 (1.7 %)	0
Respiratory system						
Epistaxis	7 (5.9 %)	2 (1.6 %)	3 (2.4 %)	0	0	0
Nasal mucous blood tinge	2 (1.7 %)	1 (0.8 %)	3 (2.4 %)	0	0	0
Nosebleed	4 (3.4 %)	6 (4.9 %)	8 (6.5 %)	1 (1.6 %)	1 (1.7 %)	1 (1.7 %)
Coughing	3 (2.5 %)	1 (0.8 %)	1 (0.8 %)	2 (3.2 %)	1 (1.7 %)	1 (1.7 %)
Nasal congestion	1 (0.8 %)	0	2 (1.6 %)	0	0	1 (1.7 %)
Pharyngitis	0	3 (2.5 %)	5 (4.1 %)	0	0	0

\* Events reported by ≥1% of patients any ANS groups is listed (number and percentage) as WHO system organ class and preferred term  
Source: v 7, p 13-16

Table 13. Common\* respiratory system adverse events reported during follow-up

	ANS	ANS + Decofed	ANS + Ryna liq	Placebo	Placebo + Decofed	Placebo + Ryna liq
Total treated	119	122	123	63	60	60
Total with any adverse event	26 (22 %)	32 (26 %)	31 (25 %)	12 (19 %)	18 (30 %)	12 (20 %)
Respiratory system						
Epistaxis	3 (2.5 %)	1 (0.8 %)	1 (0.8 %)	0	1 (1.7 %)	0
Nosebleed	1 (0.8 %)	0	2 (1.6 %)	0	0	0
Coughing	3 (2.5 %)	4 (3.3 %)	2 (1.6 %)	2 (3.2 %)	3 (5.0 %)	1 (1.7 %)
Nasal congestion	4 (3.4 %)	1 (0.8 %)	0	0	0	1 (1.7 %)
Pharyngitis	1 (0.8 %)	3 (2.5 %)	2 (1.6 %)	0	1 (1.7 %)	1 (1.7 %)
Bronchospasm	3 (2.5 %)	0	0	0	0	0

\* Events reported by ≥1% of patients any ANS groups is listed (number and percentage) as WHO system organ class and preferred term  
Source: v 7, p 19

Table 14. Patients with severe adverse events

Patient number	Treatment	Adverse event	Onset of event		Duration (days)
			Study period	Study day	
3244	ANS	Otitis media	Treatment	3	13
3557	ANS	Influenza-like symptoms	Treatment	1	6
3281	ANS + Decofed	Somnolence	Treatment	1	2
3827	Placebo + Ryna	Abdominal pain	Treatment	1	4

Patient number	Treatment	Adverse event	Onset of event		Duration (days)
			Study period	Study day	
3262	ANS + Ryna	Rhinorrhea	Follow-up	8	6
3289	ANS + Ryna	Frequent micturation	Follow-up	9	4
3377	ANS + Ryna	Pruritus	Follow-up	10	7
3641	ANS + Ryna	Rhinitis	Follow-up	5	13
3509	Placebo + Decofed	Epistaxis	Follow-up	5	5
		Nasal edema	Follow-up	5	3

Source: v 5, p 71

### c) Premature withdrawals

A total of 4 patients were withdrawn from the study due to adverse events. The events are summarized in Table 8.

### d) Physical examination

There were no clinically relevant changes between treatment groups in vitals, physical examinations, nasal examination, and otoscopic examination. All patients had nasal findings consistent with the entry diagnosis of common cold. Most had rhinorrhea with erythematous and edematous nasal mucosa. The majority of the patients showed improvements of the nasal findings over the study period, which is consistent with the natural history of the disease. There was no evidence of nasal rebound upon discontinuation of Atrovent nasal spray (v 5, p 12, 83-90).

### e) Laboratory measures

There were no safety laboratory measures done in this study.

## 12. Conclusion from study results

This study assesses the safety of Atrovent nasal spray 0.06% administered as a monotherapy and in combination with a decongestant and a decongestant/antihistamine preparation for relief of rhinorrhea associated with common cold in children aged 6 to 12 years. Efficacy was evaluated secondarily from the patient recording of symptoms and from questionnaire given to parents and guardians. A total of 547 patients were enrolled in the study of which 364 received Atrovent nasal spray with or without concomitant medications. The patients were treated for 4 days and then followed-up for an additional 10 days. Atrovent nasal spray was well tolerated by the patients in this study. The commonest drug related adverse event was nasal bleeding. Results of the efficacy assessment showed that the mean symptom scores generally improved over the treatment period for patients in all groups. Atrovent tended to have a more favorable response for rhinorrhea during the treatment period. Parents and guardians rated Atrovent nasal spray more favorably with a greater percentage indicating that the product was more useful than placebo and they would like to use Atrovent again for treatment of cold in their child. Overall, the study supports the safety of Atrovent nasal spray either used alone, or with decongestant/antihistamine for treatment of common cold in children. The study was not designed to test efficacy. Although the trend was in favor of Atrovent, this study alone does not support efficacy of Atrovent nasal spray for treatment of common cold.

## VIII. Overview of efficacy

Atrovent nasal spray 0.06% was approved on October 1995 (NDA 20-394) for the symptomatic relief of rhinorrhea associated with common cold in adults and children 12 years of age and older. The purpose of this supplemental NDA is to obtain approval for a labeling extension for children 5 years of age and older. In support of the labeling change, the sponsor has submitted results from 2 studies (244.2448 and 244.2465). Treatment schedules, patient distribution by age, and primary endpoint assessed in the 2 studies are summarized in Table 15. Neither of the studies were designed to study efficacy. In 244.2448 there were no efficacy measures and in 244.2465 efficacy measures were a secondary endpoint.

**Table 15. Summary of Atrovent nasal spray 0.06% trials**

Study ID	Treatment schedule and duration	Patients by age in yrs			Primary endpoint
		Total	5-12	13-18	
244.2448 (PK trial)	Atrovent nasal spray tid for 2 days	45	33	35	PK and PD measure
	Vehicle nasal spray tid for 2 days	45	35	10	
244.2465 (Safety trial)	Atrovent nasal spray tid for 4 days	364	364	0	Safety analysis
	Oral placebo suspension tid for 4 days	183	183	0	
* With and without decongestant and decongestant + antihistamine					
Source: Tables 2, 6, 12 of this review					

### A. Trial 244.2465

Children 5-12 years of age with naturally acquired common cold were enrolled and randomized into 6 treatment groups (Table 6). Patients in the 3 experimental groups were treated with Atrovent nasal spray 0.06% 2 spray/nostril tid either alone or with decongestant and decongestant and antihistamine combination. Patients in the 3 corresponding control groups were treated with oral liquid placebo with the same antihistamine/decongestant combination. Oral placebo rather than the traditional nasal vehicle placebo was used in this study to avoid the potential beneficial placebo effect of vehicle nasal spray and the rationale that in clinical practice Atrovent nasal spray is likely to be used in combination with over-the-counter liquid preparation for treating common cold. In this study, patients were treated for 4-days and followed up for an additional 10 days. Efficacy measures included patient recording of symptom severity on a 10 point continuous visual analog scale and general comments of parents and guardians on the usefulness of the nasal spray. During the treatment period and the follow-up period, mean symptom scores improved in all study groups. Patients on Atrovent showed a greater relief of rhinorrhea severity, and patients on placebo had a greater relief for nasal congestion and sneezing (Table 10). Parents and guardians rated Atrovent nasal spray favorably with a greater percentage indicating that the product was more useful than placebo and a greater percentage stated that they would like to use Atrovent nasal spray for treatment of common cold in their child in future (Table 11). Although in this study patients on Atrovent nasal spray showed some improvement in rhinorrhea severity, which is consistent with the known pharmacological effect of Atrovent, the study was not

designed to measure efficacy. The study was not double blinded, there was no control group to differentiate from the placebo effect of Atrovent nasal spray, and the sample size was not calculated based on power consideration.

## **B. Efficacy determination**

Efficacy of Atrovent nasal spray 0.06% for control of rhinorrhea associated with common cold in pediatric patients can be determined from the current state of knowledge of the common cold disease, and from extrapolation of the adult and pediatric efficacy data for Atrovent nasal spray 0.03% and 0.06%. Common cold is a self-limiting disease of the nasal mucosa caused by viruses, the commonest being rhinovirus. The pathophysiology of the common cold is the same in adults and in children. Rhinorrhea during common cold results from stimulation of the parasympathetic nerves. In other rhinitis, such as allergic rhinitis, the mechanism of rhinorrhea is also the same. Atrovent nasal spray 0.03% is effective in controlling rhinorrhea associated with perennial rhinitis in adults (NDA 20-393). The sponsor also has supported the efficacy and dose of Atrovent nasal spray 0.03% in the pediatric population based on within and cross-study extrapolation from adults, which led to the approval of the product for children down to the age of 6 years (NDA 20-393 pediatric supplement). Since Atrovent nasal spray 0.03% has been demonstrated to control rhinorrhea in children, the same drug at a concentration of 0.06% is also expected to have an effect on rhinorrhea in children. Atrovent nasal spray 0.06% is known to be effective in controlling rhinorrhea associated with common cold in adults (NDA 20-394). Since the pathophysiology of the common cold is same in adults and in children, the same drug should also be effective in children. The effective dose of Atrovent nasal spray 0.06% is expected to be the same as that of adults because the dose of Atrovent nasal spray 0.03% for children was the same as the adult dose (NDA 20-393 pediatric supplement). In keeping with these contentions, in study 244.2465, Atrovent was found to have a favorable trend in reducing rhinorrhea in children. Overall, there is adequate evidence to support the efficacy of Atrovent nasal spray 0.06% for control of rhinorrhea associated with common cold in the pediatric population.

