CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-394/S004

Trade Name: Atrovent®

Generic Name: Ipratropium Bromide

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 10/27/2000

Indication: This supplemental new drug application provides for the use of Atrovent Nasal Spray 0.06% for symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older.

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APPLICATION NUMBER:

20-394/S004

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 20-394/S-004

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

Attention: C. Richard Tamorria, Ph.D.
Sr. Associate Director, Drug Regulatory Affairs

Dear Dr. Tamorria:

Please refer to your supplemental new drug application dated December 29, 1999, received December 30, 1999, 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 22, October 23, 24, and 26, 2000.

This supplemental new drug application provides for the use of Atrovent Nasal Spray 0.06% for symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in patients 5 years of age and older.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 26, 2000).

Please submit 20 paper 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. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-394/S-004." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of the necessary further pediatric studies until June 2, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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 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-42
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, call Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-394
HFD-570/Div. Files
HFD-570/L.Jafari
HFD-570/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT
HFD-093/DDMS-IST (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: LJ/October 19, 2000

Initialed by: Barnes/10-24-00
Poochikian/10-24-00
McGovern/10-26-00
Huff/10-26-00
Gebert/10-25-00
Wilson/10-25-00
Chowdhury/10-25-00
Meyer/10-26-00

filename: N20394s04ap

APPROVAL (AP) (with Post Marketing (pediatric) Commitments)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

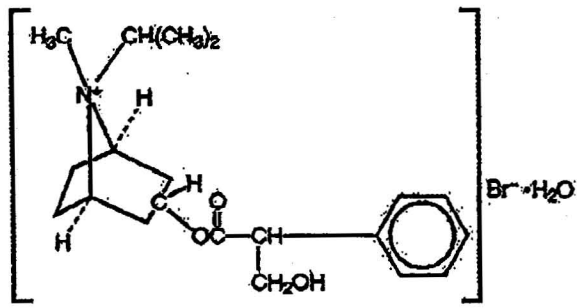
LABELING

ATTENTION PHARMACISTS: 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 (70μL) 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 membranes 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.

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 α_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 (Ae) 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 (Ae) 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 cold (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).

Clinical Trials 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 three times daily versus four times daily treatment.

One clinical trial was conducted with ATROVENT® Nasal Spray 0.06%, administered four times daily for three weeks, in 218 patients with rhinorrhea associated with Seasonal Allergic Rhinitis (SAR), compared to its vehicle in 211 patients. Patients in this trial were adults and adolescents 12 years of age and above. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% was significantly more effective in reducing the severity and duration of rhinorrhea over the three weeks of the study, as measured by daily patient symptom scores. There was no difference between treatment groups in the effect on nasal congestion, sneezing or itching eyes.

INDICATIONS AND USAGE ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis 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 or seasonal allergic rhinitis.

The safety and effectiveness of the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond four days in patients with the common cold or beyond three weeks in patients with seasonal allergic rhinitis 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 medications with anticholinergic properties, including ATROVENT® for oral inhalation.

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^2 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^2 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^2 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^2 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^2 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^2 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. 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 safety of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% at a dose of two sprays (84 mcg) per nostril four times a day (total dose 672 mcg/day) for three weeks in pediatric seasonal allergic rhinitis patients

down to 5 years is based upon the safety demonstrated in the pediatric common cold trials and the trial in adult and adolescent patients 12 to 75 years of age with seasonal allergic rhinitis. The effectiveness of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% for the treatment of rhinorrhea associated with the common cold and seasonal allergic rhinitis 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 the conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of adults. The recommended dose for common cold for the pediatric population is based on cross-study comparisons of the efficacy of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in adult and pediatric patients and on its safety profile in both adults and pediatric common cold patients. The recommended dose for seasonal allergic rhinitis for the pediatric population down to 5 years is based upon the efficacy and safety of ATROVENT® (ipratropium bromide) Nasal Spray in adults and adolescents 12 years of age and above with seasonal allergic rhinitis and the safety profile of this dose in both adult and pediatric common cold 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.

Table 1 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.

Table 1 % of Patients with Common Cold Reporting Events[1]

	ATROVENT® Nasal Spray 0.06%	Vehicle Control
No. of Patients	352	351
Epistaxis[2]	8.2%	2.3%
Nasal Dryness	4.8%	2.8%
Dry Mouth/Throat	1.4%	0.3%
Nasal Congestion	1.1%	0.0%

[1] 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.

[2] 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.

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 that 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. No controlled trial was conducted to address the relative incidence of adverse events for three times daily versus four times daily therapy.

Nasal adverse events seen in the clinical trial with seasonal allergic rhinitis (SAR) patients (see Table 2) were similar to those seen in the common cold trials. Additional events were reported at a higher rate in the SAR trial due in part to the longer duration of the trial and the inclusion of upper respiratory tract infection (URI) as an adverse event. In common cold trials, URI was the disease under study and not an adverse event.

Table 2 % of Patients with SAR Reporting Events[1]

	ATROVENT® Nasal Spray 0.06%	Vehicle Control
No. of Patients	218	211
Epistaxis[2]	6.0%	3.3%
Pharyngitis	5.0%	3.8%
URI	5.0%	3.3%
Nasal Dryness	4.6%	0.9%
Headache	4.1%	0.5%
Dry Mouth/Throat	4.1%	0.0%
Taste Perversion	3.7%	1.4%
Sinusitis	2.8%	2.8%
Pain	1.8%	0.9%
Diarrhea	1.8%	0.5%

[1] 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.

[2] Epistaxis reported by 3.7% of ATROVENT® patients and 2.4% of vehicle patients, blood tinged nasal mucus by 2.3% of ATROVENT® patients and 1.9% of vehicle patients.

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 common cold and SAR trials. Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm, and anaphylactic reaction have been reported with other ipratropium bromide products.

OVERDOSAGE Acute overdosage 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^2 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^2 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^2 basis).

DOSAGE AND ADMINISTRATION

For Symptomatic Relief of Rhinorrhea Associated with the Common Cold

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) in adults and children age 12 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.

For Symptomatic Relief of Rhinorrhea Associated with Seasonal Allergic Rhinitis

The recommended dose of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is two sprays (84 mcg) per nostril four times daily (total dose 672 mcg/day) in adults and children age 5 years and older.

The safety and effectiveness of the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond three weeks in patients with seasonal allergic rhinitis 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 mg 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.

R_x only

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877
Licensed from: Boehringer Ingelheim International GmbH
U.S. Patent No. 4,385,048
12/98
4042182/US/1 030

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 or seasonal allergic rhinitis 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 or seasonal allergic rhinitis. Do not use ATROVENT® (ipratropium bromide) Nasal Spray 0.06% for longer than four days for a common cold or three weeks for seasonal allergic rhinitis unless instructed by your physician.

Read complete instructions carefully and use only as directed.

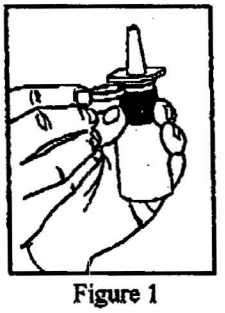


Figure 1

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.

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,

Figure 2

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.

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.

Figure 3

5. 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.

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.

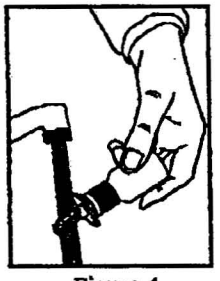


Figure 4

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.

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 for your cold or three weeks for seasonal

allergic rhinitis 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, increased sensitivity to light, and a widening of the pupil, 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.

If you have glaucoma or difficulty urinating due to an enlargement of the prostate, be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

If you are pregnant or you are breast feeding your baby, be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

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

Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

MEDICAL REVIEW(S)

I. Summary

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	**NDA 20-394**	**Application Type:**	**Pediatric supplement**
Sponsor:	**Boehringer Ingelheim**	**Proprietary Name:**	**Atrovent® Nasal Spray 0.06%**
Investigator:	**Multiple**	**USAN Name:**	**Ipratropium bromide**
Category:	**Anticholinergic**	**Route of Administration:**	**Intranasal**
Reviewer:	**Badrul A. Chowdhury, MD**	**Review Date:**	**09/05/00, revised 10/02/00**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 29, 1999	December 30, 1999	NDA supplement	41 volumes
February 11, 2000	February 14, 2000	Pediatric waiver	Waiver rejected
February 18, 2000	FAX document	Financial disclosure	No conflicts present

RELATED APPLICATIONS (If applicable)

Document Date	Application Type and Comments

REVIEW SUMMARY:

The purpose of this NDA supplement is to obtain approval for Atrovent Nasal Spray 0.06% at a dose of 2 sprays (42 mcg/spray) per nostril QID for symptomatic relief of rhinorrhea associated with seasonal allergic rhititis (SAR) in patients 5 years of age and older. The sponsor has submitted results of a single study to support the efficacy and safety claims. Two other studies are also submitted primarily to support a claim that a higher dose of Atrovent would be required for treating rhinorrhea associated with SAR than that approved for PAR. The submitted studies, along with data previously reviewed and prior regulatory knowledge on this product, are adequate to support approval of Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID for symptomatic relief of rhinorrhea associated with SAR.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION:

New clinical studies	_____	**Clinical Hold**	_____	**Study May Proceed**	
NDA, Efficacy/Label supplement:	X	**Approvable**	_____	**Not Approvable**	

SIGNATURES: **Medical Reviewer:** Badrul A. Chowdhury **Date:** 10/10/00

Division Director: [signature] **Date:** 10/10/00

II. Table of Contents

III. List of tables

IV. Executive summary

A. Administrative

The purpose of this NDA supplement is to obtain approval for Atrovent Nasal Spray 0.06% at a dose of 2 sprays (42 mcg/spray) per nostril QID for the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis (SAR) in patients 5 years and older. The application was received by the Agency on December 30, 1999. The goal date for action on this application is October 30, 2000.

B. Background and regulatory history

Boehringer Ingelheim Pharmaceutics, Inc., currently markets two strengths of Atrovent Nasal Spray, 0.03% and 0.06%, in US. The two strengths have different indications. Atrovent Nasal Spray 0.06% is approved for symptomatic relief of rhinorrhea in common cold in patients 5 years and older. The recommended dose is 2 sprays per nostril TID or QID. Atrovent Nasal Spray 0.03% is approved for symptomatic relief of rhinorrhea in allergic and nonallergic perennial rhinitis in patients 6 years and older. The recommended dose is 2 sprays per nostril BID or TID. (b) (4)

(b) (4)

(b) (4)

(b) (4) The sponsor met with the Agency on July 24, 1997, (b) (4)

(b) (4) Atrovent Nasal Spray 0.06%. Based on the meeting, the sponsor has submitted this NDA supplement to gain the SAR indication for Arovent Nasal Spray 0.06%.

C. Clinical program

The sponsor has submitted results of a single study to support the claim that Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID is effective in symptomatic relief of rhinorrhea in patients with SAR. Two other study results are also included as supportive evidence. The salient features of the pivotal study 244.2475 and the supporting studies 244.2435 and 244.2405 are summarized in Table 1. The sponsor claims that for treating SAR, a higher dose of Atrovent (0.06%) than that approved for allergic and nonallergic perennial rhinitis (0.03%) is necessary. The sponsor is using the supporting studies to substantiate that claim. Although the sponsor has not meticulously explored the 0.03% strength and a lower dosing frequency for the 0.06% strength, the submitted data support that a higher dose of Atrovent may be required for treating rhinorrhea in patients with SAR as compared to patients with PAR. The three studies are briefly reviewed in the following sections.

Table 1. List of clinical studies

Study ID	Design	Patients	Treatment	Patient number	Treatment duration
244.2475 U98-3130	R, DB, PC	SAR Ages 12-75	Atrovent NS 0.06%, 2 sp QID Placebo NS	218 211	3 weeks

Study ID	Design	Patients	Treatment	Patient number	Treatment duration
(Pivotal)					
244.2435 U96-3120 (Supporting)	R, DB, PC	SAR Ages 12-75	Atrovent NS 0.03%, 2 sp TID Placebo NS Atr NS 0.03% 2 sp TID + Seldane Placebo NS + Seldane	106 100 103 103	4 weeks
244.2405 U93-0726 (Supporting)	R, DB, PC	PAR Ages 18-75	Atrovent NS 0.06%, 2 sp BID Atrovent NS 0.12%, 2 sp BID Placebo NS	63 66 64	8 weeks
R is randomized, DB is double-blind, PC is placebo-controlled					
Source: volume 1, pages 31, 32, 36-40; converted from text and merged information from various tables					

1. Study 244.2475

This was a two-arm, 1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for three weeks. The study enrolled 12 to 75 year old (overall mean age 34.1 years) patients with SAR in 13 US centers during the fall of 1997. To be eligible, patients were required to have SAR with clinically significant rhinorrhea during the prior year's ragweed season.

The study had a one-to-two-week placebo run-in period followed by three-week double-blind treatment period. The treatment arms were Atorvent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID and placebo nasal spray. Efficacy assessment was primarily based on patient scoring of rhinorrhea severity reflective over a 12-hour time period on a 6-point scale, and rhinorrhea duration by estimation the number of hours, to the nearest hour, that occurred over a 12-hour time period. Safety assessment included adverse event recording, vital signs, physical examination, detailed nasal examination, laboratory assessment, and nasal rebound following discontinuation of therapy.

A total of 429 patients were randomized, approximately equally to the two treatment arms. Approximately 90% of patients completed the study. Results of efficacy variable analyses using data from one week of active treatment that had the highest ragweed pollen count (primary efficacy variable), and also the three weeks of treatment (this Division's preferred way of analysis) support the efficacy of Atrovent Nasal Spray 0.06%. Effect size, defined as the difference between the active treatment and placebo groups, was 8% for rhinorrhea severity and 10% for rhinorrhea duration. Atrovent Nasal Spray 0.06% was well tolerated in this study. Adverse events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Efficacy and safety analyses of subgroups based on age, and gender did not reveal any clinically meaningful differences. This study supports the efficacy and safety of Atrovent Spray 0.06% at a dose of 2 spray per nostril QID for symptomatic relief of rhinorrhea in patients 12 years and above with SAR. This study did not include any patients between the ages of 5 and 11 years and therefore does not support claims for patients down to the age of 5 years.

2. Study 244.2435

This was a four-arm, 1:1:1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of Atrovent Nasal Spray 0.03% alone and with Seldane for four weeks. The study enrolled 12 to 75 year old (overall mean age 31.7 years) patients with SAR in 10 US centers.

The study had a one-week screening period followed by a two two-week double-blind treatment period. The treatment arms for the two treatment periods were same, except that the escape medications were different. The treatment arms were Atrovent Nasal Spray 0.03% at a dose of 2 sprays per nostril TID, placebo nasal spray, Atrovent Nasal Spray 0.03% at a dose of 2 sprays per nostril TID plus Seldane, placebo nasal spray plus Seldane. Efficacy assessment was primarily based on patient scoring of rhinorrhea severity and rhinorrhea duration as in the previous study. Primary comparison was between the Atrovent and the placebo arms. Safety assessment included adverse event recording, vital signs, physical examination, detailed nasal examination, ECG, and laboratory assessment.