## **IX. Overview of Safety**

The safety data on the use of Atrovent nasal spray 0.06% in children with common cold comes from the studies 244.2448 and 244.2465 submitted in this NDA. Number of patients enrolled and exposed to Atrovent is listed in Table 15.

### **A. Trial 244.2448**

The pharmacokinetic (urine excretion and plasma levels) characteristics of ipratropium bromide in 90 children aged 5-18 years suffering from the common cold were studied. The children were stratified across age categories and 68 patients were between 5 and 12 years of age. Atrovent was administered as 2 sprays/nostril (84 µg/nostril) tid over 2 days. A two-dose interval urine collection was done and pre-dose and post-dose plasma samples were obtained. Pharmacodynamic parameters (vital signs and pupillary diameter measurements) were also obtained to assess systemic anticholinergic effects. Results obtained from this study were comparable to the results of

adult studies of the sponsor. Although the drug was systemically absorbed in some patients (ipratropium was detected in the blood of 15 patients) and excreted unchanged in the urine in all patients, none had any potential systemic anticholinergic effects. Therefore, this study supports the safety of Atrovent nasal spray 0.06% in children 5-18 years of age.

### B. Trial 244.2465

This trial was designed to obtain safety information on Atrovent nasal spray 0.06% when administered alone or in combination with other over-the-counter medications used for treating common cold. A total of 547 patients aged 6-12 years with common cold were enrolled in this study. Atrovent nasal spray 0.06% was administered as 2 sprays/nostril (84 µg/nostril) tid over 4 days. The study was single-blinded and an oral placebo was used as the control rather than a vehicle nasal spray. The over-the-counter therapies chosen for this study were liquid preparations of pseudoephedrine chloride and a combination of pseudoephedrine chloride and chlorpheniramine maleate. Results of this study demonstrated that Atrovent nasal spray 0.06% was safe when administered alone or with concomitant decongestant or decongestant and antihistamine combination to children aged 6-12 years suffering from common cold.

### C. Overall exposure to Atrovent in the clinical trials

In study 244.2448 Atrovent nasal spray 0.06% was administered as 2 sprays/nostril tid over a 2-day dosing period, and in study 244.2456 Atrovent nasal spray 0.06% was administered as 2 sprays/nostril tid over a 4-day dosing period. Total number of patients enrolled in the 2 studies were 637 of which 565 were between the ages of 5 and 11 years, the age group proposed to be added to the labeling of the product. The extent of exposure to Atrovent in the 2 studies are summarized in Table 16. Based on the dosing schedule (2 spray/nostril tid) the total daily dose was 504 µg. In study 244.2448 the total exposure was 1,008 µg and in study 244.2456 the total exposure was 2,016 µg. Some patients took Atrovent for more than protocol specified duration. Two patients (3979 and 3980 from 244.2465) took the drug for 8 days, and 7 patients (from both the studies) for 1 extra day. There were no adverse events associated with these patients during the extra days of treatment (v 5, p132, 137-140).

Table 16. Extent of exposure to Atrovent nasal spray 0.06% in the pediatric trials

	ANS <sup>*</sup>		ANS + Decofed <sup>†</sup>	ANS + Ryna <sup>†</sup>
	5-11 yrs	12-18 yrs	5-12 yrs	5-12 yrs
Length of exposure, n (%)				
1-2 days	31 (22.0 %)	14 ( 60.9 %)	1 (0.8 %)	1 (0.8 %)
3-4 days	109 (77.3 %)	9 (39.1 %)	120 (98.4 %)	119 (96.7 %)
> 4 days	1 (0.7 %)	0	1 (0.8 %)	3 (2.4 %)
Mean (range)	3.5 (1-5)	2.8 (2-4)	4.0 (2-5)	4.0 (1-8)
Total treated	141	23	122	123
<sup>*</sup> Contains integrated exposure information from trials 244.2448 and 244.2465				
<sup>†</sup> Contains exposure information from trial 244.2465				
Source: v 1, p 139				

### D. Adverse events

In Table 17 the drug related adverse events from the 2 pediatric studies (244.2448, and 4-day treatment period of 244.2465) are summarized and compared to the 2 adult studies of the sponsor (00729A and 00730A) that were submitted in the original NDA 20-394 and formed the basis of the current Atrovent nasal spray 0.06% package insert safety information. Adverse event reporting of children aged 5-11 years was comparable to the adults and to 12-18 year-olds from the package insert trial. When Atrovent was coadministered with decongestant or decongestant and antihistamine combination, the adverse event reporting did not change. However, a greater percentage of patients receiving Atrovent nasal spray 0.06% reported adverse events than those receiving oral placebo suspension (Table 12).

A total of 14 (9.9%) patients aged 5-11 years experienced adverse events that were considered by the investigator to be related to Atrovent nasal spray 0.06% (Table 17). Most of the adverse events was nasopharyngeal in nature and included epistaxis, blood tinged nasal mucosa, pharyngitis, and nasal and oral dryness. Addition of decongestant or decongestant and antihistamine combination to Atrovent did not change the adverse event profile. The commonest adverse event related to Atrovent nasal spray was nasal bleeding which included frank nasal bleeding or epistaxis, and blood tinged nasal mucus that indicated a lesser amount of nasal bleeding with patients often noticing blood streaks in handkerchiefs. Nasal bleeding was rarely reported from patients who received placebo (Table 12). The majority of the nasal bleeding were mild in nature and did not result in patient discontinuation from the study. However, some patients in study 244.2465 required reduction in their dose of study medication and some sought additional treatment for nasal bleeding events. Eight patients (3311, 3329, 3394, 3485, 3516, 3658, 3720, and 3962) required a reduction in their study medication dosage. All patients recovered after the dose reduction. Five patients (3415, 3485, 3647, 3658, and 3720) required therapy for their nasal bleeding events. The therapies consisted of local pressure, swabbing of nasal passages with saline, cold water, cotton balls, and aloe lotion.

Overall, Atrovent nasal spray 0.06% with or without decongestant and antihistamine was well tolerated, and the reported incidences of adverse events were comparable to the currently marketed Atrovent nasal spray 0.06% label. There were no unique trends or new adverse events reported by 5-11 year old patients when using Atrovent alone or in combination with over-the-counter decongestant and antihistamine preparations (v 1, p 132, 137, 140-152).

**Table 17. Comparative summary of drug related adverse events for Atrovent nasal spray 0.06%**

	Package insert data <sup>†</sup>		ANS pediatric data <sup>‡</sup> without Decofed/Ryna		ANS pediatric data <sup>‡</sup>	
	12-18 yrs	>18 yrs	5-11 yrs	12-18 yrs	+Decofed 5-12 yrs	+Ryna 5-12 yrs
Total treated	28	324	141	23	122	123
Any adverse event	5 (17.9)	66 (20.4)	30 (21.3)	8 (30.4)	27 (22.1)	35 (28.5)
Drug related adverse event	3 (10.7)	51 (15.7)	14 (9.9)	5 (21.7)	13 (10.7)	16 (13.0)

	Package insert data <sup>†</sup>		ANS pediatric data <sup>‡</sup> without Decofed/Ryna		ANS pediatric data <sup>§</sup>	
	12-18 yrs	>18 yrs	5-11 yrs	12-18 yrs	+Decofed 5-12 yrs	+Ryna 5-12 yrs
Body as a whole						
Headache	0	6 (1.9)	1 (0.7)	0	0	2 (1.6)
Nervous system						
Hyperkinesia	0	0	0	1 (4.3)	1 (0.8)	0
Somnolence	0	0	0	0	1 (0.8)	3 (2.4)
Gastrointestinal system						
Dry mouth	0	2 (0.6)	1 (0.7)	1 (4.3)	0	0
Dry throat	0	3 (0.9)	2 (1.4)	1 (4.3)	2 (1.6)	0
Respiratory system						
Epistaxis	2 (7.1)	14 (4.3)	7 (5.0)	2 (8.7)	8 (6.6)	10 (8.1)
Blood tinged nasal mu.	1 (3.6)	7 (2.2)	2 (1.4)	0	1 (0.8)	3 (2.4)
Coughing	0	0	0	0	1 (0.8)	0
Nasal dryness	0	17 (5.2)	1 (0.7)	1 (4.3)	0	0
Nasal congestion	0	0	0	0	0	1 (0.8)
Pharyngitis	0	1 (0.3)	1 (0.7)	2 (8.7)	0	1 (0.8)
Nasal irritation	0	0	1 (0.7)	0	0	0
Skin and appendages						
Pruritus	0	0	1 (0.7)	0	0	0
Skin discoloration	0	0	0	0	1 (0.8)	0
Psychiatric disorders						
Emotional lability	0	0	0	0	1 (0.8)	0
Vision disorders						
Conjunctivitis	0	0	0	0	1 (0.8)	0

<sup>\*</sup> Events reported as number (percentage) as WHO system organ class and preferred term  
<sup>†</sup> Includes protocols 00729A and 00730A  
<sup>‡</sup> Includes 244.2448 and 244.2465 (for 4-day treatment period)  
<sup>§</sup> Includes protocol 244.2465 (for 4-day treatment period)

Source: v 5, Tables from p 141, 142, 145, 146 merged

## 1. Serious adverse events and adverse events leading to discontinuation

The majority of the adverse events reported in the pediatric studies submitted were of mild or moderate intensity. There were a total of 9 severe adverse events reported by 8 patients, all from study 244.2465. The severe adverse events are listed in Table 14. All patients with severe adverse events recovered with no sequelae. Four adverse events led to patient withdrawal (Table 8), 2 of which were classified as serious (influenza like symptom in patient 3557 from the Atrovent group, and abdominal pain in patient 3827 from the Placebo + Ryna group) and 2 as not serious, (red eye in patient 3671 from the Atrovent + Decofed group, and mild hyperkinesia in patient 3953 from the placebo + Decofed group) lead to patient withdrawal. Of the adverse events that led to patient withdrawal, only hyperkinesia was considered to be study drug related. The rate of discontinuation for adverse events in the pediatric studies (0.6%, 4 out of 637) was comparable to that of the adult studies of the sponsor (0.3%, 2 out of 703). No death was reported in any patient in the Atrovent studies. Overall, the frequency of serious adverse

events and discontinuation rates for adverse events from the pediatric studies were low and similar to the sponsor's adult program (v 1, p 147, 157).

## 2. Adverse events by gender

The adverse event were experienced by a higher percentage of female pediatric patients than males in their corresponding age categories. The higher reporting in females was not due to any particular event and was not clinically relevant. Comparative reporting of males and females for nasal adverse event is shown in Table 18 (v 1, p 153).

**Table 18. Comparative reporting of nasal adverse events\* reporting by gender**

	Package insert data <sup>†</sup>		ANS pediatric data <sup>‡</sup> without Decofed/Ryna		ANS pediatric data <sup>‡</sup> +Decofed +Ryna	
	12-18 yrs	>18 yrs	5-11 yrs	12-18 yrs	5-12 yrs	5-12 yrs
	Total treated	28	324	141	23	122
Any adverse event	5 (17.9)	66 (20.4)	30 (21.3)	8 (30.4)	27 (22.1)	35 (28.5)
Total males treated	8	155	80	16	66	68
Nasal adverse event	2 (25)	16 (10.3)	6 (7.5)	1 (6.3)	2 (3.0)	7 (10.3)
Total females treated	20	169	61	7	56	55
Nasal adverse event	3 (15)	21 (12.4)	10 (16.4)	2 (28.6)	7 (12.5)	8 (14.5)

\* Events reported as number (percentage)  
<sup>†</sup> Includes protocols 00729A and 00730A  
<sup>‡</sup> Includes 244.2448 and 244.2465 (for 4-day treatment period)  
<sup>§</sup> Includes protocol 244.2465 (for 4-day treatment period)

Source: v 1, p 153

## 3. Potential systemic anticholinergic events

Potential anticholinergic adverse events were reported infrequently (1.1%, 7 out of 637) in the two pediatric trials. Two patients in trial 244.2440 and 5 patients in trial 244.2465 reported dry mouth and dry throat, which were anticholinergic adverse events (Table 4, Table 12). The events were mild or moderate in intensity and did not cause discontinuation of study medication and did not require additional treatment for recovery. These local anticholinergic effects were reported similarly in the adult population (1.4% in the package insert). Additional potential anticholinergic events, such as palpitation, tachycardia, thirst, and abnormal vision were reported by patients in the adult studies; however, these events were not seen in the pediatric studies (v 1, p 157).

## 4. Potential nasal rebound

In study 244.2465, nasal symptoms were recorded by the patients before treatment, during the 4 days of active treatment, and during 10 days of follow-up. No rebound of nasal symptoms was seen after discontinuation of Atrovent nasal spray.

## E. Pharmacokinetics of Atrovent

Pharmacokinetics of Atrovent was studied in study 244.2448. In this study Atrovent 0.06% was used over 2 days and plasma and urine was sampled for ipratropium

at different time points. All of the study patients excreted the drug in urine and about a third of the patients had detectable blood levels of ipratropium. However, none of the patients had potential systemic anticholinergic adverse events. This study suggests that the pharmacokinetics of ipratropium is different in the pediatric age group compared to the adults, but this is possibly not of clinical significance.

#### **F. Physical examination**

Vitals, nasal examination, and general physical examination were done on entry into the study, on completion of the study, and at some interim time points. There were no consistent differences or patterns seen in any of the parameters either within or between treatment groups which would indicate a treatment effect. On entry into the study, nasal mucosal examination showed signs of inflammation, edema, and congestion attributable to the underlying rhinitis. These findings changed over time which was consistent with the natural history of common cold (v 1, p 161-165).

#### **G. Laboratory measures**

No safety laboratory measures were done in the pediatric studies submitted.

#### **H. Abuse potential**

Atrovent nasal spray does not have any abuse or addiction potentials. Spontaneous reporting of adverse events also does not suggest that patients have abused Atrovent.

#### **I. Human reproductive data**

Data on human reproduction were not available from the submitted studies. Although the studies were pediatric, some study subjects of 244.2448 were of reproductive age (Table 2). None of the patients became pregnant during the study. Female subjects of 244.2465 were required to be premenarchal.

#### **J. Overdose experience**

No patients overdosed Atrovent nasal spray 0.06% in any of the clinical studies submitted in this supplemental NDA.

#### **K. Postmarketing spontaneous adverse event reports**

Atrovent nasal spray 0.06% has been approved and marketed in 2 countries to date, the USA, and Canada. The total units sold in the 2 countries since marketing and as of August 1, 1997 is \_\_\_\_\_ of which \_\_\_\_\_ were sold in USA and \_\_\_\_\_ were sold in Canada. The post marketing experience for Atrovent nasal spray 0.06% is based on \_\_\_\_\_ patient-years. The calculation is based on the recommended dose of 2 sprays each nose qid for 4 days, units sold, and the assumption that each unit represents one unique patient ( \_\_\_\_\_ x 4/365). Atrovent nasal spray 0.03% has been approved and marketed in 4 countries to date, the USA, Canada, Switzerland, and New Zealand. The total units sold in the 4 countries since marketing and as of August 1, 1997 is \_\_\_\_\_ of which \_\_\_\_\_ were sold in USA. The post marketing experience for Atrovent nasal spray 0.03% is \_\_\_\_\_

based on . . . patient-years. The calculation is based on the recommended dose of 2 spray each nose tid, units sold, and number of sprays per bottle.

On the worldwide spontaneous adverse event reports, a total of 22 patients reported adverse events for Atrovent nasal spray 0.06% and 45 patients reported adverse events for Atrovent nasal spray 0.03%. No death has been reported. No serious adverse events have been reported from patients who received Atrovent nasal spray 0.06% and 2 serious adverse events were reported in 1 patient who received Atrovent nasal spray 0.03%. The serious event was reported from a US patient who was hospitalized for tremor and weakness after about 1 month use of Atrovent nasal spray 0.3% at the recommended dose. The patient was also on anti-depressant, which was thought to have contributed to the adverse events. The other reported events were consistent with the clinical study results and predicted from the pharmacology of Atrovent. The reported events include headache, rhinitis, epistaxis, nasal irritation, pharyngitis, loss of smell, nausea, dermatitis, facial flushing, urinary retention, blurred vision, tachycardia, palpitation, chest tightness, shortness of breath, syncope, and decreased therapeutic response (v 1, p 166-179). None of these raises any new safety concerns with the use of Atrovent nasal spray 0.03% or 0.06% in adults and in children.

#### **L. Summary of the safety database**

The safety determination of Atrovent nasal spray 0.06% was made from the 2 pediatric common cold studies. The total number of patients in the 2 studies were 637 of which 565 were between the ages of 5 and 11 years. Adverse events reported from this patient group was comparable to the currently marketed Atrovent nasal spray label. Majority of adverse events were respiratory in nature and consisted of nasal adverse events. The most frequently reported adverse event was nasal bleeding. Concomitant use of decongestant and antihistamine with Atrovent nasal spray 0.06% during active common cold did not change the adverse event profile. The only concern is for potential systemic anticholinergic adverse events, because in study 244.2448 a larger percentage of ipratropium was absorbed from the nasal mucosa of children as compared to the sponsor's historical adult studies. However, in this study, the increased absorption was not associated with systemic anticholinergic effects. No new adverse event or unique adverse event in children is evident from the clinical studies submitted in this NDA and from the world-wide postmarketing database for the Atrovent nasal sprays 0.03% and 0.06%. Therefore, Atrovent nasal spray 0.06% is safe for use in children upto the age of 5 years with common cold either alone or in combination with over-the-counter decongestant and antihistamine preparations.

#### **X. DSI review**

No DSI review was done for this supplemental NDA, because the drug is already approved for use in adults, there is adequate experience with the use of the drug, and a review of sites was done in the context of original NDA submission.