A total of 416 patients were randomized, approximately equally to the four treatment arms. Over 90% of patients completed the study. Results of efficacy variable analyses showed that Atrovent Nasal Spray 0.03% alone did not reduce rhinorrhea severity and duration any more than placebo nasal spray. Patients receiving both Atovent and Seldane tended to have less rhinorrhea than patients receiving placebo nasal spray plus Seldane. The differences were numerically small and statistically not significant. In patients who were on Seldane, which has some beneficial effect on SAR symptoms, addition of Atrovent numerically further reduced rhinorrhea severity and rhinorrhea duration. The effect sizes for reduction in rhinorrhea severity and rhinorrhea duration by Atrovent for this subgroup of patients who were on Seldane were comparable to those of the previous study 244.2475. Atrovent Nasal Spray 0.03% was well tolerated in the study. Adverse events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Combined use of Atrovent and Seldane did not alter the safety profile. This study suggests that SAR patients treated with Atrovent Nasal Spray may required a higher dose and/or frequency of drug administration than that used in this study.

3. Study 244.2405

This was a three-arm, 1:1:1 randomized, multicenter, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of Atrovent Nasal Spray 0.06% and 0.12% at doses of 2 spray per nostril BID for eight weeks. The study had one-year safety extension, which is not included in this submission. The study enrolled 18 to 75 year old (overall mean age 38.6 years) patients with perennial allergic rhinitis (PAR) in 13 US centers.

The study had a one-week screening period, one-week baseline period, and eight-week double-blind treatment period. The treatment arms were Atrovent Nasal Spray 0.12% and 0.06% doses of 2 sprays per nostril BID, and placebo nasal spray. Efficacy assessment was primarily based on patient scoring of rhinorrhea severity and rhinorrhea duration as in the previous studies. Safety assessment included adverse event recording, vital signs, physical examination, detailed nasal examination, and laboratory assessment.

A total of 400 patients were randomized, approximately equally to the three treatment arms. Results of efficacy variable analyses showed that both doses of Atrovent Nasal Spray were numerically superior to placebo. Atrovent Nasal Spray 0.12% was statistically superior to placebo for both rhinorrhea severity and rhinorrhea duration. Atrovent Atrovent Nasal Spray 0.06% was statistically superior to placebo for rhinorrhea severity and not for rhinorrhea duration. Atrovent was well tolerated in this study, although nasal irritation, nasal dryness, nasal bleeding, and epistaxis were seen more frequently in Atrovent groups and there was dose ordering for these events.

The sponsor performed further analyses comparing patients who had pure PAR to those who had mixed SAR-PAR. Approximately half of the patients enrolled in this study had pure PAR and half had mixed SAR-PAR. This analyses has limited utility, because of the post-hoc nature, however, the sponsor states that patients who had mixed SAR-PAR had a larger response to the Atrovent Nasal Spray 0.12% compared to Atrovent Nasal Spray 0.06%. This indirectly supports that SAR patients may benefit from a higher dose of Atrovent Nasal Spray.

D. Efficacy assessment

This application supports the efficacy of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for symptomatic relief of rhinorrhea in patients with SAR. Results of study 244.2475 show that patients on Atrovent Nasal Spray 0.06% had statistically significant reductions of rhinorrhea severity ($p=0.0024$) and rhinorrhea duration ($p=0.0083$) over the three weeks of treatment. Percent changes during the three weeks for of treatment for rhinorrhea severity were –18% for the Atrovent group and –10% for the placebo group. Percent changes during the three weeks for of treatment for rhinorrhea duration were –13% for the Atrovent group and –3% for the placebo group.

The sponsor was not asked to replicate the finding in another study because Atrovent Nasal Spray is already approved for symptomatic control of rhinorrhea in PAR, non-allergic perennial rhinitis, and in common cold. The pathophysiology of rhinorrhea is similar in these different types of rhinitis, and the response to treatment by Atrovent Nasal Spray is expected to be similar. Therefore, this single study is adequate to support an efficacy claim.

The dose chosen by the sponsor appears to be empiric. However, the two supporting studies, 244.2435 and 244.2405, lends support to the sponsor's conclusion that for treating rhinorrhea in SAR a larger dose or increased frequency of Atrovent would be necessary than that required for treating rhinorrhea in PAR. Study 244.2435 failed to show superiority of Atrovent Nasal Spray 0.03% at a dose of 2 sprays each nostril TID over placebo in controlling rhinorrhea in SAR patients. However, Atrovent was numerically superior to placebo when the patients were concurrently treated with Seldane. Although the differences did not reach statistical significance, the effect sizes for reduction in rhinorrhea severity and rhinorrhea duration by Atrovent for this subgroup of patients who were on Seldane were comparable to that of study 244.2475. It is possible that patients who were symptomatic with SAR, Atrovent 0.03% alone was not adequate to have an effect detectable by the patients. With Seldane, the symptoms of SAR were reduced, which allowed the effect of Atrovent to be noticeable. Patients with SAR in general are likely to be more symptomatic than patient with PAR and therefore

may require a larger dose of Atrovent. Subgroup analyses of study 244.2405 supports this hypothesis. Approximately half of the patients in study 244.2405 had pure PAR and the other half had mixed SAR-PAR. The sponsor compared the response of these subgroups of patients to the two strengths of Atrovent used in this study. This analyses has limited utility, because of the post-hoc nature, however, patients with mixed SAR-PAR was noted to have a larger response to the Atrovent Nasal Spray 0.12% compared to Atrovent Nasal Spray 0.06%. These two supporting studies support the conclusion that SAR patients may benefit from a larger dose of Atrovent Nasal Spray.

E. Safety assessment

This application supports safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID for symptomatic control of rhinorrhea in SAR in patients ages 12 years and above. In study 244.2475 a total of 218 patients were treated with Atrovent Nasal Spray 0.06% at a dose of 2 spray each nostril QID (total daily dose 334 mcg) for three weeks. In study 244.2405 a total of 129 patients were treated with Atrovent Nasal Spray 0.12% at a dose of 2 sprays each nostril BID (total daily dose 334 mcg) for four weeks. These two studies provide adequate safe data for patients 12 years and above. Atrovent was well tolerated in the studies. Most of the adverse events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Some of the common adverse events that occurred more frequently in Atrovent treated patients compared to placebo were nasal irritation, nasal dryness, nasal bleeding and epistaxis. The updated label will contain these information.

The sponsor has submitted no safety data in patients between the ages of 5 and 11 years in this submission. The pediatric efficacy supplement of Atrovent Nasal Spray 0.06% for common cold had safety data from 364 patients between the ages of 5 and 12 years exposed for 4 days to Atrovent 0.06% at a dose of 2 sprays per nostril TID (MO review dated June 23, 1998). Although patients with SAR is likely to be treated for longer periods of time compared to common cold, and the proposed dosing frequency is higher than the common cold indication, the adverse events are likely to similar to those seen in older children in the studies submitted in this sNDA, and to those seen in younger children in studies submitted in the pediatric efficacy supplement for Atrovent 0.06%. The adverse events seen in these studies occurred mostly in the nose, and the frequently reported events were nasal irritation, nasal dryness, nasal bleeding and epistaxis. The current product label of Atrovent Nasal Spray 0.06% already includes these adverse events. Therefore, no further studies would be necessary to further assess safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID in patients between the ages of 5 and 11 years.

F. Recommended regulatory action

The sNDA is recommended an approvable action from a clinical standpoint. The sponsor has submitted adequate data to support efficacy and safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for symptomatic relief of rhinorrhea associated with SAR in patients 5 years and above.

V. Administrative issues and conduct of the review

This NDA supplement was received by the Agency on December 30, 1999. The submission consists of 41 volumes. User fee goal date for action on this application is October 30, 2000. This NDA supplement includes three clinical studies, of which the sponsor has identified one as pivotal. All three studies are reviewed in depth in this document. Throughout the review, reference to the NDA submission (as v for volume, and p for page number) is made to indicate the source of information.

VI. Chemistry/manufacturing and controls

Atrovent (ipratropium bromide) Nasal Spray 0.06% is a metered-dose, manual pump spray unit that delivers 42 mcg ipratropium bromide (on an anhydrous basis) per spray (70 microL) in an isotonic, aqueous solution with pH-adjusted to 4.7. Ipratropium bromide (the active ingredient) is a synthetic quaternary ammonium compound, chemically related to atropine. The drug product also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. The product is currently marketed in US. There is no new CMC information in this submission.

VII. Preclinical pharmacology and toxicology, clinical pharmacology, biopharmaceutics

Boehringer Ingelheim Pharmaceutics, Inc., currently markets Atrovent (ipratropium bromide) Nasal Spray 0.06% and Atrovent (ipratropium bromide) Nasal Spray 0.03% in US. No new preclinical pharmacology, toxicology, clinical pharmacology, and biopharmaceutics data were submitted with this application.

VIII. Background

A. Clinical Rationale

Treatment options for allergic rhinitis include corticosteroids, H_1 anithistamines, decongestants, cromolyn, ipratropium, allergen avoidance, and allergy immunotherapy[1]. Treatment options for allergic rhinitis may be non-specific such as intranasal corticosteroids, or symptoms specific such as decongestant for nasal congestion, or intranasal anticholinergic agent for rhinorrhea. Nasal submucosal glands have abundant parasympathetic innervation, therefore, the rhinorrhea associated with rhinitis is amenable to treatment with topical anticholinergic drugs. With that premise, the sponsor has developed Atrovent nasal spray for symptomatic treatment of rhinorrhea in rhinitis.

The sponsor has two strengths of Atrovent nasal spray approved and marketed in US. Atrovent Nasal Spray 0.03% is approved for symptomatic relief of rhinorrhea in allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. The recommended dose is 2 sprays per nostril two or three times a day (total daily dose

[1] Spector S. Ideal pharmacotherapy for allergic rhinitis. J Allergy Clin Immunol 1999; 103:S386.

168 to 252 mcg/day). Atrovent Nasal Spray 0.06% is currently approved for symptomatic relief of rhinorrhea in common cold for adults and children age 5 year and older. The recommended dose is 2 sprays per nostril three or four times a day (total daily dose 504 to 672 mcg/day).

The sponsor now wishes to seek approval of Atrovent Nasal Spray 0.06% for symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis in adults and children age 5 years and older. The mechanism of rhinorrhea is presumably the same irrespective of the underlying disease entity causing the rhinorrhea. Therefore, it is not unreasonable to expect that the higher strength approved for the common cold (0.06% TID or QID) would work for seasonal allergic rhinitis, particularly when a lower strength has already shown to be effective for perennial allergic rhinitis (0.03% BID or TID). The question would remain though, whether a larger dose is necessary or not.

B. Regulatory history

A meeting was held between representatives of Boehringer Ingelheim Pharmaceutics, Inc., and the Divisions of Pulmonary Drug Products and (b) (4) of the Food and Drug administration on July 24, 1997, to discuss the sponsor's (b) (4) The sponsor has included the minutes of the meting in the submission for reference (v 1, p 12-17). In the meeting is was agreed that "a single trial [for SAR] should be acceptable provided that it supports the proposed label claims, e.g., (b) (4) (b) (4) QID doses are safe and effective." At the time of the meeting the sponsor was planning on conducting two SAR studies. Based on that meeting, the second study was not conducted (v 1, p 10). This sNDA submission therefore contains results from one pivotal study. However, in the submitted study (b) (4) QID doses were not addressed. The study only compared the QID dosing to placebo.

The lowest age of patients included in the submitted study was 12 year. However, the sponsor is seeking approval down to 5 years, which is the current lowest age of approval for Atrovent Nasal Spray 0.06% for the common cold indication. The sponsor refers to the July 24, 1997, meeting and states that "it was also agreed at the meeting that no further seasonal allergic rhinitis study would be required in children below the age of 12 years" (v 1, p 10). The minutes of the meeting do not support that conclusion.

IX. Clinical studies

The purpose of this sNDA is to obtain approval for the use of Atrovent Nasal Spray 0.06% at a dose of 2 sprays (42 mcg/spray) per nostril four times a day for the symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis (SAR) in patients 5 years and older. Atrovent Nasal Spray 0.06% is currently approved for symptomatic relief of rhinorrhea associated with the common cold for adults and children age 5 year and older.

Three clinical studies are submitted in this sNDA of which the sponsor has identified one as pivotal and two as supporting. The salient features of the studies are listed in Table 1. Study 244.2475 is the pivotal study for this application. Review of data shows that patients on Atrovent Nasal Spray 0.06% had statistically significant reductions of rhinorrhea severity (p=0.0024) and rhinorrhea duration (p=0.0083) over the 3 weeks of treatment; however, the effect sizes were relatively small. Percent changes for rhinorrhea severity during the three weeks of treatment were –18% for the Atrovent group and –10% for the placebo group (volume 1, page 47). This study will be reviewed in depth. The two supporting studies will also be reviewed in depth, but more from a safety perspective. The sponsor is using the results of the two supporting studies to justify why a higher dose is necessary for SAR. In study 244.2435, there was no difference between Atrovent Nasal Spray 0.03% and placebo. In study 244.2405, both the doses of Atrovent were numerically better than placebo, however, statistical separation was not achieved for all the parameters.

Table 2. List of clinical studies

Study ID	Design	Patients	Treatment	Patient number	Treatment duration
244.2475 U98-3130 (Pivotal)	R, DB, PC	SAR Ages 12-75	Atrovent NS 0.06%, 2 sp QID Placebo NS	218 211	3 weeks
244.2435 U96-3120 (Supporting)	R, DB, PC	SAR Ages 12-75	Atrovent NS 0.03%, 2 sp TID Placebo NS Atr NS 0.03% 2 sp TID + Seldane Placebo NS + Seldane	106 100 103 103	4 weeks
244.2405 U93-0726 (Supporting)	R, DB, PC	PAR Ages 18-75	Atrovent NS 0.06%, 2 sp BID Atrovent NS 0.12%, 2 sp BID Placebo NS	63 66 64	8 weeks
R is randomized, DB is double-blind, PC is placebo-controlled					
Source: volume 1, pages 31, 32, 36-40; converted from text and merged information from various tables					

The sponsor originally submitted one volume for each study, which included the study report, study protocol, and list of investigators. The submission did not include statistical methods, subject data listings, and case summaries of serious adverse events, deaths, and drop-outs due to adverse events were. The sponsor provided an index that listed these items and referred to the study reports submitted earlier with the IND for

details on these items. On our request, the sponsor subsequently submitted these volumes to the sNDA application.