**APPEARS THIS WAY  
ON ORIGINAL**

## **XI. Executive summary and conclusion**

Atrovent nasal spray 0.06% is currently approved for symptomatic relief of rhinorrhea associated with common cold in adults and children 12 years of age and older. This supplemental NDA is to lower the age of approval to 5 years. The sponsor has submitted results of 2 clinical studies (244.2448, 244.2465) in support of the application. Both the studies were primarily designed to assess safety of Atrovent nasal spray 0.06%. In study 244.2448, 90 children between the ages of 5 and 12 years with naturally acquired common cold were treated with Atrovent nasal spray 0.06% or vehicle nasal spray, 2 sprays/nostril tid for 2 days. Pharmacokinetic characteristics (urinary excretion and plasma levels of ipratropium) and pharmacodynamic effects (vitals signs and pupillary diameter) were measured to assess systemic exposure and systemic anticholinergic effects. In study 244.2465, 547 children between the ages of 6 and 12 years with naturally acquired common cold was treated with Atrovent nasal spray 0.06%, 2 sprays/nostril tid, or oral placebo suspension, either alone or with a decongestant or a decongestant and antihistamine combination for 4 days. Safety was assessed from adverse event reporting and efficacy was secondarily assessed from patient recording of symptom severity on a visual analog scale and patient/guardian comment on usefulness of the nasal spray.

In both the studies, Atrovent nasal spray 0.06% was well tolerated. The adverse event profile was similar to the current label. Majority of the adverse events were nasal in nature and the commonest adverse event reported was nasal bleeding. Concomitant use of decongestant/antihistamine did not change the adverse event profile. No new or unique adverse event was evident from the 2 submitted studies and from the world-wide postmarketing database for Atrovent nasal spray 0.03% and 0.06%. Therefore, Atrovent nasal spray 0.06% is safe for use in children with common cold.

Efficacy of Atrovent nasal spray 0.06% for treatment of common cold in children is supported by extrapolation of the pediatric efficacy data of Atrovent nasal spray 0.03% for control of rhinorrhea in perennial rhinitis, and adult efficacy data of Atrovent nasal spray 0.06% for control of rhinorrhea associated with common cold. Rhinorrhea in rhinitis is caused by parasympathetic nerve stimulation and the mechanism is the same irrespective of the etiology of rhinitis and age of the patient. The etiology, course, and pathophysiology of common cold is similar in adults and in children. Atrovent nasal spray 0.03% was determined to be effective in controlling rhinorrhea associated with perennial rhinitis in children down to the age of 6 years (NDA 20-393 pediatric supplement). Atrovent nasal spray 0.06% is approved for treatment of rhinorrhea associated with common cold in adults and children down to the age of 12 years (NDA 20-394). Since Atrovent is topically applied to nasal mucosa, pharmacokinetic study for estimation of dose in children is not relevant. There is no reason to suspect that children between the age of 5 and 11 years would respond to a dose different than the dose used in adults and children down to the age of 12 years. The dose proposed by the sponsor, and used in the studies was the same as that approved for adults. Since Atrovent nasal spray 0.03% is known to reduce rhinorrhea from perennial rhinitis in children down to the age of 6 years (NDA 20-393 pediatric supplement), the same drug for the same age group at a higher dose should also have an effect in controlling rhinorrhea from common cold. In study 244.2465, Atrovent tended to reduce rhinorrhea, and this effect is consistent with the 0.03% data and the pharmacology of the drug. This submission satisfies the "pediatric

use" statements in Federal Register (v 59, no. 238, p 64241), which states that "A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult population to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted". Therefore, a pediatric use statement supporting the use of Atrovent nasal spray 0.06% for common cold in children up to the age of 5 years is justified.

## **XII. Recommendations**

Results of the clinical studies submitted in this supplemental NDA taken in the context of pathophysiology of common cold disease, adult data for Atrovent nasal spray 0.06%, and pediatric data for Atrovent nasal spray 0.03% support efficacy of Atrovent nasal spray 0.06% for control of rhinorrhea in common cold in children up to the age of 5 years. The database also supports the safety of Atrovent used either alone or in combination with decongestant/antihistamine for treatment of common cold in children up to the age of 5 years. This supplemental NDA is therefore approvable. The label will need to be modified as outlined in section XIII.

## **XIII. Labeling review**

In the 'pharmacokinetics' section of the label, a paragraph is added based on the pharmacokinetic results of study 244.2448. The section states that the amount of ipratropium excreted in urine was not associated with age or gender and the plasma ipratropium concentration was not correlated with systemic anticholinergic adverse events. The statement is supported by adequate data and is acceptable.

In the 'indications and usage' and 'dosage and administration' sections of the label, the age has been changed from 12 years to 5 years and reference made to studies 244.2448, and 244.2465. The change of age is acceptable and is supported by the referenced studies.

A new 'pediatric use' section has been added which summarizes the results of the 2 common cold studies (244.2448, and 244.2465). This section will be modified to be consistent with Atrovent nasal spray 0.03% label. The modified section of the label is given below.

### **Pediatric use**

The safety of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% at a dose of two sprays (84 mcg) per nostril three times daily (total dose 504 mcg/day) for two to four days has been demonstrated in two clinical trials involving 565 pediatric patients 5-11 years of age with naturally acquired common cold (xxx patients were on ATROVENT®). The effectiveness of ATROVENT® Nasal Spray 0.06% for the treatment of rhinorrhea associated with the common cold in this pediatric age group is based on an extrapolation of the demonstrated efficacy of ATROVENT® Nasal Spray 0.06% in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's

effects are substantially similar to that of the adults. The recommended dose for the pediatric population is based on cross-study comparisons of the efficacy of ATROVENT® Nasal Spray 0.06% in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of Atrovent Nasal Spray 0.06% in pediatric patients under 5 years of age have not been established.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-394/S001**

**CHEMISTRY REVIEW(S)**

<b>CHEMIST'S REVIEW</b> # 1		1. ORGANIZATION HFD-570 DPDP		2. NDA NUMBER 20-394 MAR 11 1998	
NAME AND ADDRESS OF APPLICANT (City and State) Boehringer Ingelheim Pharmaceuticals Inc 900 Ridgebury Road, P. O. Box 368 Ridgefield, Connecticut 06877				4. AP NUMBER	
				5. SUPPLEMENT (S) NUMBER (S) DATES (S)	
6. NAME OF DRUG Atrovent Nasal Spray, 0.06%		7. NONPROPRIETARY NAME Ipratropium bromide monohydrate nasal spray solution		SE1-001 SE1-001BC	12/17/97 3/11/98 <i>Receipt date 3/11/98 P. Ng</i>
8. SUPPLEMENT PROVIDES FOR: Labeling revisions to include children years and older - pediatric labeling.				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Anticholinergic		11. HOW DISPENSED RX <u>X</u> otc _____		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Topical intranasal solution		14. POTENCY 0.06% as IB anhydrous, 0.070 mL or 0.042 mg per spray;			
CHEMICAL NAME AND STRUCTURE Ipratropium bromide monohydrate (IB)				16. RECORDS AND REPORTS CURRENT YES _____ NO _____ REVIEWED YES _____ NO _____	
17. COMMENTS  FT by: LNg 3/11/98 R/D Init. by <u>LSI</u> 3/11/98 File: 2039401AREV					
18. CONCLUSIONS AND RECOMMENDATIONS The supplement is approvable. The labeling comments should be forwarded to the firm.					
19. REVIEWER					
NAME Linda L. Ng, Ph.D.		SIGNATURE <u>LSI</u>		DATE COMPLETED 3/11/98	
DISTRIBUTION ORIGINAL JACKET NDA20-394 DIVISION FILE HFD-570 REVIEWER LNg CSO DToyer SUP. CHEMIST GPoochikian					

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**APPLICATION NUMBER: 20-394/S001**

**PHARMACOLOGY REVIEW(S)**

**DIVISION OF PULMONARY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**  
Labeling Review

NDA No. 20-394

Submission Date: 19 DEC 97

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 8 JUL 98

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Drug Name: *Generic:* ipratropium bromide    *Commercial:* Atrovent® Nasal Spray 0.06%

The sponsor submitted draft labeling for Atrovent® Nasal Spray 0.06% pediatric supplement in support of the inclusion of children 5 years and above. Ipratropium has been approved as a nasal spray for rhinorrhea associated with allergic rhinitis treatment. It has also been approved as a metered dose inhaler (MDI) and inhalation solution formulations for COPD and as a MDI in combination with albuterol sulfate (Combivent) for treatment of COPD. The most recent approved labeling for an ipratropium product is the Atrovent® Nasal Spray 0.03% pediatric supplement (see approval letter dated 01 April 1998, for NDA 20-393/SE1-001). The revised preclinical labeling recommended below is based on that labeling with appropriate modifications reflecting differences in the two products with respect to maximum recommended dose.

Recommended dose:

Adults:	16 sprays/day	42 µg/spray	0.01344 mg/kg
Children (5 years of age):	12 sprays/day	42 µg/spray	0.0315 mg/kg

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3 Page(s) Redacted

Draft  
Labeling

Preclinical Labeling Calculations:

# BEST POSSIBLE COPY

Drug: **Atrovent NS**  
0.06%

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m <sup>2</sup>
Pediatric	5	0.042	12	0.504	16	0.0315	25	0.79
Adult	>12	0.042	16	0.672	50	0.01344	37	0.50

	route /	mg/kg/d	conv. factor	mg/m <sup>2</sup>	Dose Ratio		Rounded Dose Ratio	
					Adults	Children	Adults	Children
<b>Carcinogenicity:</b>								
rat	oral	50	6	36	72.4	45.71429	70	45
mouse	oral	50	3	18	36.2	22.85714	35	25
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
<b>Reproduction and Fertility:</b>								
rat	oral	500	6	300	603.3	N/A	600	N/A
rat	oral	500	6	3000	6032.8	N/A	6000	N/A
extra			---	---	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
<b>Teratogenicity:</b>								
mouse	oral	10	3	30	60.3	N/A	60	N/A
rat	oral	1000	6	6000	12065.6	N/A	12000	N/A
rabbit	oral	125	12	1500	3016.4	N/A	3000	N/A
rat	oral	30	6	540	1085.9	N/A	1100	N/A
rabbit	inhalation	1.8	12	21.6	43.4	N/A	45	N/A
<b>Overdosage:</b>								
mouse	oral	1000	3	3000	6032.8	3809.524	6000	3800
rat	oral	1700	6	10200	20511.6	12952.38	21000	13000
dog	oral	400	20	8000	16087.5	10158.73	16000	10000
extra			---	---	---	---	---	---
<b>Other:</b>								
teratogenicity								
rat	inhalation	1.5	6	9	18.1	N/A	20	N/A
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

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**APPLICATION NUMBER: 20-394/S001**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA: 20-394  
Ipratropium Bromide

SUBMISSION DATE:  
12/19/97 (Serial No. SEI-001)

BRAND NAME:  
Atrovent Nasal Spray 0.06% (42 µg/spray)

SPONSOR:  
Boehringer Ingelheim

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Pediatric Supplement

Code: 3S

TITLE: "Review of Human Pharmacokinetic and Bioavailability Studies To Support The Pediatric Supplement of Atrovent Nasal Spray"

I. BACKGROUND:

Ipratropium bromide is a quaternary ammonium compound with structure and anticholinergic activity similar to those of the tertiary amine alkaloid, atropine. Previously, Atrovent (ipratropium bromide, 18 µg/inhalation) for meter dose inhaler (MDI) that was filed under NDA 19-085 by Boehringer Ingelheim (BI) was approved by the Agency on 12/29/86. Atrovent is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. No review records for this NDA, however, were found in the drug files of the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II).

On 09/29/93, NDA 20-228 (Atrovent 0.02% Inhalation Solution) was approved by the Agency for the same indication as that for NDA 19-085. Six studies (in vivo and in vitro) submitted to Human Pharmacokinetics and Bioavailability (PK/Bio) section (Item 6) of NDA 20-228 were reviewed by OCPB on 07/08/93. Later, both NDA 20-393 [Atrovent Nasal Spray (NS) 0.03%] for symptomatic relief of rhinorrhea (runny nose) associated with allergic and nonallergic perennial rhinitis and NDA 20-394 (Atrovent NS 0.06%) for symptomatic relief of rhinorrhea associated with common cold for adults or children 12 years and older were approved on 10/20/95. For these two NDAs, four PK/Bio studies were reviewed by OCPB on 07/06/94. A \_\_\_\_\_ assay method for plasma and urinary levels of ipratropium was reviewed and found acceptable.

On 03/31/97, BI submitted a pediatric supplement (Serial No. SEI-001) for children 6 to 11 years that was filed under NDA 20-393 (Atrovent NS 0.03%).

The above pediatric supplement Serial No. SEI-001 has been reviewed by OCPB/DPE II dated 03/03/98 and it was found overall acceptable.

II. SYNOPSIS:

On 12/19/97, BI submitted a pediatric supplement (Serial No. SEI-001) that was filed under NDA 20-394 (Atrovent NS 0.06%) for children 5 to 11 years. The current recommended dosing regimen for adults and children 12 years and older is 2 x 42 µg/spray per nostril TID or QID (total dose 504 to 672 µg/day). The sponsor is seeking approval for only the TID dosing regimen for younger children between 5 and 11 years (total dose 504 µg/day). Please see the package insert (PI) in Appendix 1 for details.

Submitted under the pediatric supplement (Serial No. SEI-001) of NDA 20-394 were a pivotal human PK/Bio study No. 244.2448 and 4 supportive studies (Nos. 847/848, 899, 779, and 612/614). They have been reviewed previously. For the pivotal study No. 244.2448 and the supportive study No. 847/848, please see OCPB review dated 03/03/98 for NDA 20-393 pediatric supplement for details. For the supportive study Nos. 899, 779, and 612/614, please see OCPB review dated 07/06/94 for the original NDA 20-394 for details.

III. RECOMMENDATION:

The pediatric supplement (Serial No. SEI-001) for Atrovent NS 0.06% was submitted on 12/19/97. Since the 4 human PK/Bio studies included have been reviewed previously by OCPB/DPE II and found overall acceptable, only its PI was reviewed. The following Labeling Comments (on pages 3 and 4) need to be conveyed to the sponsor ASAP.

**/S/**

03/09/98

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Mei-Ling Chen, Ph.D.

**/S/**

FT initialed by Mei-Ling Chen, Ph.D.

**/S/**

3/15/98

cc: NDA 20-394, HFD-570 (Chowdhury, Toyer), HFD-870 (M.L. Chen, T.M. Chen), CDR (B. Murphy).

IV. LABELING COMMENTS: (Need to be sent to the sponsor)

1. It is recommended that the following paragraph which is not related to pharmacokinetics be moved to Clinical Pharmacology section of the Package insert:

Controlled clinical trials demonstrated that intranasal fluorocarbon-propelled ipratropium bromide does not alter physiologic nasal functions (e.g., sense of smell, ciliary beat frequency, mucociliary clearance, or the air conditioning capacity of the nose).

2. The following human pharmacokinetics subsection under the Clinical Pharmacology section has been revised (Agency's version):

***Pharmacokinetics:***

***Absorption:*** Ipratropium is poorly absorbed into the systemic circulation following oral administration (2-3%). Less than 20% of an 84 mcg per nostril dose was absorbed from the nasal mucosa of normal volunteers, induced-cold patients, or perennial rhinitis patients.

***Distribution:*** Ipratropium is minimally bound (0 to 9% in vitro) to plasma albumin and  $\alpha$ 1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

***Metabolism:*** Ipratropium is partially metabolized to ester hydrolysis products, tropic acid and tropane. These metabolites appear to be inactive based on in vitro receptor affinity studies using rat brain tissue homogenates.

***Elimination:*** After intravenous administration of 2 mg ipratropium bromide to 10 healthy volunteers, the terminal half-life of ipratropium was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be approximately 2505 and 1019 ml/min, respectively. The amount of the total dose (in %) excreted unchanged in the urine within 24 hours was approximately one-half of the administered dose.

***Pediatrics:*** Following administration of 84 mcg of ipratropium bromide per nostril three times a day in patients aged 5 to 18 years old, the mean amount of the total dose excreted unchanged in the urine for ipratropium (7.8 %) was higher than those reported in adults. Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.62 ng/ml). No correlation of the amount of the total dose excreted unchanged in the urine with age or gender was found in pediatric population.

*Special Populations:* Gender does not appear to influence the absorption or excretion of nasally administered ipratropium bromide. The pharmacokinetics of ipratropium bromide have not been studied in patients with hepatic or renal insufficiency or in the elderly.

*Drug-Drug Interaction:* No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions.

*Pharmacodynamics:* In two single-dose pharmacokinetic trials (n=17), doses of up to 336 mcg ipratropium bromide did not significantly affect pupillary diameter, heart rate or systolic/diastolic blood pressure. Similarly, in patients with induced-colds, ATROVENT (ipratropium bromide) Nasal Spray 0.06% (84 mcg/nostril four times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

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**APPLICATION NUMBER: 20-394/S001**

**ADMINISTRATIVE DOCUMENTS**



**16.0 DEBARMENT CERTIFICATION**

**CERTIFICATION STATEMENT**

Section 306(k)(1) of THE ACT

21 U.S.C. 335a(k)(1)

The undersigned certifies that Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b) ], in connection with ATROVENT® Nasal Spray.

Signature:

*Joseph M. Ferrara*

Date: 11/5/98

Name of Applicant:

Joseph M. Ferrara, R.Ph., M.Sc.  
Director, Drug Regulatory Affairs  
Boehringer Ingelheim Pharmaceuticals, Inc.

Mailing Address:

Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road  
P.O. Box 368  
Ridgefield, CT. 06877-0368

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EXCLUSIVITY SUMMARY FOR NDA # N20-394 SUPPL # SE-01

Trade Name Atrovent Nasal Spray 0.06% Generic Name Ipratropium Bromide

Applicant Name Boehringer Ingelheim HFD # 570

Approval Date If Known \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?  
YES /\_\_\_/ NO /X/

b) Is it an effectiveness supplement?  
YES /X/ NO /\_\_\_/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /\_\_\_/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?  
YES /X/ NO /\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

No time frame stipulated.