A. 244.2475: Randomized, double-blind, parallel, placebo-controlled, multi-center trial of Atrovent Nasal Spray 0.06% (84 mcg/nostril administered QID) in patients with seasonal allergic rhinitis that are sensitive to ragweed pollen

1. Investigators and centers

The study was conducted in 13 centers in US. Dr. William Busse, MD, from University of Wisconsin Medical School was the principal investigator (v 5, p 23, 27). No disqualified investigator participated in the study.

2. Objective

The objective of this study was to assess the efficacy and safety of Atrovent Nasal Spray 0.06% versus placebo nasal spray administered two spray per nostril QID for three weeks in controlling rhinorrhea in patients with seasonal allergic rhinitis (SAR) with sensitivity to ragweed pollen (v 5, p 23, 202).

3. Study population

Patients meeting the following criteria were selected for participation.

Inclusion criteria (v 5 p 211):

1) Age between 12-75 years, either sex, and any race. Female subjects were required to be not pregnant and not nursing. Patients and parent/guardian were required to give informed consent and express willingness to adhere to dose and visit schedle.
2) Clinically significant rhinorrhea defined by all of the following:
   a) History of rhinorrhea during the two year pollen seasons for more than one hour daily, at least 4 days per week.
   b) Moderately severe rhinorrhea (score of ≥ 3 as defined in the severity scale for rhinorrhea at screening visit) during the prior year's ragweed season.
   c) Average rhinorrhea severity ≥ 2 (mild) and average rhinorrhea duration ≥ 2 hours recorded during the screening period as recorded by patients during the screening week (minimum of 5 days of data must be available to make this evaluation).
3) Moderate to severe symptoms (defined as uncomfortable or annoying symptoms persisting despite use of antihistamine, or, control of symptoms requiring daily use of an antihistamine, a nasal steroid, or nasal cromolyn) in the last two consecutive years and positive skin test with causal association to ragweed allergen that is expected to

be present during the time patient is in trial, as documented by pollen count from the past two years from the geographical area where the investigator's site is located.

Exclusion criteria (v 5, p 213):

1) Fixed anatomical nasal obstruction, polyps, complete nasal obstruction, clinically significant history of sinusitis, active infectious rhinitis, upper or lower respiratory tract infection, or rhinitis medicamentosa.
2) Glaucoma, symptomatic prostatic hypertrophy, significant renal disease, significant hepatic disease, or hypersensitivity to atropinic, Atrovent, or benzalkonium chloride.

4. Medication restrictions

Medication washout periods prior to screening (v 5, p 214):

1) Three days before:
   a) Anticholinergics (intranasal, oral, intravenous, or opthalmic). Use of inhaled ipratropium for pulmonary indications was permitted.
   b) Antihistamines (oral and/or nasal, including OTC), with the exception of Atarax, Doxepin, or Hismanal
   c) Sympathomimetic decongestants, including OTC medications
   d) Nasal and/or ocular cromolyn
2) One week before:
   a) Antihistamines such as Atarax, or Doxepin
   b) Antidepressants and tranquilizer with anticholinergic effects. Patients on Prozac or Zoloft were admitted with the approval of the medical monitor.
3) Two weeks before:
   a) Intranasal, ocular, and inhaled steroids. Topical steroids for dermatitis were allowed.
4) Four weeks before:
   a) Steroids (oral and injectable)
   b) Accolate or Zileuton
   c) Other investigational drugs
5) Twelve weeks before:
   a) Hismanal

5. Study design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study that included one week single-blind placebo run-in period, three weeks double-blind treatment period, and one week single-blind placebo washout period (v 5, p 222).

6. Study procedures

The study was conducted between July 1997 and October 1997. The study procedures are outlined in Table 3. Pollen counts were done daily for a minimum of five days a week during the entire period of patient participation (v 5, p 216, 220).

At the screening visit patient's history and clinical condition were checked against the inclusion exclusion criteria to determine eligibility. Eligible patients entered one

week single-blind placebo run in period during which they received placebo nasal spray at a dose of two sprays per nostril QID. At the end of one week of screening if the patients did not meet the rhinorrhea symptom severity (≥mild) and duration of rhinorrhea (≥2 hours) criteria they continued for an additional week of screening. A third week of screening was allowed only upon approval of the medical monitor. Following the run-in period, patients who qualified were randomized at 1:1 ratio to received Atrovent Nasal Spray 0.06% or placebo nasal spray. The nasal spray was administered at a dose of two sprays per nostril QID at 8 AM, 12 PM, 4 PM, and 8 PM. The Atrovent dose was 84 mcg/nostril QID. At the end of double-blind treatment period, patients were continued for a further one week of single-blind treatment with placebo nasal spray at a dose of two spays per nostril QID (v 5, p 216, 219, 220, 222).

Each patient treatment unit was identical in appearance to ensure blinding. Compliance to treatment was assessed by weighing the container. First dose of the study medication was administered in the clinic. Throughout the study, only Clear Eyes was allowed as rescue treatment for ocular itching. No other medication or additional treatment for rhinitis symptoms was permitted. Patients who required additional treatment for unbearable symptoms were discontinued (v 5, p 217, 218, 222).

Efficacy assessment included patient recording of symptoms in diary cards, patient and physician global assessment of effectiveness of therapy, and quality of life assessment (Table 3). Patients recorded severity of five nasal symptoms (severity of rhinorrhea, duration of rhinorrhea, severity of nasal congestion, severity of ocular itching, and severity of sneezing) daily on a 6-point scale (Table 4). Recording was to reflect the period from 8 AM to 8 PM. Patients also recorded duration of rhinorrhea by estimating the number of hours, to the nearest hour, that occurred between 8 AM and 8 PM. Patient and physician global assessment were based on a 4 point scale (1= no effect, 2= doubtful effect, 3= good effect, 4= excellent effect) of overall effectiveness of the treatment in controlling rhinitis symptoms during the previous week. Quality of life was assessed using the Juniper RQLQ Quality of Life questionnaire (v 5, p 219, 220, 223).

Safety assessment included adverse event recording, vital signs, physical examination, detailed nasal examination, laboratory assessment, and nasal rebound following discontinuation of therapy (v 5, p 43, 220).

The protocol specified study procedures as described above were followed in conduct of the study (v 5, p 39-47).

Table 3. Schedule of observations

	Screen Pbo run-in	**Active Treatment**				**Washout**
	Visit 1	Visit 2	Visits 3	Visit 4	Visit 5	Visit 6
	Day –7 to 0	Day 7	Day 14	Day 21	Day 28	Day 29
Consent, enroll, history, and skin test	x					
Physical exam, vitals, lab tests	x				x	
Nasal exam	x	x	x	x	x	x
Dispense study medication	x	x	x		x	
Return and weigh study medication		x	x		x	x
Dispense diary card	x	x	x	x	x	
Return diary card		x	x	x	x	x

	Screen Pbo run-in	Active Treatment				Washout
	Visit 1	Visit 2	Visits 3	Visit 4	Visit 5	Visit 6
	Day –7 to 0	Day 7	Day 14	Day 21	Day 28	Day 29
Patient's symptom assessment		x	x	x	x	x
Physician's symptom assessment			x	x	x	
QOL questionnaire		x			x	
Concomitant therapy	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x
* Complete urinalysis, complete blood count, and clinical chemistry (creatinine, BUN, glucose, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, serum IgE) (v 5 p 43).						
Source: v 5, p 203						

Table 4. Scale used for assessing rhinitis symptom severity

	Score	Description	Definition
Symptom* severity scale:	0	None	None
	1	Very Mild	Doubtful, trivial, or just noticeable
	2	Mild	Present but not uncomfortable
	3	Moderate	Present and somewhat uncomfortable/annoying but does not interfere with daily activities
	4	Severe	Present and definitely uncomfortable/annoying but does interfere with daily activities
	5	Unbearable	Totally restricts activities and/or requires withdrawal from trial due to symptoms
* Nasal symptom: severity of rhinorrhea, duration of rhinorrhea, severity of nasal congestion, severity of ocular itching, and severity of sneezing (v 5, p 219).			
Source: v 5, p 219			

7. Efficacy variables

The primary efficacy variable was daily patient recorded assessment of the severity and duration of rhinorrhea. The primary efficacy comparison was made using the data from a single week of active treatment period during which there was the highest ragweed pollen count. Seven contiguous days out of the three weeks of active treatment was chosen as the week for comparison, presumably done in a blinded fashion. Secondary efficacy variables included daily patient assessment of nasal congestion, ocular itching, sneezing, patient and physician global assessments of control rhinorrhea, and the quality of life assessment (v 5, p 219, 220, 225).

8. Safety evaluations

Safety evaluations included adverse event reporting, vital signs, physical examination, detailed nasal examination, laboratory assessment, and assessment of nasal rebound following discontinuation of therapy (v 5, p 220).

9. Statistical considerations

Sample size:

The study was designed to have a power of 90% to detect a 15% difference between treatment groups in the average severity of rhinorrhea. This required 150 patients per treatment group, using a two-sided 0.05 significance level with a standard deviation of 48% of the mean rhinorrhea severity. The estimate accounted for a 10% dropout rate for patients. The standard deviation was estimated from a previous study of the sponsor (U93-0726) that had 99 patients classified as having a "seasonal component" to their allergic rhinitis (v 5, p 48, 227).

Statistical analysis:

The primary efficacy variable was analyzed by analysis of variance that extracted sources of variation due to treatment, center, and treatment by center interactions. Score from the placebo run-in week was used as cavoriate in the analysis model. No estimation of missing data was made with the reasoning that variability of pollen count would make estimation of missing data difficult (v 5, p 48, 225).

Data sets analyzed:

Prior to unblinding the database, sponsor had a "blinded report planning meeting" to determine the data set to be used efficacy analysis. This was specified in the protocol. It was decided that patients who had at lest three complete days of evaluable diary data, no concurrent illness that prohibited the evaluation of the treatment effect, and no major protocol violations would be included for primary efficacy analysis. The data sets for secondary efficacy analysis would include all patients contained in the primary efficacy analysis for which data were available for the endpoint of interest (v 5, p 57, 227).

10. Results

a) Patients enrolled and analyzed

A total of 677 patients were screened and 429 patients were randomized. The number of patient randomized in each of the 15 centers varied from 19 to 37. Thirty-seven patients (9%) discontinued the study prior to scheduled completion. Disposition of the patients is shown in Table 5 (v 5, p 50-52).

Of the 429 randomized patients, 424 were included in the primary efficacy analysis. Five patients, two from placebo arm and three from Atrovent arm, were excluded because they did not have at least three days of diary data (v 5, p 57). Number of patients included in each of the analysis datasets is shown in Table 6.

Table 5. Disposition of study patients

	Atrovent	Placebo	Total
Number randomized	218	211	429
Number completed	196	196	392
Reasons for discontinuation:			
Adverse event	10	7	17
Administrative*	3	5	8
Protocol violation	1	0	1
Lack of efficacy	8	3	11

	Atrovent	Placebo	Total
* Include lost to follow-up, withdrawal of consent, etc.			
Source: v 5, p 51			

Table 6. Number of patients in the efficacy analysis datasets

		Atrovent	Placebo	Total
Diary assessment of rhinorrhea	- High pollen week	215	209	424
	- 3 week average	215	209	424
	- Washout week	196	195	391
Patient global assessment		213	208	421
Physician global assessment		214	207	420
Quality of life assessment		214	205	419
Source: v 5, p 58				

b) Patient demographics and baseline disease characteristics

Demographics and disease characteristics of patients are shown in Table 7. The groups were comparable. The whole age spectrum was adequately represented.

Table 7. Demographic summary and baseline disease characteristics

	Atrovent	Placebo	Total
Number randomized	218	211	429
Sex: male/female	83/135	79/132	162/267
Age (yr): mean ± SD	34.5 ± 11.5	33.6 ± 12.5	34.1 ± 12.0
Age: patient 12-18 yr old	23	31	54
Age: patient 19-39 yr old	118	121	239
Age: patient 40-75 yr old	77	59	136
Race: cauc./others	204/14	187/24	391/38
Disease duration: yrs, mean ± SD	19.4 ± 11.7	20.2 ± 12.5	19.8 ± 12.1
Rhinorrhea severity	2.94 ± 0.67	2.96 ± 0.68	
Rhinorrhea duration	5.19 ± 2.59	5.20 ± 2.57	
Source: v 5, p 53, 54			

c) Protocol deviations

There were no significant protocol deviations in the study. Nine patients took prohibited medications and should have been excluded at entry based on entry criteria. These patients were included in the efficacy and safety analyses (v 5, p 52).

d) Efficacy endpoint outcomes

Analyses of the efficacy variables are shown in Table 8 through Table 12. The study was overpowered, with over 200 patients completing each treatment arm, as opposed to 150 that was required based on power calculation. Given this limitation, results of the high pollen week (protocol specified primary endpoint) and the entire three weeks of double-blind treatment support the efficacy of Atrovent (84 mcg/nostril QID) in

reducing rhinorrhea severity and duration (Table 8). Effect sizes separating the two groups for rhinorrhea severity and duration were reasonable (Table 9). Atrovent nasal spray was also significantly better than placebo in global patient and physician assessments of rhinorrhea control (Table 10). Atrovent nasal spray had no effect on nasal congestion, sneezing, and ocular itching (Table 8). Given the putative mechanism of these symptoms and the mechanism of action of Atrovent, lack of effect on these variables is expected. Atrovent nasal spray and placebo both had positive effects on quality of life assessment by patients; none of the differences were statistically significant (Table 11). Analysis of rhinitis symptoms during the washout week demonstrated no evidence of rebound effect following cessation of treatment with Atrovent nasal spray (Table 12). The severity of symptoms generally remained same or declined slightly after treatment was stopped, as would be expected in a SAR study where the peak pollen period had ended (v 5, p 58-73). The sponsor also performed subgroup analyses to evaluate effect of age (below and above 19 years), gender, baseline rhinorrhea severity, pure and mixed ragweed allergy (data not present in this review) (v 5, p 77). None of these analyses revealed any clinically meaningful differences.

Table 8. Daily patient diary assessments of rhinitis symptoms*

Parameters	High pollen week			Three weeks of treatment		
	Atrovent	Placebo	P-value	Atrovent	Placebo	P-value
Rhinorrhea severity (Baseline = 2.95)	2.54 ±0.06 (215)	2.77 ±0.06 (209)	0.0051	2.42 ±0.05 (215)	2.65 ±0.05 (209)	0.0024
Rhinorrhea duration, hr (Baseline = 5.19)	4.74 ±0.16 (215)	5.27 ±0.16 (209)	0.0209	4.51 ±0.14 (215)	5.05 ±0.15 (209)	0.0083
Congestion severity (Baselin = 2.53)	2.66 ±0.06 (215)	2.55 ±0.06 (209)	0.1996	2.59 ±0.05 (215)	2.48 ±0.05 (209)	0.1556
Sneezing severity (Baseline = 2.44)	2.46 ±0.06 (214)	2.42 ±0.06 (209)	0.6510	2.31 ±0.05 (215)	2.30 ±0.05 (209)	0.8978
Ocular itching severity (Baseline = 1.96)	1.96 ±0.06 (215)	2.00 ±0.06 (209)	0.6103	1.82 ±0.05 (215)	1.85 ±0.05 (209)	0.5943
* Results expressed as Mean ± SEM (n)						
Source: v 5, p 59, 63						

Table 9. Percent change from baseline of rhinitis symptoms

Parameters	High pollen week		Three weeks of treatment	
	Atrovent	Placebo	Atrovent	Placebo
Rhinorrhea severity	-14 %	- 6%	- 18%	- 10%
Rhinorrhea duration	-9 %	+ 2%	- 13%	- 3%
Congestion severity	+5 %	+ 1%	+ 2%	- 2%
Sneezing severity	+1 %	- 1%	- 5%	- 6%
Ocular itching severity	0 %	+ 2%	- 7%	- 6%
Source: v 5, p 60, 64				

Table 10. Global assessments of the control of rhinorrhea during the three weeks of treatment*

	Atrovent	Placebo	P-value
Patient assessment (Base 1.98)	2.54 ± 0.05 (198)	2.32 ± 0.06 (198)	0.0009

	Atrovent	Placebo	P-value
Physician assessment	2.34 ± 0.05 (198)	2.12 ± 0.05 (197)	0.0067
* Results expressed as Mean ± SEM (n)			
Source: v 5, p 67			

Table 11. Quality of life assessments during the three weeks of treatment

	Atrovent	Placebo	P-value
QOL assessment*			
Practical problems (Base 3.32)	0.71 ± 0.09 (214)	0.65 ± 0.10 (205)	0.6746
Non-SAR symptoms (Base 2.21)	0.17 ± 0.08 (214)	0.33 ± 0.08 (205)	0.1384
Nasal symptoms (Base 3.48)	0.62 ± 0.08 (214)	0.68 ± 0.09 (205)	0.5787
Eye symptoms (Base 2.20)	0.39 ± 0.08 (214)	0.40 ± 0.08 (204)	0.9050
Activities (Base 3.16)	0.66 ± 0.08 (214)	0.69 ± 0.09 (203)	0.7821
Emotions (Base 2.36)	0.33 ± 0.08 (214)	0.34 ± 0.09 (204)	0.9161
Sleep, adults only (Base 1.95)	0.01 ± 0.09 (194)	0.18 ± 0.09 (178)	0.1917
Overall QOL (Base 2.62)	0.38 ± 0.07 (214)	0.46 ± 0.07 (205)	0.4362
RQLQ question†			
Troubled by runny nose	44, 20.6 % (214)	31, 15.2 % (204)	0.3347
Troubled by need to rub eye/nose	36, 16.9 % (213)	26, 12.7 % (205)	0.6481
Troubled by need to blow nose	20, 9.3 % (214)	29, 14.1 % (205)	0.1827
* Results expressed as Mean ± SEM (n) † Results expressed as change from baseline to final visit as number, and percentage of patients (n)			
Source: v 5, p 68, 69			

Table 12. Daily patient diary assessments of rhinitis symptoms during the washout week*

	Atrovent	Placebo	P-value
Rhinorrhea severity (Base 2.95)	2.32 ± 0.07 (196)	2.24 ± 0.07 (195)	0.4096
Rhinorrhea duration (Base 5.19)	4.37 ± 0.18 (196)	4.42 ± 0.18 (195)	0.8357
Congestion severity (Base 2.53)	2.17 ± 0.07 (196)	2.26 ± 0.07 (195)	0.3832
Sneezing severity (Base 2.44)	1.95 ± 0.07 (196)	1.93 ± 0.07 (195)	0.8421
Ocular itch severity (Base 1.96)	1.45 ± 0.07 (196)	1.42 ± 0.07 (195)	0.8035
* Results expressed as Mean ± SEM (n)			
Source: v 5, p 72			

11. Safety outcomes

a) Total drug exposure

The extent of exposure by treatment groups is shown in Table 13. Treatment duration was similar among the groups. The majority of patients received the planned 3 weeks of active treatment (v 5, p 78).

Table 13. Extent of exposure during active treatment period

	Atrovent	Placebo	Total
Total treated	218	211	429
0-6 days	8	3	11

	Atrovent	Placebo	Total
7-13 days	8	5	13
14-20 days	21	22	43
21-26 days	181	181	362
Mean exposure in days	20.6	21.0	20.8
Source: v 5, p 78			

b) Adverse events

Atrovent nasal spray 84 mcg/nostril QID was well tolerated in this study. Adverse events reported by at least 1% of patients in Atrovent group and more commonly in the Atrovent group compared to the placebo group during the active treatment period are shown in Table 14. Most of these events were potentially due to anticholinergic effects of Atrovent, occurred locally in the nose, and were mild to moderate in intensity. The sponsor also looked at adverse events classified by age, and gender. These analyses did not reveal any clinically meaningful differences (v 5, p 78-85).

Table 14. Common* adverse events reported by patients during active treatment period

	Atrovent	Placebo
Total treated	218	211
Total with adverse events	84 (38.5 %)	62 (29.4 %)
Body as a whole		
Headache	9 (4.1 %)	1 (0.5 %)
Pain	4 (1.8 %)	2 (0.9 %)
Gastrointestinal system		
Appetite increased	3 (1.4 %)	0 (0.0 %)
Diarrhea	4 (1.8 %)	1 (0.5 %)
Dry mouth	4 (1.8 %)	0 (0.0 %)
Dry throat	5 (2.3 %)	0 (0.0 %)
Respiratory mechanism disorder		
Bronchitis	2 (0.9 %)	0 (0.0 %)
Epistaxis	8 (3.7 %)	5 (2.4 %)
Blood tinged nasal mucosa	5 (2.3 %)	4 (1.9 %)
Nose dryness	10 (4.6 %)	2 (0.9 %)
Pharyngitis	11 (5.0 %)	8 (3.8 %)
Upper respiratory tract infections	11 (5.0 %)	7 (3.3 %)
Special senses		
Taste perversion	8 (3.7 %)	3 (1.4 %)
Vision disorders		
Conjunctivitis	3 (1.4 %)	2 (0.9 %)
* Events reported by ≥1 % of patients in the Atrovent group and more commonly in the Atrovent group compared to the placebo group. Events listed as number and % by WHO System Organ Class.		
Source: v 5, p 80, 136-142, created from two tables		

c) Discontinuation or treatment interruption due to adverse events

Seventeen patients (10 from Atrovent group, and 7 from placebo group) discontinued treatment prematurely because of adverse events. These events are listed in Table 15. None of these are of new safety concerns.

Table 15. Patients who discontinued due to adverse events

Patient ID	Age/sex	Adverse event	Severity	Relationship to treatment
Atrovent:				
4333	52 yr/F	Headache	Severe	Possible
		Nasal dryness	Moderate	Possible
4999	33 yr/F	Pregnancy	-	Unrelated
4379	38 yr/M	Bronchitis	Severe	Unrelated
4457	27 yr/F	Bronchitis and sinusitis	Moderate	Unrelated
4050	30 yr/M	Nasal dryness	Severe	Possible
4461	41 yr/F	Sinusitis	Severe	Possible
		Taste perversion	Moderate	Possible
4583	15 yr/F	Sinusitis	Moderate	Unrelated
4371	21 yr/M	Upper respiratory tract infection	Severe	Unrelated
4169	49 yr/F	Dermatitis	Severe	Possible
4269	45 yr/F	Urticaria	Severe	Possible
Placebo:				
4565	20 yr/F	Asthma exacerbation	Moderate	Unrelated
4271	38 yr/M	Shortness of breath	Severe	Unrelated
4463	53 yr/F	Nasal congestion	Severe	Unrelated
4383	37 yr/F	Sinusitis	Severe	Unrelated
4579	28 yr/M	Sinusitis	Moderate	Unrelated
4570	15 yr/F	Upper respiratory tract infection	Moderate	Unrelated
4051	31 yr/F	Upper respiratory tract infection	Severe	Unrelated
Source: v 5, p 76-91 narratives				

d) Serious adverse events and death

One patient had serious adverse events during the study. A 38 year old white female (No. 4125, randomized to placebo) had a miscarriage 15 days after completion of active treatment. This patient reported pregnancy at visit 6 that occurred while she was on oral contraceptives. The duration of the pregnancy was approximately 2 weeks at the time of the event. The patient had no previous history of miscarriage. No patient died during the study (v 5, p 86).

e) Physical examination, ECG, and laboratory measures

There were no clinically significant changes in vital signs, physical examination, and anterior rhinoscopic nasal examination. Nasal examination at baseline had changes consistent with the diagnosis of SAR. At the end of double blind treatment, 12% patients on Atrovent were reported by the investigators to have improvement of the nasal mucosal color as compared to 4% patients on placebo. The degree of nasal mucosal edema was not improved in either treatment group. There were no clinically meaningful changes in

mean values, individual patient values, and distribution of shifts for any of the laboratory parameters between the treatment groups. Analyses of these variables by age, and gender did not indicate any differential response to treatment (v 5, p 91-101).

12. Conclusion from study results

This study compared the efficacy and safety of Atrovent Nasal Spray 0.6% at a dose of 2 sprays per nostril QID (84 mcg/nostril QID) over a 3 week treatment period in reducing rhinorrhea severity and duration in 12 to 75 year old patients with SAR with sensitivity to ragweed pollen. Primary efficacy assessment was based on 215 patients randomized to Atrovent, and 209 patients randomized to placebo. The study was overpowered, as 150 patients in each treatment arm were required based on power calculation. Given this limitation, efficacy analysis at the high pollen week (protocol specified primary endpoint) and the three weeks of treatment supports the efficacy of Atrovent. Atrovent nasal spray was well tolerated in this study. Patients on Atrovent reported slightly more adverse events as compared to placebo. Most of these events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Efficacy and safety analyses of subgroups based on age, and gender did not reveal any clinically meaningful differences. This study supports the efficacy and safety of Atrovent Nasal Spray 0.06% at a dose of two sprays each nostril QID (84 mcg/nostril QID) for rhinorhhea in patients 12 years and above with SAR. Of note, the sponsor seeks this indication down to the age of 5 years. This study did not include any patient between the age of 5 and 11 years and therefore does not support the efficacy and safety for patients down to the age of 5 years.

B. 244.2435: Randomized, double-blind, parallel placebo-controlled trial of Atrovent Nasal Spray 0.03% (42 mcg/nostril) alone, antihistamine alone, and combination of Atrovent nasal spray with an antihistamine in patients with seasonal allergic rhinitis

1. Investigators and centers

The study was conducted in 10 centers in US. No disqualified investigators participated in the study (v 6, p 31).

2. Objective

The objective of this study was to assess the efficacy and safety of Atrovent Nasal Spray 0.03% administered two sprays per nostril TID alone and with an antihistamine for four weeks in patients with SAR (v 6, p 27, 35).

3. Study design and procedures

Patients between the ages of 12 and 75 years with a diagnosis of SAR and satisfying the eligibility criteria were recruited. Eligibility criteria were similar to study 244.2475. Sensitivity to relevant seasonal allergens was confirmed by skin tests. The study had three periods: one week screening (Part I), two weeks double-blind treatment (Part II), and another two weeks double-blind treatment (Part III). Study procedure is outline in Table 16. The treatment arms for the two double blind treatment periods (Parts II and III) were same, except that the escape medication during Part II were pseudoephedrine and Clear Eyes, and during Part III were Beconase AQ and Clear Eyes. The treatment arms were Atrovent nasal spray, placebo nasal spray, Atrovent nasal spray plus Seldane, placebo nasal spray plus Seldane. Dose of Atrovent Nasal Spray 0.03% was two sprays each nostril TID (42 mcg/nostril TID), and dose of Seldane was 60 mg by mouth BID. Prohibited medications during the study included anticholinergic agents, antihistamines, sympathomimetic decongestants, nasal cromolyn, tranquilizers with anticholinergic effects, steroids, medications contraindicated for administration with Seldane, and other investigational drugs. The primary efficacy endpoint was the assessment of severity and duration of rhonirrhea as recorded on the patient daily record. Primary comparison was between the Atrovent and placebo arms. The symptom severity scale and the method for duration of rhinorrhea assessemnt was same as study 244.2475 (section VIII.A.6, Table 4). Secondary efficacy endpoints included other symptoms of SAR, QOL questionnaires, and global assessment of control of rhinorrhea. Safety assessment included adverse event recording, vital signs, physical examination, nasal examination, ECG, and laboratory assessment. A total of 400 patients (100 patients to each treatment group) were planned to be recruited to detect a difference of 20% between Atrovent and placebo group for average rhinorrhea severity (v 6, p 35-60, 237-275).

The relevance of this study to this application is limited. The dose of Atrovent (0.03%) and frequency of use (TID) is less than what the sponsor is seeking in this application, which is 0.06% QID. Seldane is no longer an approved antihistamine in the US.

Table 16. Schedule of observations

	Part I	**Part II**		**Part III**
	Visit 1	Visit 2	Visits 3	Visit 4
	Week 0	Week 1	Week 3	Week 5
Consent, enroll, history, and skin test	x			
Vital signs	x		x	x
Physical exam, lab tests[†]	x			x
ECG	x			
Nasal exam	x	x	x	x
Dispense study medication		x		
Return and weigh study medication				x
Dispense escape medication	x	x	x	
Return escape medication		x	x	x
Dispense diary card	x	x	x	
Return diary card		x	x	x
Patient's symptom assessment		x	x	x

	Part I	Part II		Part III
	Visit 1	Visit 2	Visits 3	Visit 4
	Week 0	Week 1	Week 3	Week 5
Patient/physician global assessment			x	x
QOL questionnaire		x	x	x
Adverse events		x	x	x
* Complete urinalysis, complete blood count, and clinical chemistry (creatinine, BUN, glucose, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, serum IgE) (v 6 p 54).				
Source: v 6, p 282				

4. Results

a) Patients enrolled/analyzed

A total of 636 patients were screened and 416 were randomized. The number of patient randomized in each of the 10 centers varied from 27 to 51. Disposition of the patients is shown in Table 17 (v 6, p 61-51).

Table 17. Disposition of study patients

	Atrovent	Atrovent + Seldane	Placebo	Placebo + Seldane	Total
Number randomized	106	100	103	103	412
Number completed	103	96	98	98	395
Reasons for discontinuation:					
Adverse event	2	1	3	0	6
Administrative*	0	1	1	2	4
Protocol violation	0	2	1	3	6
Lack of efficacy	1	0	0	0	1
* Include lost to follow-up, withdrawal of consent, etc.					
Source: v 6, p 62					

b) Patient demographics and baseline disease characteristics

Demographics and disease characteristics of patients enrolled in the study are shown in Table 18. The groups were comparable.