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# <u>20-393</u>	<u>Atrovent Nasal Spray 0.03%</u>
NDA# <u>20-291</u>	<u>Combivent MDI</u>
NDA# <u>19-085</u>	<u>Atrovent Inhalation Aerosol</u>
NDA# <u>20-228</u>	<u>Atrovent Inhalation Solution</u>

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2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.**

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO /\_\_\_/

**APPEARS THIS WAY  
ON ORIGINAL**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

---

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / X / NO /    /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /    / NO / X /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /    / NO / X /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

244-2448  
244-2465

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

APPEARS THIS WAY  
ON ORIGINAL

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /  /                      NO /  /

Investigation #2                      YES /  /                      NO /  /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /  /                      NO /  /

Investigation #2                      YES /  /                      NO /  /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

244-2448 \_\_\_\_\_  
244-2465 \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

APPEARS THIS WAY  
ON ORIGINAL

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND #            YES /  / ! NO /  / Explain: \_\_\_\_\_  
! !

Investigation #2  
IND #            YES /  / ! NO /  / Explain: \_\_\_\_\_  
! !

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
YES /  / Explain \_\_\_\_\_ ! NO /  / Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
YES /  / Explain \_\_\_\_\_ ! NO /  / Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /  / NO /  /

If yes, explain: \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

ISI

Signature

Title: Project Manager

3 November 98  
Date

ISI  
~~Signature of Office/  
Division Director~~  
~~cc: Original NDA~~

11/5/98  
Date

Division File HFD-93 Mary Ann Holovac

**APPEARS THIS WAY  
ON ORIGINAL**

**13.0 PATENT INFORMATION**

**13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG**

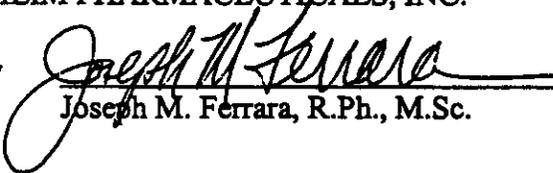
1.	Active ingredient(s)	Ipratropium bromide
2.	Strength(s)	0.06%
3.	Trade Name	ATROVENT®
4.	Dosage Form Route of Administration	Spray Nasal
5.	Indication	Treatment of Common Cold
6.	Applicant firm name	Boehringer Ingelheim Pharmaceuticals, Inc.
7.	NDA Number	20-394
8.	Approval Date	10/20/95
9.	Applicable patent numbers and expiration date of each	U.S. Patent No. 4,385,048 May 24, 2000
10.	Type of patent	Method of use
11.	Name of patent owner	Boehringer Ingelheim International GmbH

**12. Certification with respect to Method of Use patents:**

The undersigned certifies that Patent No. 4,385,048 covers the use of ipratropium bromide that is the subject of this application for which approval is being sought.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By

  
Joseph M. Ferrara, R.Ph., M.Sc.

Title Director, Drug Regulatory Affairs

Date

11/4/98

13.0 PATENT INFORMATION

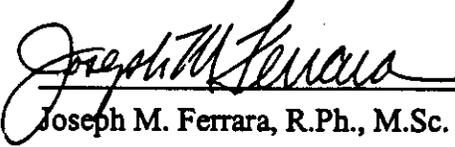
13.1 EXCLUSIVITY INFORMATION:

1. Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) believes that after approval of the Supplemental New Drug Application, ATROVENT® Nasal Spray 0.06% is entitled to a period of marketing exclusivity under the provisions of 21 CFR 314.108, and is, therefore claiming exclusivity.
2. Reference is made to 21 CFR 314.108, Part (b)(5), to support BIPI's claim of exclusivity for ATROVENT® Nasal Spray.
3. BIPI claims exclusivity under 21 CFR 314.108, Part (b)(5), which states that the clinical investigations in its application (BIPI's NDA 20-394/S-001 for ATROVENT® Nasal Spray 0.06%) are "new clinical investigations", "essential to approval of the application", and "conducted or sponsored by BIPI".

(a) "New Clinical Investigations" – Certification:

To the best of BIPI's knowledge, the clinical investigations included in the application meet the definition of "new" and "clinical investigations" set forth in 21 CFR 314.108(a).

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By   
Joseph M. Ferrara, R.Ph., M.Sc.

Title Director, Drug Regulatory Affairs

Date 10/30/98

13.0 PATENT INFORMATION

13.1 EXCLUSIVITY INFORMATION (continued):

(b) "Essential to Approval" – Certification

BIPI has thoroughly searched the scientific literature and, to the best of BIPI's knowledge, there are no published results involving this ATROVENT® Nasal Spray product utilized in the treatment of rhinorrhea associated with the common cold in addition to the trials conducted and sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. under IND

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By Joseph M. Ferrara  
Joseph M. Ferrara, R.Ph., M.Sc.

Title Director, Drug Regulatory Affairs

Date 10/30/98

(c) "Conducted or Sponsored by" – The IND Number

The Investigational New Drug Application (IND) number, under which BIPI was named as the sponsor in the Form FDA-1571 for which the new clinical investigations that are essential to the approval of this application were conducted, is IND

APPEARS THIS WAY  
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN  
ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: April 30, 2000  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER  
NDA 20-394

APPLICANT INFORMATION

NAME OF APPLICANT BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		DATE OF SUBMISSION October 14, 1998
TELEPHONE NO. (Include Area Code) (203) 798-4344		FACSIMILE (FAX) NUMBER (Include Area Code) (203) 791-6262
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) ipratropium bromide	PROPRIETARY NAME (trade name) IF ANY ATROVENT®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 8-azoniabicyclo (3.2.1) octane,3-(3-hydroxy-1-oxo-2-phenylpropoxy) -8-methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-,(±)-	CODE NAME (if any)	
DOSAGE FORM: Spray	STRENGTHS: 0.06%	ROUTE OF ADMINISTRATION: Nasal

(PROPOSED) INDICATION(S) FOR USE:

Symptomatic relief of rhinorrhea associated with the common cold for adults and children age 12 years and older

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR PART 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
REASON FOR SUBMISSION: RESPONSE TO FDA REQUEST
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

9 Page(s) Redacted

**DRAFT**

**Labeling**

**16.0 DEBARMENT CERTIFICATION**

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**CERTIFICATION STATEMENT**

Section 306(k)(1) of THE ACT

21 U.S.C. 335a(k)(1)

The undersigned certifies that Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b) ], in connection with ATROVENT® Nasal Spray.

Signature:



Name of Applicant:

Joseph M. Ferrara, R.Ph., M.Sc.  
Director, Drug Regulatory Affairs  
Boehringer Ingelheim Pharmaceuticals, Inc.

Mailing Address:

Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Road  
P.O. Box 368  
Ridgefield, CT. 06877-0368

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-394/S001**

**CORRESPONDENCE**

Toyer

RECORD OF TELEPHONE CONVERSATION

NDA: 20-394/SE-01      DATE: September 30, 1998  
 SPONSOR: Boehringer Ingelheim (BIPI)  
 DRUG: Atrovent Nasal Spray 0.06%  
 INITIATED BY:        X   APPLICANT             FDA  
 NAMES AND TITLES OF PERSONS WITH WHOM CONVERSATION WAS HELD:  
 FDA: Dr. Albert Chen, Dr. Badrul Chowdhury, Dr. Joseph Sun, Dr. Denise Toyer and Dr. Ramana Uppoor  
 BIPI: Ms. Holly Dursoma, Dr. Tom McGregor, Ms. Mary Nier, Dr. Richard Tamorria, Dr. Chet Wood,

BACKGROUND

On August 14, 1998, the Division faxed labeling comments to BIPI. On September 2, 1998 BIPI submitted their comments to the Division's labeling comments. On August 19, 1998, the Division faxed BIPI further comments on the labeling. The objective of this telecon is discuss the Division's labeling comments in comparison with BIPI's September 2, 1998 submission.

TELECON

The following changes will be made to the labeling. All additions are listed in bold and the deletions are listed as strikeouts.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: . . . was absorbed from the nasal mucosa of normal volunteers, **induced-cold adult volunteers, naturally-acquired common cold pediatric patients, or perennial rhinitis adult patients.**

Elimination: . . . (Ae) within 24 hours was approximately one-half of the  administered dose.

Pediatrics: . . . three times a day in patients 5-18 years old (n=42) with a naturally-acquired common cold, the mean amount of the total dose **excreted unchanged in the urine of 7.8% was comparable to 84 mcg per nostril four times a day in an adult induced common cold population (n=22) of 7.3 to 8.1% . . . in the pediatric population.**

Special Populations: Gender does not appear [redacted] to influence.

Pharmacodynamics: In two single dose, [redacted] trials (n=17), [redacted] doses up to 336 mcg . . . Similarly, ATROVENT Nasal Spray 0.06% in adult patients (n=22) with induced colds (84 mcg/nostril four times a day) and in pediatric patients (n=45) with naturally-acquired common cold (84 mcg/nostril three times a day) had no significant effects on pupillary diameter, heart rate, or systolic/diastolic blood pressure.

#### PRECAUTIONS

##### Carcinogenesis, Mutagenesis, Impairment of Fertility

. . . (approximately 70 and 35 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 45 and 25 times the . . .

**Pregnancy TERATOGENIC EFFECTS** Pregnancy Category B. Because animal reproduction studies are not always predictive of human response, ipratropium bromide should be used during pregnancy only if clearly needed.

. . . naturally acquired common colds. In this pediatric population ATROVENT (ipratropium bromide) Nasal Spray 0.06% had an adverse event profile similar to that observed in adolescent and adult patients. When ATROVENT was concomitantly administered with an oral decongestant (pseudoephedrine HCl) in 122 children ages 5-12 years, and concomitantly administered with an oral decongestant/antihistamine combination (pseudoephedrine HCl/chlorpheniramine maleate) in 123 children ages 5-12 years, adverse event profiles were similar to ATROVENT alone. The effectiveness of . . .

Oral median lethal doses of ipratropium bromide were greater than: 1,000 mg/kg in mice (approximately 6,000 and 3,800 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m<sup>2</sup> basis), 1,700 mg/kg in rats (approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a

mg/m<sup>2</sup> basis), and 400 mg/kg in dogs (approximately 16,000 and 10,000 times the maximum recommended daily intranasal dose in adults and children, respectively on a mg/m<sup>2</sup> basis). (Note: The above calculations were made using 16 kg and a factor of 25 for pediatric patients.)

### **DOSAGE AND ADMINISTRATION**

. . . for symptomatic relief of rhinorrhea associated with the common cold in adults and children age 5 years and older . . .

### **Other Issues**

BIPI contacted Ms. Khatyi Roberts (Science Policy Analyst, HFD-006) and Ms. Cathie Schumaker (Chief, Project Management Staff, HFD-570) to discuss the pediatric exclusivity rule as it pertains to Atrovent Nasal Spray 0.03% and 0.06%. BIPI noted that Ms. Roberts stated that Atrovent Nasal Spray 0.03% would not be eligible for the extra six months exclusivity because it was submitted prior to enactment of the rule. Atrovent Nasal Spray 0.06% was submitted on December 19, 1997, but BIPI indicated that Ms. Roberts and Ms. Schumaker informed them that they may be required to submit additional safety data to receive the additional exclusivity. BIPI indicated that at this time they do not see a benefit to conducting studies in populations below the age of five and would like to obtain additional exclusivity based on the studies that they have submitted to the Agency. BIPI does not think that the drug is used below the age of five and they do not intend to seek approval to lower the age further at this time. BIPI also asked for a clarification from the Division on the reasons the Division may ask for further data for ages below five years. Dr. Chowdhury requested data from BIPI pertaining to the usage of Atrovent 0.06% in populations younger than age five.

### **Action Items**

NDA 20-394/SE-01

Page 4

**/S/**

Denise Toyer, R.Ph., Pharm.D.  
Project Manager

cc:

Orig. NDA 20-394

HFD-570/Division File

HFD-570/Chowdhury/9-30-98

HFD-570/Chen

HFD-570/Sun

HFD-570/Uppoorr

HFD-570/Toyer

**APPEARS THIS WAY  
ON ORIGINAL**

JAN 27 1998

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: January 23, 1998

To: Director, Mei-Ling Chen, Ph.D. (HFD-870)  
Deputy Director, Mr. John Hunt (HFD-870)

/S/

1/27/98

From: Tien-Mien Chen, Ph.D. (HFD-870)

/S/

1/27/98

RE: Filing Meeting for Clinical Supplement of NDA 20-394 (Atrovent Nasal Spray 0.06%; ipratropium bromide)

SYNOPSIS:

On 12/19/97, Boehringer Ingelheim submitted a pediatric supplement (Serial No. SE1-001) to the Agency that was filed under NDA 20-394 for Atrovent Nasal Spray 0.06% (ipratropium bromide). The original NDA was reviewed and approved by the Agency on 10/20/95 for the indication of symptomatic relief of rhinorrhea associated with common cold for adults and children 12 years and older. The recommended dosing regimen is 2 x 42 µg/sprays to each nostril TID or QID (total dose of 504 to 672 µg/day).

The pediatric supplement (Serial No. SE1-001) is submitted to support the labeling revision to include children 5 to 11 years old. The recommended dosing regimen for children 5 to 11 years old is 2 x 42 µg/sprays to each nostril TID (total dose of 504 µg/day). Please see the package insert (12/19/97 version) in Attachment 1 for details.

Submitted under Human Pharmacokinetics and Bioavailability section of the pediatric supplement is a summary report obtained from 5 pharmacokinetic and bioavailability (PK/Bio) studies, i.e., Nos. 612A/614A, 779A, 899A, 847A/848A, and 244.2448. The first three studies had been reviewed previously under original NDA by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPEII). The rest of two PK/Bio studies need to be reviewed. Study No. 244.248 is considered to be pivotal which was conducted in 42 children of 5 to 17 years old of age, however, the study results are embedded and only briefly reported in the clinical report. The assay validation for its drug levels in plasma or urine is provided in the clinical report. For the supportive PK study, No. 847A/848A, there is no record in OCPB drug review files to show whether the study has been submitted and reviewed previously by OCPB or not.

**RECOMMENDATION:**

The pediatric supplement (Serial No. SE1-001) that was submitted under NDA 20-394 on 12/19/97 by Boehringer Ingelheim was briefly reviewed by OCPB/DPEII for filing purposes. OCPB/DPE II is of the opinion that this pediatric supplement is acceptable for filing. The following comment has been communicated to the sponsor on 01/23/98 through the CSO.

**COMMENT:** (Needs not to be sent to the sponsor)

It is reported that the human pharmacokinetic (PK) study No. 847A/848A was submitted under Item 6 of this pediatric supplement. However, there is no study report provided. It is not known as to whether the study report has been submitted and reviewed previously by the Agency or not.

Therefore, it is recommended that the date of submission and NDA No. be provided, if the PK study No. 847A/848A has been submitted previously. If the study has not been submitted previously, it is recommended that a complete study report including the validation of the assay method used be submitted to the Agency for review as soon as possible.

**APPEARS THIS WAY  
ON ORIGINAL**

cc: NDA 20-394, HFD-570 (Chowdhury, Toyer), HFD-870 (M. L. Chen, T. M. Chen),  
CDR (B. Murphy).

**BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**

900 RIDGEBURY ROAD  
P.O. BOX 368  
RIDGFIELD, CT 06877

TELEFAX

NO. OF PAGES 7  
(Including Cover Page)

Date: October 29, 1998

TO: Dr. Denise Toyer Food and Drug Administration	FROM: Dr. C. R. Tamorria
FAX: (301) 827-1271	TEL: (203) 798-4344
	FAX: (203) 791-6262

Dear Dr. Toyer,

Since the submission of the ATROVENT® Nasal Spray 0.06% Supplemental NDA on December 19, 1997, there have been no clinical trials conducted in pediatric patients with ATROVENT® Nasal Spray 0.06%. During the period from December 19, 1997 to October 29, 1998, there was one case (MFR Control No. 1998-001703) with unexpected serious adverse events reported for ATROVENT® Nasal Spray 0.06% during this period, and one case for ATROVENT® Nasal Spray 0.03% (MFR Control No. 1998-002044).

If you require additional information, please contact me.

Sincerely,

*C. R. Tamorria*

C. R. Tamorria, Ph.D.  
DRA Sr. Associate Director  
Drug Regulatory Affairs  
G:\dra\atrovent\nasal\fax10-29

Attachments

APPEARS THIS WAY  
ON ORIGINAL

ATROVENT NASAL SPRAY 0.06% SAFETY UPDATE  
INDEX OF 15-DAY FOLLOW-UP REPORTS  
BY MANUFACTURER CONTROL NUMBER  
SUBMITTED 12/19/97 TO 10/29/98

MFR. CONTROL NO.	INCLUDED TERM	PREFERRED TERM	AGE	SEX	SUBMITTED	FDA
1998-001703	SWALLOWING IMPAIRED	DYSPHAGIA	35.0	M	08/03/98	
	THROAT SORE	PHARYNGITIS			08/03/98	

APPEARS THIS WAY  
ON ORIGINAL

ATROVENT NASAL SPRAY 0.06% SAFETY UPDATE  
INDEX OF 15-DAY INITIAL REPORTS  
BY MANUFACTURER CONTROL NUMBER  
SUBMITTED 12/19/97 TO 10/29/98

MFR. CONTROL NO.	INCLUDED TERM	PREFERRED TERM	AGE	SEX	SUBMITTED	FDA
1998-001703	SWALLOWING IMPAIRED	DYSPHAGIA	35.0	M	07/14/98	
	THROAT SORE	PHARYNGITIS	35.0	M	07/14/98	

APPEARS THIS WAY  
ON ORIGINAL

LISTING OF ALL 15 DAY REPORTS IDENTIFIED IN SAM  
IDENTIFIED BY STARTDATE TO FDA  
DATE: 29OCT98

OBS	BICASE	MANUFNO	LOSUSD	SD15DAY	CONTNO	D15D2DRA	D15D2FDA	RSTFDA	PERDFDA
1	98-BP-01103	1998-001703	ATROVENT NASAL SPRAY 0.06%	29JUN1998	01	01JUL1998	14JUL1998	INITIAL REPORT	1
2	98-BP-01103	1998-001703	ATROVENT NASAL SPRAY 0.06%	22JUL1998	03	27JUL1998	03AUG1998	FOLLOW-UP REPORT	2
3	98-BP-01103	1998-001703	ATROVENT NASAL SPRAY 0.06%	22JUL1998	02	27JUL1998	03AUG1998	FOLLOW-UP REPORT	2