Table 18. Demographic summary and baseline disease characteristics

	Atrovent	Atrovent + Seldane	Placebo	Placebo + Seldane	Total
Number randomized	106	100	103	103	412
Sex: male/female	42/64	31/69	47/56	44/59	164/248
Age (yr): mean ± SD	33.2 ± 11.7	31.3 ± 11.9	30.3 ± 10.6	31.9 ± 12.3	31.7 ± 11.7
Age: patient 12-18 yr old	13	16	17	14	60
Age: patient 19-39 yr old	63	63	65	65	256
Age: patient 40-75 yr old	30	21	21	24	96
Race: cauc./others	94/12	79/21	84/19	85/18	342/70

	Atrovent	Atrovent + Seldane	Placebo	Placebo + Seldane	Total
Disease duration*	17.3 ± 11	15.2 ± 10.1	16.6 ± 10.6	16.2 ± 11.3	
Rhinorrhea severity*	3.04 ± 0.72	3.01 ± 0.63	3.00 ± 0.61	3.01 ± 0.64	
Rhinorrhea duration*	5.92 ± 2.90	5.93 ± 2.92	5.40 ± 2.57	5.99 ± 2.88	
* Expressed as mean ± SD					
Source: v 1, p 39; v 6, p 65, 66					

c) Protocol deviations

There were no significant protocol deviations that impacted the efficacy or safety analyses. Sixteen patients had SAR symptoms less than required by the entry cirteria. These patietns had ample evidence of SAR, and all were included in the efficacy and safety analyses (v 6, p 63).

d) Efficacy endpoint outcomes

Atrovent nasal spray alone did not reduce rhinorrhea severity and duration any more than placebo nasal spray (Table 19, Table 20). Patients receiving both Atrovent and Seldane tended to have less rhinorrhea than patients receiving placebo nasal spray plus Seldane. The differences were small and statistically not significant. In patients who were on Seldane, addition of Atrovent tended to reduce rhinorrhea severity and duration further. Presumably, Seldane had some beneficial effects on SAR symptoms, and addition of Atrovent then allowed the effect of Atrovent noticeable by the patients. The effect sizes for rhinorrhea serverity and rhinorrhea duration for this subgroup of patients who were on Seldane were comparable to the previous study (Table 20). Overall, there was a large placebo response in the study. Escape medications were used infrequently and similarly across treatment groups. No differences between treatment arms were seen for other efficacy measures, such as patient rating of rhinorrhea, congestion, sneezing, and ocular symptoms (Table 19), patient and physician rating of global efficacy, and quality of life assessment (data not shown) (v 6, p 70-104).

Table 19. Adjusted* means for rhinitis symptoms† during the four weeks of treatment*

Parameters	Treatment				Comparison P-value	
	Atrovent (n = 103)	Placebo (n = 96)	Atrovent + Seldane (n = 98)	Placebo + Seldane (n = 98)	Atrovent vs placebo	Atr+Sel vs Pb+Sel
Rhinorrhea severity (Baseline = 3.03)	2.29	2.30	1.88	2.12	0.9070	0.0584
Rhinorrhea duration (Baseline = 5.85)	4.64	4.88	3.63	4.18	0.4367	0.0761
Congestion severity (Baselin = 2.98)	2.53	2.32	2.32	2.23	0.0974	0.4446
Sneezing severity (Baseline = 2.56)	2.00	1.91	1.64	1.67	0.4292	0.7618
Ocular itching severity (Baseline = 2.641.96)	1.85	1.83	1.43	1.38	0.8914	0.6808

Parameters	Treatment				Comparison P-value	
	Atrovent (n = 103)	Placebo (n = 96)	Atrovent + Seldane (n = 98)	Placebo + Seldane (n = 98)	Atrovent vs placebo	Atr+Sel vs Pb+Sel
* Adjusted for baseline assessment, center, and treatment-center interaction † Severity scored by patients on 6 point scale: 0= none, 1= very mild, 2= mild, 3= moderate, 4= severe, and 5= unbearable. Duration expressed in hours.						
Source: v 6, p 79, 85						

Table 20. Percent change from baseline of rhinitis symptoms

Parameters	Atrovent (n = 103)	Placebo (n = 96)	Atrovent + Seldane (n = 98)	Placebo + Seldane (n = 98)
Rhinorrhea severity	- 24 %	- 24 %	- 38 %	- 30 %
Rhinorrhea duration	- 21 %	- 17 %	- 38 %	- 29 %
Congestion severity	- 15 %	- 22 %	- 22 %	- 25 %
Sneezing severity	- 22 %	- 24 %	- 36 %	- 35 %
Ocular itching severity	- 30 %	- 31 %	- 46 %	- 48 %
Source: v 6, p 80, 86				

5. Safety outcomes

a) Total drug exposure

The extent of exposure is shown in Table 21. Treatment duration was similar among the groups. Majority of the patients received the planned 4 weeks of treatment during the double-blind period (v 6, p 105).

Table 21. Extent of exposure during active treatment phase

Parameters	Atrovent	Placebo	Atrovent + Seldane	Placebo + Seldane
Total treated	106	100	103	103
0-10 days	2	1	2	0
10-20 days	1	3	2	4
20-30 days	80	76	71	78
30-46 days	23	20	28	21
Mean exposure in days	28.3	27.6	28.3	28.5
Source: v 6, p 106				

b) Adverse events

Atrovent nasal spray was well tolerated in this study. Adverse events reported by at least 1% of the patients in Atrovent group and more commonly in the Atrovent group compared to placebo during the active treatment are shown in Table 22. There were no differences in the incidence of non-nasal or nasal adverse events between treatment groups. The nasal events seen were primarily nasal dryness or irritation, blood tinged

nasal mucus, and epistaxis. All reports of nasal events were mild or moderate in severity except two patients, one on Atrovent nasal spray and one on placebo, reported severe nasal dryness. Use of Atrovent with Seldane did not increase the incidence of nasal, non-nasal, or anticholinergic adverse events compared to Atrovent or Seldane alone. Comparison of adverse events between part II and part III of the study, reflecting the effect of added pseudoephedrine or Beconase as escape medication, did not reveal and difference (data not shown in this review). Adverse event analyses by age, and gender did not reveal any clinically meaningful differences (v 6, p 106-116).

Table 22. Common adverse events reported by patients during active treatment period *

	Atrovent	Placebo	Atrovent + Seldane	Placebo + Seldane
Total treated	106	100	103	103
Total with adverse events	30 (28.3 %)	31 (31.0 %)	22 (21.4 %)	24 (23.3 %)
Application site disorder				
Contact dermatitis	0 (0.0 %)	0 (0.0 %)	2 (1.9 %)	0 (0.0 %)
Body as a whole				
Headache	10 (9.4 %)	8 (8.0 %)	8 (7.8 %)	9 (8.7 %)
Gastrointestinal system				
Diarrhea	4 (3.8 %)	1 (1.0 %)	0 (0.0 %)	0 (0.0 %)
Dyspepsia	2 (1.9 %)	0 (0.0 %)		
Musculo-skeletal system				
Myalgia	2 (1.9 %)	1 (1.0 %)	2 (1.9 %)	1 (1.0 %)
Respiratory mechanism disorder				
Nose dryness	3 (2.8 %)	2 (2.0 %)	2 (1.9 %)	1 (1.0 %)
Nasal irritation	2 (1.9 %)	0 (0.0 %)	1 (1.0 %)	2 (1.9 %)

* Events reported by ≥1 % of patients in the Atrovent group and more commonly in the Atrovent group compared to the placebo group. Events listed as number and % by WHO System Organ Class.

Source: v 6, p 114, 173-177, created from two tables

c) Discontinuation or treatment interruption due to adverse events

Six patients discontinued study treatment prematurely because of adverse events. These events are listed in Table 23. None of these are of new safety concerns.

Table 23. Patients who discontinued due to adverse events

Patient ID	Age/sex	Adverse event	Severity	Relationship to treatment
Atrovent:				
2063	18 yr/M	Sinusitis	Moderate	Unrelated
1837	59 yr/F	Sinusitis	Moderate	Unrelated
Placebo:				
2077	44 yr/F	Sinusitis	Moderate	Unrelated
Atrovent + Seldane:				
1975	18 yr/M	Influenza like symptoms	Severe	Unrelated
2166	30 yr/F	Dizziness, confusion	Moderate	Related
		Mouth dryness, headache	Severe	Related

Patient ID	Age/sex	Adverse event	Severity	Relationship to treatment
Seldane:				
1962	37 yr/F	Headache Infectious rhinitis	Severe Moderate	Unrelated Unrelated
Source: v6, p 119-120 narratives				

d) Serious adverse events and death

One patient had serious adverse events during the study. A 54 year old white female patient (No. 2055, randomized to placebo nasal spray plus Seldane) was hospitalized due to kidney stone 29 days into treatment. The event was judged by the investigator to be not related to study drug. No patient died during the study (v 6, p 117).

e) Physical examination, ECG, and laboratory measures

There were no clinically significant changes in vital signs, physical examination, and anterior rhinoscopic nasal examination. Nasal examination at baseline had changes consistent with the diagnosis of SAR. At the end of double blind treatment, there was a slight improvement in the nasal mucosal color in all four treatment groups with 9-17% more patients having a normal mucosal color. The degree of mucosal edema also improved in all treatment groups with 12-15% more patients had none to mild edema after final week of treatment. The differences between the groups for mucosal color and edema were not significantly different. There were no clinically meaningful changes in mean values, individual patient values, and distribution of shifts for any of the laboratory parameters between the treatment groups. Analyses of these variables by age, and gender did not indicate any differential response to treatment (v 6, p 120-133).

6. Conclusion from study results

This study assessed the efficacy and safety of Atrovent Nasal Spray 0.03% at a dose of two sprays each nostril TID (42 mcg/nostril TID) alone and with Seldane 60 mg by moputh BID over a 4 week treatment period in controlling rhinorrhea severity and duration in 12 to 75 year old patients with SAR. The relevance of this study to this application is limited because the sponsor is seeking to gain approval for the 0.06% strength at 2 sprays each nostril QID (84 mcg/nostril QID) for SAR. Data presented in this study do not support the use of Atrovent 0.03% at two sprays each nostril TID in reducing rhinorrhea severity and duration. Adding H1 antihistamine to Atrovent nasal spray did not provide any significant advantage over using either drug alone. However, in patients who were on Seldane, which presumably had some effect on SAR symptom severity, addition of Atrovent tended to reduce rhinorrhea severity and duration further. The effect sizes for rhinorrhea serverity and rhinorrhea duration for this subgroup of patients who were on Seldane were comparable to the previous study 244.2475. Atrovent was well tolerated in this study. Patients on Atrovent reported slightly more adverse events as compared to placebo. Most of these events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Combined use of Atrovent with Seldane did not alter the safety profile of Atrovnet. This study does not lend any further support to the previous study (244.2475) towards efficacy

claim for Atrovent Nasal Spray 0.06% at a dose of two sprays each nostril QID for rhinorhhea in patients with SAR. This study, as in the study 244.2475, did not include any patient between the age of 5 and 11 years. Of note, the sponsor seeks this indication down to the age of 5 years.

C. 244.2405: Randomized, double-blind, parallel comparison of Atrovent Nasal Spray 0.06% and 0.12% (84 mcg or 168 mcg per nostril) versus placebo BID in allergic perennial rhinitis

1. Investigators and centers

The study was conducted in 13 centers in the US. No disqualified investigators participated in the study (v 7, p 3).

2. Objective

The objective of this study was to assess efficacy and safety of Atrovent nasal spray 0.06% and 0.12% versus placebo nasal spray administered two spray per nostril BID for eight weeks for controlling rhinorrhea in patients with perennial allergic rhinitis (PAR), and to assess one-year safety of Atrovent Nasal Spray 0.06% or 0.12% administered QD to TID (v 7, p 267). One-year safety data are not included in this submission (v 7, p 30).

3. Study design and procedure

Patients between the ages of 18 and 75 years with a diagnosis of PAR were recruited for the study. Eligibility criteria and medication washout were similar to study 244.2475, except that the patients were required to have sensitivity to perennial rather than seasonal allergens. Sensitivity to relevant allergens was confirmed by skin tests. The study protocol is summarized in Table 24. The protocol consisted of a short-term efficacy and safety portion (Parts I-IV), and a long-term safety portion (Part V). Data from short-term efficacy and safety portion is reported in this submission (v 7, p 30, 268-276).

The short-term efficacy and safety portion included one week of screening (Part I), one week of placebo run-in during which baseline was established (Part II), and eight weeks of double-blind treatment (Part III). Treatment arms were Atrovent 0.06% administered as two sprays per nostril BID (84 mcg/nostril BID), Atrovent 0.12% administered as two spray per nostril BID (168 mcg/nostril BID), and placebo nasal spray administered as two sprays per nostril BID. Nasal rebound of symptoms was assessed in Part IV, during which patients were not given any nasal medication. The primary efficacy endpoint was severity and duration of rhinorrhea as recorded on the patient daily diary record. The symptom severity scale and the method for duration of rhinorrhea assessment

were the same as study 244.2475 (section X.A.6, Table 4). Secondary efficacy endpoints included other symptoms of PAR, HRQOL questionnaires, and global assessment of control of rhinorrhea. Safety assessment included adverse event recording, vital signs, physical examination, detailed nasal examination, nasal cytology, ECG, and laboratory assessment (v 7, 19, 268-276, 285, 292).

Long-term (one-year) safety of Atrovent was assessed in Part V. During the first 6 months, Atrovent 0.06% or 0.12% was administered as two sprays per nostril QD to TID (84 mcg/nostril QD to TID or 168 mcg/nostril QD to TID) and a decrease in dose was only allowed for intolerable nasal effects. One-half of the patients were given Atorvent 0.06% and one-half were given Atrovent 0.12%. Each patient had a specific dosing frequency, either QD or BID or TID. During the second 6 months, investigators were allowed to change the dose of Atrovent in a pre-specified manner to maintain good control of rhinorrhea. The endpoints for this safety portion of the study were adverse events, and reasons for discontinuations (v 7, p 268-276, 292).

The relevance of this study to this application is limited. The dosing frequency of Atrovent (BID for efficacy assessment, and QD to TID for long-term safety assessment) is less than what the sponsor is seeking in this application, which is QID for Atrovent 0.06%, although the higher strengths used in this study partly offsets that. This study is important primarily from safety perspective.

Table 24. Summary of the study parts

	Part I	Part II	Part III	Part IV	Part V
Purpose	Screening	Baseline	Treatment comparisons	Follow-up	Long-term safety
Treatment	None	Placebo	Atrovent or placebo	None	Atrovent
Blind	None	Single	Double	None	Double
Duration	1 week	1 week	8 weeks	1 week	1 year
Visit	1	2	3-7	8	8-17
Source: v 7, p 268					

4. Results

a) Patients enrolled and analyzed

A total of 654 patients were screened and 400 were randomized. The number of patients randomized in each of the 13 centers varied from 17-49. Disposition of the patients is shown in Table 25. Of the 400 randomized patients, 13 discontinued prior to entering Part III treatment comparison and were not included in the efficacy and safety analyses (v 7, p 36, 44, 65).

Table 25. Disposition of study patients

	Atrovent 0.12%	Atrovent 0.06%	Placebo	Total
Number randomized	133	131	136	400

	Atrovent 0.12%	Atrovent 0.06%	Placebo	Total
Entered Part II	133	131	136	400
Entered Part III	129	126	132	387
Entered Part IV	108	110	113	331
Completed trial	107	110	113	330
Reasons for discontinuation (Parts I-IV combined):				
Administrative	9	7	4	20
Adverse event	17	14	15	46
Protocol violation	0	0	4	4
Source: v 7, p 46, modified				

b) Patient demographics and baseline disease characteristics

Demographics and disease characteristics of patients enrolled in the study are shown in Table 18. The groups were comparable. (v 7. p36).

Table 26. Demographic summary and baseline disease characteristics

	Atrovent 0.12%	Atrovent 0.06%	Placebo	Total
Number randomized	129	126	132	387[†]
Sex: male/female	47/82	52/74	43/89	142/245
Age (yr): mean ± SD	38.9 ± 12.3	38.5 ± 12.1	38.3 ± 11.5	38.6 ± 11.9
Age: range	19-74	18-73	17-72	17-74
Race: cauc./others	125/4	123/3	125/7	373/14
Disease duration[*]	16.9 ± 12.7	17.1 ± 13.2	16.7 ± 13.4	16.9 ± 13.1
Rhinorrhea severity[*]	3.04 ± 0.72	3.00 ± 0.61	3.01 ± 0.64	
Rhinorrhea duration[*]	5.92 ± 2.90	5.40 ± 2.57	5.99 ± 2.88	
[*] A total of 400 patients were randomized, however 13 patients discontinued prior to entering Part III treatment comparison and are not included in the efficacy and safety analysis (v 7, p 36) [†] Expressed as mean ± SD				
Source: v 7, p 36				

c) Protocol deviations

The protocol deviations were minor and not expected to impact the results of the study.

d) Efficacy endpoint outcomes

Atrovent Nasal Spray 0.12% and 0.06% controlled rhinorhea effectively when administered twice daily (Table 27). The 0.12% strength performed better than 0.06% strength. The separation between the doses was statistically significant for rhinorrhea severity at the first two weeks, and was maintained at later weeks (data not shown in this review). Patient and physician assessment of rhinorrhea supported efficacy for both the doses and showed separation of the doses. Atrovent 0.12% and 0.06% doses also tended to improve HRQOL measures. The difference of Atrovent 0.12% with placebo was statistically significant for rhinorrhea interfering with daily activities (v 7, p 21).

The sponsor has performed analyses comparing patients who had pure PAR to those who had mixed SAR-PAR. Approximately half of the patients had pure PAR and the rest half had mixed SARR-PAR. This analyses has limited utility, because of the post-hoc nature, however, the sponsor states patients who had mixed SAR-PAR had a larger response to the Atrovent Nasal Spray 0.12% compared to Atrovent Nasal Spray 0.06% (v 1,p 32). This indirectly supports that SAR patients may benefit from a larger dose of Atrovent Nasal Spray.

Table 27. Adjusted* means for rhinitis symptoms† during the eight weeks of treatment*

Parameters	Treatment			Comparison P-value	
	Atrovent‡ 0.12%	Atrovent 0.06%	Placebo	Atrovent 0.12% vs pbo	Atrovent 0.06% vs pbo
Rhinorrhea severity (Baseline = 2.60)	1.62 (38 %)	1.78 (32 %)	2.00 (23 %)	**<0.01**	**0.03**
Rhinorrhea duration (Baseline = 5.62)	3.32 (41 %)	3.66 (35 %)	4.09 (27 %)	**0.01**	0.09
Congestion severity (Baseline = 2.90)	2.32 (20 %)	2.28 (21 %)	2.47 (15 %)	0.20	0.11
Sneezing severity (Baseline = 2.66)	1.78 (33 %)	2.11 (21 %)	1.99 (25 %)	0.11	0.34
Postnasal drip severity (Baseline = 2.641.96)	2.14 (25 %)	2.28 (20 %)	2.31 (19 %)	0.24	0.85
* Adjusted for baseline assessment, center, and treatment-center interaction † Severity scored by patients on 6 point scale: 0= none, 1= very mild, 2= mild, 3= moderate, 4= severe, and 5= unbearable. Duration scored in hours. ‡ Results expresses as mean (% decrease from baseline)					
Source: v 7, p 22, 74					

5. Safety outcomes

a) Total drug exposure

The extent of exposure by treatment groups is shown in Table 28. Treatment duration was similar among the groups. The majority of patients received the planned 8 weeks of active treatment (v 5, p 100-101).

Table 28. Extent of exposure during the double-blind treatment period (part III)

	Atrovent‡ 0.12%	Atrovent 0.06%	Placebo
Total treated	129	126	132
<1 week	5	2	3
1 week - <2 weeks	2	1	5
2 weeks - <4 weeks	9	6	3
4 weeks - <6 weeks	4	4	4
6 weeks - <8 weeks	21	25	33
8 weeks - <10 weeks	85	88	82
10 weeks - <12 weeks	3	0	2

	Atrovent‡ 0.12%	Atrovent 0.06%	Placebo
Mean exposure in weeks	7.3	7.6	7.4
Source: v 7, p 101			

b) Adverse events

Atrovent Nasal Spray 0.12% and 0.06% were well tolerated in this study. Adverse events reported by at least 1% of patients in Atrovent group and more commonly in any Atrovent group compared to the placebo group during the active treatment period are shown in Table 29. Most of these events were potentially due to anticholinergic effects of Atrovent, occurred locally in the nose, and were mild to moderate in intensity. Nasal dryness and epistaxis were the commonest drug related adverse event. The sponsor also looked at adverse events classified by age, and gender. These analyses did not reveal any clinically meaningful differences (v 7, p 23, 101-116).

Table 29. Common* adverse events reported by patients during active treatment period

	Atrovent‡ 0.12%	Atrovent 0.06%	Placebo
Total treated	129	126	132
Total with adverse events	84 (38.5 %)	62 (29.4 %)	
Body as a whole			
Headache	11 (8.5 %)	8 (6.3 %)	10 (7.6 %)
Pain	5 (3.9 %)	6 (4.8 %)	2 (1.5 %)
Nervous system			
Insomnia	2 (1.6 %)	1 (0.8 %)	0 (0.0 %)
Gastrointestinal system			
Abdominal pain	2 (1.6 %)	0 (0.0 %)	0 (0.0 %)
Dry mouth	2 (1.6 %)	5 (4.0 %)	0 (0.0 %)
Hearing and vestibular disorder			
Earache	2 (1.6 %)	0 (0.0 %)	0 (0.0 %)
Female reproductive			
Dysmenorrhea	2 (1.6 %)	0 (0.0 %)	0 (0.0 %)
Resistance disorder			
Bacterial infection	2 (1.6 %)	1 (0.8 %)	0 (0.0 %)
Respiratory mechanism disorder			
Epistaxis	22 (17.1 %)	9 (7.1 %)	6 (4.5 %)
Nasal dryness	15 (11.6 %)	7 (5.6 %)	1 (0.8 %)
Pharyngitis	10 (7.8 %)	5 (4.0 %)	2 (1.5 %)
Sinusitis	5 (3.9 %)	7 (5.6 %)	4 (3.0 %)
Nasal congestion	4 (3.1 %)	2 (1.6 %)	1 (0.8 %)
Nasal irritation	3 (2.3 %)	2 (1.6 %)	2 (1.5 %)
Coughing	2 (1.6 %)	2 (1.6 %)	1 (0.8 %)
Increased rhinitis	2 (1.6 %)	1 (0.8 %)	1 (0.8 %)
Skin disorder			
Dermatitis	2 (1.6 %)	0 (0.0 %)	0 (0.0 %)
Special senses			
Taste perversion	4 (3.1 %)	2 (1.6 %)	1 (0.8 %)
WBC and RES disorders			
Cervical lympadenopathy	1 (0.8 %)	0 (0.0 %)	0 (0.0 %)

* Events reported by ≥1 % of patients in any Atrovent group and more commonly in the Atrovent group compared to the placebo group

	Atrovent‡ 0.12%	Atrovent 0.06%	Placebo
Source: v 7, p 201-206			

c) Discontinuation or treatment interruption due to adverse events

Forty patients discontinued study treatment prematurely during double-blind treatment period because of adverse events. Of these, 14 were from placebo group, 15 were from Atrovent 0.12% group, and 11 were from Atrovent 0.06% group. None of these discontinuations were due to serious adverse event. These events are listed in Table 23. Discontinuation rates due to nasal dryness, nasal bleeding, and epistaxis was more in the Atrovent 0.12% group compared to the other groups.

Table 30. Patients who discontinued due to adverse events

Patient ID	Age/sex	Adverse event	Severity	Relationship to treatment
Atrovent 0.12%:				
1124	44 yr/F	Sinus excoriation, nasal bleeding	Mild	Probable
1323	28 yr/M	Hot flashes, nausea, palpitation	Severe	Possible
1414	60 yr/F	Nasal dryness, throat dryness	Moderate	Possible
1453	40 yr/F	Increased nasal congestion	Moderate	Possible
1605	42 yr/M	Nasal bleed	Severe	Probable
1653	57 yr/M	Increased allergic rhinitis	Moderate	Possible
1703	25 yr/F	Sinusitis	Moderate	Possible
1750	37 yr/F	Nasal burning, sinus congestion	Moderate	Possible
1908	25 yr/F	Nasal dryness	Moderate	Possible
1916	27 yr/M	Nasal dryness, epistaxis	Moderate	Possible
1115	37 yr/M	Upper respiratory tract infection	Mild	Unrelated
1121	33 yr/F	Strept throat	Moderate	Unrelated
1622	24 yr/F	Sinusitis	Severe	Unrelated
1631	38 yr/F	Sinusitis	Severe	Unrelated
2027	26 yr/F	Sinusitis	Moderate	Unrelated
Atrovent 0.06%:				
1202	35 yr/F	Otitis media, head congestion	Moderate	Possible
1718	46 yr/F	Pruritus	Moderate	Possible
1108	30 yr/F	Otitis medical, upper respiratory tract inf.	Mild	Unrelated
1113	35 yr/M	Upper respiratory tract infection	Severe	Unrelated
1123	43 yr/F	Strept throat, upper respiratory tract inf.	Mild	Unrelated
1127	56 yr/F	Increased rhinorrhea, nasal congestion	Moderate	Unrelated
1412	53 yr/M	Sinusitis	Moderate	Unrelated
1417	39 yr/M	Sinusitis	Moderate	Unrelated
1627	42 yr/F	Sinusitis	Severe	Unrelated
1706	38 yr/M	Sinusitis	Moderate	Unrelated
1935	35 yr/F	Sinusitis	Moderate	Unrelated
Placebo:				
1104	35 yr/F	Rash	Moderate	Possible
1204	34 yr/F	Intermittent heart palpitation	Mild	Possible
1606	40 yr/F	Increased rhinorrhea and sneezing	Moderate	Possible
2020	48 yr/M	Nasal stuffiness, postnasal drip	Severe	Possible
1107	36 yr/F	Upper respiratory tract infection	Mild	Unrelated

Patient ID	Age/sex	Adverse event	Severity	Relationship to treatment
1205	39 yr/F	Bronchitis	Moderate	Unrelated
1251	30 yr/M	Epistaxis	Moderate	Unrelated
1404	40 yr/M	Sinusitis	Moderate	Unrelated
1536	72 yr/M	Leucocytosis, pneumonia	Moderate	Unrelated
1836	42 yr/F	Sneezing	Moderate	Unrelated
1924	48 yr/M	Upper respiratory tract infection	Moderate	Unrelated
1929	42 yr/M	Allergic rhinitis	Moderate	Unrelated
1933	35 yr/M	Sinusitis	Moderate	Unrelated
2013	21 yr/F	Bronchitis	Moderate	Unrelated
Source: v 7, p 115-128 narratives				

d) Serious adverse events and death

Two patients had serious adverse events during the double-bind treatment period of the study. A 32 year old white female (No. 1126, randomized to Atrovent 0.12%) developed right peri-tubal cyst with bilateral tubo-ovarian adhesions 14 days into treatment. A 60 year old whilte female (No. 1212, randomized to Atrovent 0.06%) developed lesion on her left cheek 25 days into treatment. The lesion was later diagnosed to be basal cell carconima. Both the events were judged by the investigators to be not related to study drug. There were no deaths in this study (v 7, p 23, 116-117).

e) Physical examination, and laboratory measures

There were no clinically significant changes in vital signs, physical examination, anterior rhinoscopic nasal examination, and nasal smear cytology. Nasal examination at baseline had changes consistent with the diagnosis of PAR. Mucosal edema and abnormal red mucosa was noted in most of the patients. At the end of double blind treatment, slight improvement of mucosal edema and color was noted almost equally in all groups. Nasal cytology at baseline showed presence of eosinophils and basophils in a large number of patients. These did not change appreciably with treatment. There were no clinically meaningful changes in mean values, individual patient values, and distribution of shifts for any of the laboratory parameters between the treatment groups. One patient (#1208; 38 year old female randomized to Atrovent 0.06%) had elevation of SGOT from 31 U/L at baseline to 84 U/L to the end of double-blind treatment. This was concluded by the investigator to be not drug related. Analyses of safety variables variables by age, and gender did not indicate any differential response to treatment (v 7, p 133-147).

6. Conclusion from study results

This study assessed the efficacy and safety of Atrovent Nasal Spray 0.06% and 0.12% at a dose of two sprays each nostril BID (84 and 168 mcg/nostril BID) versus placebo nasal spray in controlling rhinorrhea severity and duration in 12 to 75 year old patients with PAR. The relevance of this study to this application is limited because the sponsor is seeking to gain approval for the 0.06% strength at 2 sprays each nostril QID (84 mcg/nostril QID) for SAR. In this study patients had PAR, the dosing frequency was BID, and the lower dose studied was less than the proposed dose. Keeping these

limitations in mind, data presented in this study support the use of both doses of Atrovent in reducing rhinorrhea severity and duration. On post-hoc analyses, the sponsor identified that patients who had mixed SAR-PAR had a larger response than patients who had pure PAR, suggesting that SAR patients may benefit from a larger dose of Atrovent. Atrovent was well tolerated in this study, although nasal irritation, nasal dryness, nasal bleeding, and epistaxis were seen more in the Atrovent groups and there was dose ordering for these events. More patients in the Atrovent 0.12% group discontinued because of these adverse events that in other groups. This study does not lend any further support to study 244.2475 towards efficacy claim for Atrovent Nasal Spray 0.06% at a dose of two sprays each nostril QID for rhinorhhea in patients with SAR. This study, as in studies 244.2475 and 244.2435, did not include any patient between the age of 5 and 11 years. Of note, the sponsor seeks this indication down to the age of 5 years.