APPEARS THIS WAY  
ON ORIGINAL

LISTING OF ALL 15 DAY REPORTS IDENTIFIED IN SAM  
 IDENTIFIED BY STARTDATE TO FDA  
 DATE: 29OCT98

OBS	BICASE	MANUFNO	LOSUSD	SD15DAY	CONTNO	D15D2DRA	D15D2FDA	RSTFDA	PERDFDA
1	96-BP-01109	MATN3 08/11/96	ATROVENT NASAL SPRAY 0.03%	11AUG1996	02	23AUG1996	27AUG1996	INITIAL REPORT	1
2	96-BP-01109	MATN3 08/11/96	ATROVENT NASAL SPRAY 0.03%	11AUG1996	01	23AUG1996	27AUG1996	INITIAL REPORT	1
3	97-BP-01883	MATN3 11/25/97	ATROVENT NASAL SPRAY 0.03%	25NOV1997	01	01DEC1997	10DEC1997	INITIAL REPORT	1
*4	98-BP-01334	1998-002044	ATROVENT NASAL SPRAY 0.03%	03AUG1998	01	05AUG1998	14AUG1998	INITIAL REPORT	1
5	98-BP-01334	1998-002044	ATROVENT NASAL SPRAY 0.03%	17SEP1998	02	21SEP1998	02OCT1998	FOLLOW-UP REPORT	2

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NDA SAFETY UPDATE ATROVENT NASAL SPRAY 0.03%  
INDEX OF 15-DAY INITIAL REPORTS  
BY MANUFACTURER CONTROL NUMBER  
SUBMITTED 12/19/97 TO 10/29/98

MFR. CONTROL NO.	INCLUDED TERM	PREFERRED TERM	AGE	SEX	SUBMITTED	FDA
1998-002044	CHEST PAIN	CHEST PAIN	84.0	M	08/14/98	

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NDA SAFETY UPDATE ATROVENT NASAL SPRAY 0.03%  
INDEX OF 15-DAY FOLLOW-UP REPORTS  
BY MANUFACTURER CONTROL NUMBER  
SUBMITTED 12/19/97 TO 10/29/98

MFR. CONTROL NO.	INCLUDED TERM	PREFERRED TERM	AGE	SEX	SUBMITTED	FDA
1998-002044	CHEST PAIN	CHEST PAIN	84.0	M	10/02/98	

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Toyer

INTEROFFICE MEMORANDUM

TO: NDA 20-394

FROM: MARTIN H. HIMMEL, MD  
DEPUTY DIVISION DIRECTOR, HFD-570

SUBJECT: SECONDARY REVIEW MEMO - PEDIATRIC COMMON COLD SUPPLEMENT

DATE: JUNE 24, 1998

CC: HFD-570: JENKINS, HIMMEL, CHOWDHURY, WILSON, GEBERT, TOYER

Handwritten notes and stamps: "ISI" (three instances), "6/24/98", and "6/28/98".

This efficacy supplement was submitted to support revising the package insert of Atrovent Nasal Spray .06% to include use in patients down to 5 years of age. The indications would be the same as for the adult population and the dosage would be two sprays per nostril three times daily (in adults the drug is dosed up to four times daily). In support of the safety and efficacy of Atrovent Nasal Spray .06% the sponsor has submitted two studies, one is a pharmacokinetic trial and the second is a four day safety trial with some efficacy secondary endpoints.

The four day safety trial, while supporting the safety of a four day course of Atrovent Nasal Spray .06% in children down to age 5, is inadequate to support the efficacy of the drug. The reasons for this are the lack of an adequate placebo arm for Atrovent, single blind nature of the trial, and there were no efficacy primary endpoints. However, the application is approvable, from the clinical standpoint, based on the available pediatric safety data and application of the pediatric rule. Specifically, it is expected that the symptom of rhinorrhea in the common cold would be similar in children and adults. In addition, based on the recently reviewed Atrovent Nasal Spray .03% it has been determined that children require the same dose as adults for this drug to adequately treat rhinorrhea, in this case 2 sprays per nostril three times daily. The four day study included in this application is also suggestive of the fact that lower doses of Atrovent Nasal Spray .06% would not likely be efficacious based on the similar symptom scores between drug and oral placebo.

Based on the safety profile of Atrovent Nasal Spray and extrapolation of effect for pediatric patients from adults, this pediatric efficacy supplement is approvable. Specific labeling comments regarding the pediatric section of the package insert will be forwarded to the sponsor. Further details regarding the individual trials and the conduct of the review can be found in the medical officer's review of this efficacy supplement.

APPEARS THIS WAY  
ON ORIGINAL



# Boehringer Ingelheim

Boehringer Ingelheim  
Pharmaceuticals, Inc.  
a subsidiary of  
Boehringer Ingelheim Corporation  
900 Ridgebury Rd.  
P.O. Box 368  
Ridgefield, Connecticut 06877

October 12, 1998

Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-155)  
Document Control Room #17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Attention: John K. Jenkins, M.D., Director  
Division of Pulmonary Drug Products

Re: ATROVENT® Nasal Spray 0.06%  
(ipratropium bromide)  
NDA 20-394

Dear Dr. Jenkins:

We are submitting herewith final draft labeling for ATROVENT® Nasal Spray 0.06% for the pediatric indication.

Please contact me if there are any questions relating to this draft labeling.

Sincerely,

A handwritten signature in cursive script that reads "C. R. Tamoria".

C. R. Tamoria, Ph.D.  
DRA Sr. Associate Director  
Drug Regulatory Affairs  
Phone: (203) 798-4344  
Fax: (203) 791-6262

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ON ORIGINAL

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# DUPLICATE Boehringer Ingelheim

Boehringer Ingelheim  
Pharmaceuticals, Inc.  
a subsidiary of  
Boehringer Ingelheim Corporation  
900 Ridgebury Rd.  
P.O. Box 368  
Ridgefield, Connecticut 06877

October 14, 1998

Food and Drug Administration  
Center for Drug Evaluation and Research (HFD-155)  
Document Control Room #17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Attention: John K. Jenkins, M.D., Director  
Division of Pulmonary Drug Products

Re: ATROVENT® Nasal Spray 0.06%  
(ipratropium bromide)  
NDA 20-394

## FINAL DRAFT LABELING

Dear Dr. Jenkins:

We are submitting herewith final draft labeling for ATROVENT® Nasal Spray 0.06% for the pediatric indication. This draft labeling is identical to that sent by fax to you on October 12, 1998 except for the following editorial corrections:

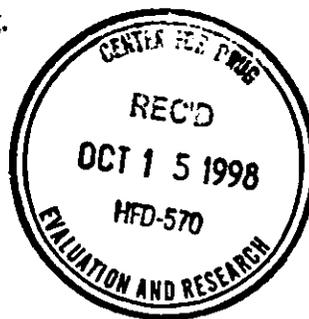
- Deletion of the word "respectively" (and commas) from line 8 of the section Pregnancy TERATOGENIC EFFECTS.
- Relocation of Figure 3 and Figure 4 within the PATIENT'S INSTRUCTIONS FOR USE. Figure 3 now follows #4 and Figure 4 follows the section "To Clean:"

Please contact me if there are any questions relating to this draft labeling.

Sincerely,



C. R. Tamorria, Ph.D.  
DRA Sr. Associate Director  
Drug Regulatory Affairs  
Phone: (203) 798-4344



10 Page(s) Redacted

Draft  
Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

MEMORANDUM

DATE: 11/02/98

FROM: Denise P. Toyer, R.Ph. [Signature] 11/2/98  
Project Manager, DPDP

THRU: Badrul Chowdhury, M.D. [Signature] 11/3/98  
Clinical Reviewer

Guirag Poochikian, Ph.D. [Signature] 11/4/98  
Chemistry, Team Leader

SUBJECT: Modification to Medical Officer and Chemistry Reviews

TO: NDA 20-394, Atrovent Nasal Spray 0.06%

The applicant proposes expanding the age range from 12 years of age and older to 5 years of age and older. The following modifications should be made to the June 24, 1998, clinical review and the March 1, 1998, chemistry, manufacturing, and controls review.

**Clinical Review**

**Page One, Last sentence**

The sentence reads as follows: "[sic] The safety and efficacy data from this submission taken in the context that the pathophysiology of common cold disease is the same in adults and children support the use of Atrovent nasal spray 0.06% in children up to the age of 5 years for control of rhinorrhea in common cold. This sentence should be modified to read: "The safety and efficacy data from this submission taken in the context that the pathophysiology of common cold is the same in adults and children supports the use of Atrovent Nasal Spray 0.06% in children five years of age and older for the control of rhinorrhea in common cold."

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**Section XII, Second sentence**

The sentence reads as follows: "[sic] The database also supports the safety of Atrovent used either alone or in combination with decongestant/antihistamine for treatment of common cold in children up to the age of 5 years. This sentence should be modified to read: "The database also supports the safety of Atrovent Nasal Spray 0.06% used either alone or in combination with a decongestant/antihistamine for the treatment of common cold in children five years of age and older."

**Chemistry Review**

**Section Eight, Supplement provides for:**

The sentence reads as follows: "Labeling revisions to include children years and older-pediatric labeling. The sentence should be modified to read: "Labeling revisions to include children 5 years and older-pediatric labeling."

Cc:

HFD-570/Original NDA

HFD-570/Division File

HFD-570/Poochikian

HFD-570/Chowdhury

HFD-570/Toyer

Initialed by: 10-28-98/Schumaker

**APPEARS THIS WAY  
ON ORIGINAL**