X. Overview of Efficacy

The sponsor has submitted the results of a single study to support the claim that Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID is effective in symptomatic relief of rhinorrhea in patients with SAR. Two other study results are also included as supportive evidence. The salient features of the three studies are summarized in Table 1. The design of the studies, dose of Atrovent nasal spray used, and patients population in the three studies were different. Therefore, the results of the three studies are not integrated in this overview of efficacy. The rationale for establishing efficacy, and the dose selection is presented in the subsequent sections. The summary efficacy results of the three studies are presented in Table 31 for ease of reference.

Table 31. Adjusted means* of patient diary assessment for rhinorrhea severity and duration† during the double-blind treatment period in the three submitted studies

Study ID	Patients: Disease, age	Treatment‡; duration in weeks (n)	Change from baseline	p - vs. Pbo
Rhinorrhea severity†:				
244.2475	SAR, 12-75 yrs	ANS 0.06%, 84 mcg QID; 3 wks (215) Placebo nasal spray; 3 wks (209)	– 0.53 (– 14 %) – 0.30 (– 06 %)	**0.0024**
244.2435§	SAR, 12-75 yrs	ANS 0.03%, 42 mcg TID; 4 wks (103) Placebo nasal spray; 4 wks (96)	– 0.74 (– 24 %) – 0.73 (– 24 %)	0.9070
244.2405	PAR, 18-75 yrs	ANS 0.12%, 168 mcg BID; 8 wks (129) ANS 0.06%, 84 mcg BID; 8 wks (126) Placebo nasal spray; 8 wks (132)	– 0.98 (– 38 %) – 0.82 (– 32 %) – 0.60 (– 06 %)	**<0.01** **0.03**
Rhinorrhea Duration†:				
244.2475	SAR, 12-75 yrs	ANS 0.06%, 84 mcg QID; 3 wks (215) Placebo nasal spray; 3 wks (209)	– 0.68 (– 09%) – 0.14 (– 02%)	**0.0083**
244.2435§	SAR, 12-75 yrs	ANS 0.03%, 42 mcg TID; 4 wks (103) Placebo nasal spray; 4 wks (96)	– 1.21 (– 21 %) – 0.97 (– 17 %)	0.0761
244.2405	PAR, 18-75 yrs	ANS 0.12%, 168 mcg BID; 8 wks (129) ANS 0.06%, 84 mcg BID; 8 wks (126) Placebo nasal spray; 8 wks (132)	– 2.30 (– 38 %) – 1.96 (– 35 %) – 1.53 (– 23 %)	**0.01** **0.09**
* Adjusted for baseline assessment, center, and treatment-center interaction. † Severity scored by patients on 6 point scale: 0= none, 1= very mild, 2= mild, 3= moderate, 4= severe, and 5= unbearable. Duration scored by patients in hours. ‡ ANS is Atrovent nasal spray, Placebo is placebo nasal spray § Two of the four treatment arms that are relevant for this application is shown				
Source: Table 8, Table 9, Table 19, Table 20, and Table 27 of this review				

A. Clinical studies

1. Study 244.2475

This study evaluated the efficacy and safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for three weeks in patients with SAR. A total of 429 patients were randomized approximately equally to two treatment arms that included

Atrovent and placebo. In this study Atrovent was numerically and statistically superior to placebo in controlling rhinorrhea severity and duration (Table 8, Table 9). This study supports the proposed label claim that Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID is effective in symptomatic relief of rhinorrhea in patients with SAR.

2. Study 244.2435

This study evaluated the efficacy and safety of Atrovent Nasal Spray 0.04% at a dose of 2 sprays per nostril TID alone and with Seldane for four weeks in patients with SAR. A total of 416 patients were randomized approximately equally to four treatment arms that included Atrovent, placebo, Atrovent and Seldane, and placebo and Seldane. In this study Atrovent was not different than placebo (Table 19), suggesting that perhaps the dose approved for rhinorrhea in PAR (Atrovent Nasal Spray 0.03% at a dose of 2 sprays each nostril BID or TID) was not effective for SAR and that a higher dose may be necessary. Exploration of the data further supports that contention. Patients receiving both Atovent and Seldane tended to have less rhinorrhea than patients receiving placebo nasal spray and Seldane (Table 19). The differences were numerically small and statistically not significant. In patients who were on Seldane, which has some beneficial effect on SAR symptoms, addition of Atrovent numerically further reduced rhinorrhea severity and rhinorrhea duration. The effect sizes for reduction in rhinorrhea severity and rhinorrhea duration by Atrovent for this subgroup of patients who were on Seldane (Table 20) were comparable to those seen in study 244.2475 (Table 9).

3. Study 244.2405

This study evaluated the efficacy and safety of Atrovent Nasal Spray 0.06% and 0.12% at a dose of 2 sprays per nostril BID in patients with PAR. A total of 400 patients were randomized approximately equally to three treatment arms that included Atrovent 0.06%, Atrovent 0.12%, and placebo. In this study Atrovent Nasal Spray 0.12% was numerically and statistically superior to placebo for both rhinorrhea severity and rhinorrhea duration, and Atrovent Atrovent Nasal Spray 0.06% was numerically and statistically superior to placebo for rhinorrhea severity and numerically by not statistically superior to placebo for rhinorrhea duration. The sponsor perfomed some post-hoc analyses comparing patients who had pure PAR to those who had mixed SAR-PAR that suggest that patients with SAR may benefit from higher dose of Atrovent. Approximately half of the patients enrolled in this study had pure PAR and half had mixed SAR-PAR. The sponsor states that patients who had mixed SAR-PAR had a larger response to the Atrovent Nasal Spray 0.12% compared to Atrovent Nasal Spray 0.06%.

B. Efficacy determination

This application supports the efficacy of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for symptomatic relief of rhinorrhea in patients with SAR. Results of study 244.2475 show that patients on Atrovent nasal spray 0.06% had statistically significant reductions of rhinorrhea severity ($p=0.0024$) and rhinorrhea duration ($p=0.0083$) over the three weeks of treatment (Table 8). Percent changes during the three weeks for of treatment for rhinorrhea severity were –18% for the Atrovent group and –10% for the placebo group. Percent changes during the three weeks for of treatment

for rhinorrhea duration were –13% for the Atrovent group and –3% for the placebo group (Table 9).

The sponsor was not asked to replicate the finding in another study because Atrovent Nasal Spray is already approved for symptomatic control of rhinorrhea in PAR, non-allergic perennial rhinitis, and in common cold. The pathophysiology of rhinorrhea is similar in these different types of rhinitis, and the response to treatment by Atrovent Nasal Spray is expected to be similar. Therefore, this single study is adequate to support an efficacy claim.

C. Dose selection

The dose chosen by the sponsor appears to be empiric. However, the two supporting studies, 244.2435 and 244.2405, lends support to the sponsor's conclusion that for treating rhinorrhea in SAR a larger dose or increased frequency of Atrovent would be necessary than that required for treating rhinorrhea in PAR. Study 244.2435 failed to show superiority of Atrovent Nasal Spray 0.03% at a dose of 2 sprays each nostril TID over placebo in controlling rhinorrhea in SAR patients (Table 19). However, Atrovent was numerically superior to placebo when the patients were concurrently treated with Seldane. Although the differences did not reach statistical significance, the effect sizes for reduction in rhinorrhea severity and rhinorrhea duration by Atrovent for this subgroup of patients (Table 20) who were on Seldane were comparable to that of study 244.2475 (Table 9). It is possible that patients who were symptomatic with SAR, Atrovent 0.03% alone was not adequate to have an effect detectable by the patients. With Seldane, the symptoms of SAR were reduced, which allowed the effect of Atrovent to be noticeable. Patients with SAR in general are likely to be more symptomatic than patient with PAR and therefore may require a larger dose of Atrovent. Subgroup analyses of study 244.2405 supports this hypothesis. Approximately half of the patients in study 244.2405 had pure PAR and the other half had mixed SAR-PAR. The sponsor compared the response of these subgroups of patients to the two strengths of Atrovent used in this study. On this post-hoc analyses patients with mixed SAR-PAR was noted to have a larger response to the Atrovent Nasal Spray 0.12% compared to Atrovent Nasal Spray 0.06%. These two supporting studies support the conclusion that SAR patients may benefit from a larger dose of Atrovent Nasal Spray.

D. Subset efficacy analysis

The efficacy data from the studies stratified based on gender and race and analyzed. The numbers were small for definitive conclusion, however no numerical trends were seen that would suggest a differential response based on gender and race. Atrovent Nasal Spray is a well studies molecule, and differential responses among gender and racial subgroups were not seen in the previous studies submitted in the NDA and subsequent supplements.

XI. Overview of safety

The sponsor has submitted the results of a single study to support the claim that Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID is safe and effective in symptomatic relief of rhinorrhea in patients with SAR. Two other study results are also included as supportive evidence. The salient features of the three studies re summarized in Table 1. Since, the design of the studies, dose of Atrovent nasal spray used, and patients population in the three studies were different, the safety results of the three studies are not integrated in this overview of efficacy. In the subsequent sections a general commentary on the safety of this drug product is made.

A. Design features of the clinical studies

The three studies included patients ages 12 and above with SAR or PAR. In the pivotal study 244.2475 a total of 218 patients were exposed to Atrovent nasal spray at a dose of 2 sprays each nostril QID for three weeks. In supporting study 244.2405 a total of 129 patients were exposed to Atrovent Nasal Spray at a dose of 2 sprays each nostril BID for eight weeks. In these two studies the total daily dose was 334 mcg. These two studies provide adequate safety data for patients 12 years and above. Safety assessment in the clinical studies included adverse event recording, vital signs, physical examination, detailed nasal examination, laboratory assessments, ECG, and in study 244.2475 assessment of nasal rebound after discontinuation of therapy.

B. Study patients

Details of the patients who entered, completed, and discontinued the studies are shown in appropriate sections of the study reviews (Table 5, Table 17, and Table 25). Discontinuations due to adverse events were small and comparable across treatment arms.

C. Extent of exposure

The extent of exposure to treatment in the three studies are shown in Table 13, Table 21, and Table 28. Exposure to Atrovent Nasal Spray was adequate to characterize the safety profile in general and at the recommended dosage.

D. Incidence of adverse events

Atrovent nasal spray was well tolerated in the clinical studies. Most of the adverse events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose. Some of the common adverse events that occurred more frequently in Atrovent treated patients compared to placebo were nasal irritation, nasal dryness, nasal bleeding and epistaxis (Table 14Table 22Table 29). Nasal dryness and epistaxis were the commonest drug related adverse events, and in study 244.2405 these were dose ordered.

1. Discontinuations due to adverse events

The incidence of discontinuation because of adverse events was small in all studies, and no pattern was observed, suggesting no particular risk for treatment. Discontinuations for each study are tabulated separately in other sections of this review (Table 15, Table 23, Table 30).

2. Serious adverse events and death

Serious adverse events are discussed separately for each study in other sections of this review (sections IX.A.11.d, IX.B.11.d, and IX.C.11.d). None of the serious adverse events was caused by Atrovent. No deaths were reported in any study patient.

E. Vital signs

No clinically relevant changes from baseline were observed in mean values for the pooled safety population as a whole or in shift analyses.

F. Physical, and nasal examinations

General physical examination and anterior rhinoscopic examination was unremarkable, with no evidence of any drug-related finding. Nasal examination at baseline had changes consistent with the diagnosis of SAR. At the end of treatment some investigators reported improvement in nasal examination finding. The changes were not consistent across any treatment group.

G. Electrocardiogram

None of the patients in any treatment group in any of the studies had clinically significant abnormal ECG or significant ECG changes on treatment.

H. Laboratory test results

The laboratory test results were unremarkable. There were no clinically meaningful changes in mean values, individual patient values, and distribution of shifts for any of the laboratory parameters between treatment groups in any of the studies.

I. Effects on pregnancy

One patient randomized to placebo in study 244.2475 reported pregnancy at visit 6 while she was on oral contraceptives. The pregnancy ended up in miscarriage at approximately week 2 of conception.

J. Withdrawal effects and abuse potential

Withdrawal effects were specifically studied in study 244.2475. Analyses of nasal symptoms during the washout week demonstrated to rebound or withdrawal effect following cessation of treatment with Atrovent Nasal Spray.

K. Drug-drug interaction

Drug interactions with Atrovent Nasal Spray were not studied in this program. Based on the NDA studies, significant drug interactions with Atrovent Nasal Spray that is unique for SAR patients is not anticipated.

L. Drug-disease interaction

Drug-disease interaction with Atrovent Nasal Spray was not studied in this program. Based on the NDA studies, drug-disease interactions with Atrovent Nasal Spray that is unique for SAR patients is not anticipated.

M. Safety data analysis by race, and gender

Analysis of adverse events, physical examination, ECG, and laboratory measures stratified by race, and gender did not indicate any differential response to treatment.

N. Summary of safety

This application supports safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID for symptomatic control of rhinorrhea in SAR in patients ages 12 years and above. The submitted study results provide adequate safe data for patients 12 years and above. Atrovent was well tolerated in the studies. Most of the adverse events were mild to moderate in intensity, resulted from anticholinergic effects of Atrovent, and occurred locally in the nose.

The sponsor has submitted no safety data in patients between the ages of 5 and 11 years in this submission. The pediatric efficacy supplement of Atrovent Nasal Spray 0.06% for common cold had safety data from 364 patients between the ages of 5 and 12 years exposed for 4 days to Atrovent 0.06% at a dose of 2 sprays per nostril TID (MO review dated June 23, 1998). Although patients with SAR is likely to be treated for longer periods of time compared to common cold, and the proposed dosing frequency is higher than the common cold indication, the adverse events are likely to similar to those seen in older children in the studies submitted in this sNDA, and to those seen in younger children in studies submitted in the pediatric efficacy supplement for Atrovent 0.06%. The adverse events seen in these studies occurred mostly in the nose, and the frequently reported events were nasal irritation, nasal dryness, nasal bleeding and epistaxis. The current product label of Atrovent Nasal Spray 0.06% already includes these adverse events listed. Therefore, no further studies would be necessary to further assess safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays each nostril QID in patients between the ages of 5 and 11 years

XII. DSI audit

No DSI audit was conducted for this NDA supplement. Atrovent is an approved product and there is no reason to believe that 0.06% dose strength would not be effective for SAR when 0.03% is already approved for PAR.

XIII. Financial conflict

The sponsor reported that none of the investigators had any financial interest with the sponsor that is reportable under the current regulation.

XIV. Recommendation

The sNDA is recommended an approvable action from a clinical standpoint. The sponsor has submitted adequate data to support efficacy and safety of Atrovent Nasal Spray 0.06% at a dose of 2 sprays per nostril QID for symptomatic relief of rhinorrhea associated with SAR in patients 5 years and above.

XV. Labeling Review

The sponsor has proposed changes in the Clinical Trials subsection of Clinical Pharmacology, Indications and Usage, Adverse Reactions, Dosage and Administration, and Patient's Instructions for Use sections of the label. The proposed changes are reasonable. They are summarized below with some pertinent comments. Final labeling language will be negotiated with the sponsor.

CLINICAL PHARMACOLOGY
Clinical Trials:
Efficacy claim for Atrovent Nasal Spray 0.06% is made in this section. The pivotal study 244.2475 forms the basis of the proposed addition to the section.
Comment: The efficacy claim is supported by the submitted studies, prior submitted, and extrapolation. The proposed language is appropriate.

INDICATIONS AND USAGE
This section is updated to indicate that Atrovent Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with SAR in patients 5 years and older, and that safety and effectiveness of Atrovent Nasal Spray 0.06% beyond three weeks has not been established.
Comment: The proposed changes are supported by the submitted studies, prior submitted data, and extrapolation. The proposed language is appropriate.

ADVERSE REACTIONS
This section is updated to include information from the pivotal SAR study 244.2475. An adverse event summary table is included.
Comments: Additions proposed in this section is supported by the submitted studies. The following two changes are suggested. (a) To be consistent with the to be added

adverse event table, the existing Table with the heading "% of Patients Reporting Events" should be changed to "% of Patients with Common Cold Reporting Events." (b) The wording "as an adverse event" should be inserted after the second sentence of the new section that describes the adverse events seen in the SAR studied. The second sentence should read as "Additional events were reported at a higher rate in the seasonal allergic rhinitis trial due in part to the longer duration of the trial and the inclusion of upper respiratory tract infection (URI) as an adverse event."

DOSAGE AND ADMINISTRATION
This section contains a statement that the proposed dose of Atrovent Nasal Spray 0.06% for symptomatic relief of rhinorrhea associated with SAR in adults and children down to 5 years is 2 sprays each nostril QID.
Comment: The proposed changes are supported by the submitted studies and the language is appropriate.

PATIENT'S INSTRUCTION FOR USE
This section is updated to indicate that Atrovent Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with SAR in patients 5 years and older, and that Atrovent Nasal Spray 0.06% should not be used beyond three weeks for SAR.
Comment: The proposed additions are appropriate.

PRECAUTIONS
Pediatric Use
The sponsor has not proposed any additions or changes to this section. The sponsor should be asked to include statements in this section according to the provision of 21 CFR 201.57 (f) (9) (iv).

Jafari
FEB 22 2000

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

Application #:	~~20-391~~ 20-394 Sm	**Application Type:**	**NDA supplement**
Sponsor:	**Boehringer Ingelhiem**	**Proprietary Name:**	**Atrovnet Nasal Spray 0.06%**
Investigators:	**Multiple**	**USAN Name:**	**Ipratropium bromide**
Category:	**Anticholinergic**	**Route of Administration:**	**Intranasal**
Reviewer:	**Badrul A. Chowdhury**	**Review Date:**	**February 18, 2000**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 29, ~~2000~~ 1999	December 30, ~~2000~~ 1999	NDA supplement	Filing and planning review
February 11, 2000	February 14, 2000	Pediatric waiver	None
February 18, 2000	FAX document	Financial disclosure	No conflicts present

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a filing and planning review for Atrovent Nasal Spray 0.06% NDA 20-394. Atrovent Nasal Spray 0.06% is currently approved and marketed for treating rhinorrhea associated with common cold in patients ages 5 years and above. The sponsor is applying to expand the approval to include rhinorrhea associated with allergic rhinitis. Currently Atrovent Nasal spray 0.03% has the rhinits indication (b) (4) (b) (4 (b) (4) One pivotal study and two supportive studies are submitted to support the SAR indication for Atrovent Nasal Spray 0.06%. The sponsor has submitted one volume for each study, which includes the study report, study protocol, and list of investigators. Statistical methods, subject data listings, and case summaries of serious adverse events, deaths, and drop-outs due to adverse events are not submitted with the application. The sponsor has included a complete index for each study that lists these items but refers us to the study reports submitted to the IND for the contents. Other than this deficiency, from a clinical standpoint the submission is complete and ready for full review.

OUTSTANDING ISSUES:

The sponsor will be asked to submit complete study reports for the three studies submitted.

RECOMMENDED REGULATORY ACTION: N drive location: None

New clinical studies	_____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement:	X	**Filed**	_____	**Not Filed**

SIGNATURES: **Medical Reviewer:** Badrul A. Chowdhury **Date:** 2/22/00

Division Director: [signature] **Date:** 2/22/00

I. General Information

Atrovent Nasal Spray is currently approved and marketed as a 0.06% spray for treating rhinorrhea associated with common cold in patients ages 5 years and above, and as a 0.03% spray for treating rhinorrhea associated with seasonal allergic rhinitis (SAR) and nonallergic perennial rhinitis (NAPR) in patients 6 years and above. This NDA supplement by Boehringer Ingelheim is to expand the approved indication of Atrovent Nasal Spray 0.06% to included SAR for patients down to 5 years of age. (b) (4) (b) (4) (b) (4) The sponsor met with the Agency on June 24, 1997, to discuss (b) (4)

No CMC and PharmTox issues are expected in this application, since Atrovent Nasal Spray 0.06% is an approved drug product and the sponsor is not proposing to go down below the currently approved age.

No barred investigators participated in any of the studies. None has any financial conflict according to the financial disclosure statement submitted by the sponsor.

II. Clinical studies

Three clinical studies are submitted in this NDA of which the sponsor has identified one as pivotal and two as supporting. The salient features of the studies are listed in Table 1. Study 244.2475 is the pivotal study for this application. Preliminary review of data shows that patients on Atrovent nasal spray 0.06% had statistically significant reduction of rhinorrhea severity (p=0.0024) and rhinorrhea duration (p=0.0083) over the 3 weeks of treatment; however, the effect sizes were relatively small. Percent changes during the three weeks of treatment were –18% for the Atrovent group and –10% for the placebo group for rhinorrhea severity (volume 1, page 47). This study will be reviewed in depth. The two supporting studies will also be reviewed in depth but more from a safety perspective.

Table 1. List of clinical studies

Study ID	Design	Patients	Treatment	Patient number	Treatment duration
244.2475 U98-3130 (Pivotal)	R, DB, PC	PAR Ages 12-75	Atrovent NS 0.06%, 2 sp QID Placebo NS	218 211	3 weeks
244.2435 U96-3120 (Supporting)	R, DB, PC	SAR Ages 12-75	Atrovent NS 0.03%, 2 sp TID Placebo NS Atr NS 0.03% 2 sp TID + Seldane Placebo NS + Seldane	106 100 103 103	4 weeks
244.2405 U93-0726 (Supporting)	R, DB, PC	NAPR Ages 18-75	Atrovent NS 0.06%, 2 sp BID Atrovent NS 0.12%, 2 sp BID Placebo NS	63 66 64	8 weeks
R is randomized, DB is double-blind, PC is placebo-controlled					
Source: volume 1, pages 31, 32, 36-40; converted from text and merged information from various tables					

The sponsor has submitted one volume for each study, which includes the study report, study protocol, and list of investigators. Statistical methods, subject data listings, and case summaries of serious adverse events, deaths, and drop-outs due to adverse events are not submitted for the studies. The sponsor provides index that lists these items but refers to the study reports submitted earlier with the IND for details on these items. We will ask the sponsor to submit all volumes for the three studies to complete the submission. This will change the volume numbering of the submission.

II. Scopes and limitations of the clinical program

The sponsor has submitted one clinical study to support the claim. One study will probably be adequate if the review shows that the drug was convincingly effective and safe. Other data must also be supportive. At the July 24, 1997, meeting with the sponsor, the Agency agreed that the sponsor might get the claim with one study. One apparent problem is that patients below the age of 12 years were not assessed in the program. The currently approved lower age for Atrovent nasal spray is 6 years for SAR and NAPR (0.03% dose strength), and 5 years for common cold (0.06% dose strength). It may be problematic to determine safety of the 0.06% dose strength for allergic rhinitis in patients between the ages of 5 and 11 years because this age group is not addressed in the submission. The sponsor states that at the July 24, 1997, meeting the Agency agreed that no SAR study would be required in patients below the age of 12 years (volume 1, page 10). My review of the meeting minutes does not show that such an agreement was reached. In any event, we will need to determine if there is any safety concern for 0.06% dose strength for patients between the ages of 5 and 11 years. (b) (4)

The sponsor very briefly touches on this issue in the conclusion section of the submission by stating that (b) (4) and that 0.06% was effective for SAR patients (volume 1, page 109). (b) (4)

(b) (4)

(b) (4)

(b) (4)

III. Preliminary review of the label

The sponsor has submitted an updated label for review. Proposed changes are in the clinical trials, indications and usage, adverse reactions, dosage and administration, and patient's instruction for use sections in the label. The proposed changes incorporate the findings from the pivotal study, and the proposed SAR indication.

IV. DSI audit

No sites are proposed for DSI audit at this time. Atrovent is an approved product and there is no reason to believe that 0.06% dose strength would not be effective for SAR when 0.03% is already approved for the same indication. Focus of this NDA review will be on the logic and regulatory implications of this application, in addition to the assessment of data quality and results. A need for DSI audit to verify data integrity may not be essential for this NDA.

V. Plans for the review and time line

Proposed time line for review of the three studies listed in Table 1 are end of March, April, and May, 2000. This allows one month for each study. Integrated summary of safety and integrated summary of efficacy will be completed by end of June, 2000. By the end of July, 2000, the whole review will be completed including looking through related applications, if necessary. As pointed out earlier, safety assessment of 0.06% dose for children below 12 years may require review of other Atrovent NDA action packages. Write-ups will be due for secondary review by the end of 2nd week of each month with the goal of incorporating comments and suggestions by the end of 4th week of the same month. An advisory committee meeting is not likely to be required for this application, so the proposed timeline should be adequate for final administrative processes. It is anticipated that a final action on the application will be taken by end of August, 2000, two months before the due date of October 29, 2000. (b) (4)

(b) (4)

Reviewed by:

Badrul A. Chowdhury 2/22/00

Badrul A. Chowdhury, MD, PhD
Acting Medical Team Leader, Division of Pulmonary and Allergy Drug Products

Robert Meyer, MD
Director, Division of Pulmonary Drug Products

cc: Original IND
HFD-570/Division File
HFD-570/Chowdhury/Medical Reviewer
HFD-570/ Meyer/Director
HFD-570/Wilson/Statistician
HFD-570/Jafari/CSO
HFD-570/McGovern/Pharmacologist
HFD-570/Choiyo/Biopharm

HFD-570/Khorshidi/CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

CHEMISTRY REVIEW(S)

Khorshidi

FEB 1 2000

CHEMIST'S REVIEW	1. ORGANIZATION HFD-570 DPDP	2. NDA NUMBER 20-394
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Boehringer Ingelheim Pharmaceutical Inc 900 Ridgebury Road, P.O.Box 368 Righefield, Conneticut 06877		4. AF NUMBER 5. SUPPLEMENT(S) *SEI-004 12/29/1999 * subject of this review
6. NAME OF DRUG: Atrovent® Nasal Spray 0.06%	7. NONPROPRIETARY NAME Ipratropium bromide monohydrate nasal solution	
8. SUPPLEMENT PROVIDES FOR: Expansion of the approved indication to include seasonal allergic rhinitis (SAR).		9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S)
10. PHARMACOLOGICAL CATEGORY Antichloninergic	11. HOW DISPENSED RX X OTC	
13. DOSAGE FORM(S) Topical Intranasal solution	14. POTENCY 0.06%	
15. CHEMICAL NAME AND STRUCTURE Ipratropium bromide monohydrate (IB)		16. RECORDS AND REPORTS CURRENT YES__NO__ REVIEWED YES__NO__

17. COMMENTS:

a. Reference is made to supplement 20-394/S-002 dated 5/1/98. This supplement provides for an alternative site (b) (4) (b) (4) for the manufacturing, packaging, testing and release of drug product. This supplement was approved on 1/10/2000.

18. CONCLUSIONS AND RECOMMENDATIONS:

a. No new CMC information has been provided in this efficacy supplement. Therefore, from CMC viewpoint, this supplement is approved.

cc:
Orig. NDA 20-394/SEI-004
HFD-570/div. File
HFD-570/HKhorshidi
HFD-570/GPoochikian
HFD-570/
R/D Init. by:__Poochikian
F/T by: HKhorshidi GP 2/1/00
doc # N:\NDA\20-394\SEI-004\Chem\ 2000.01.31. REV

19. REVIEWER NAME:	SIGNATURE	DATE COMPLETED
Hossein S. Khorshidi	H. S. Khorshid	1/31/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

ENVIRONMENTAL ASSESSMENT

NDA 20-394/S-004

Project Management review of request for Categorical Exclusion from Environmental Assessment

NDA	20-394/S-004
Drug	Atrovent (ipratropium bromide) Nasal Spray 0.06%
Submission date	October 20, 2000
Submission received	December 20, 2000
Applicant	Boehringer Ingelheim
Project Manager	Ladan Jafari

This efficacy supplement submitted for Atrovent Nasal Spray on December 29, 1999, provides for the use of Atrovent Nasal Spray for symptomatic relief of rhinorrhea associated with seasonal allergic rhinitis (SAR) in patients 5 years of age and older. The Categorical Exclusion was submitted October 20, 2000.

The sponsor states that the supplement qualifies for exclusion under 21 CFR 25.31 (b).

There is no information that indicates that additional environmental information is warranted.

Ladan Jafari
Project Manager

Concur:
Sandy Barnes
Chief Project Management Staff

cc:
NDA 20-394
HFD-570/Div.file
HFD-570/Poochikian
HFD-570/Jafari 10/24/00

Initialed by: Barnes 10-23-00

ENVIRONMENTAL ASSESSMENT (Categorical Exclusion)

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) requests that the Categorical Exclusion from the preparation of an Environmental Assessment (EA), as provided by 21 CFR 25.31(b), be approved for this Supplemental NDA submission.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC
900 RIDGEBURY ROAD
P.O.BOX 368
RIDGEFIELD, CT 06877

TELEFAX

NO. OF PAGES: 2
(Including Cover Page)

Date: October 20, 2000

TO: Ms. Leila Jafari

FAX: (301) 827-1271

FROM: C.R. Tamorria

TEL: (203) 798-4544

FAX: (203) 791-6262

SUBJECT: Categorical Exclusion Statement for NDA 20-394 (S-04)

Dear Ms. Jafari,

As we discussed this is the final version of our draft statement.

Thank you for your assistance,

Rick Tamorria

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

STATISTICAL REVIEW(S)

Jafari

Statistical Review and Evaluation
Clinical

SEP 13 2000

NDA #: 20-394 / SE1-004
Applicant: Boehringer Ingelheim
Name of Drug: Atrovent 0.06%
Indication: Treatment of the rhinorrhea symptom in patients with Seasonal Allergic Rhinitis (SAR)
Documents Reviewed: Volumes 1-7, datasets and SAS programs dated December 29, 1999.

This review pertains to one study in adults and adolescents with SAR.

The medical officer for this submission was B. Chowdhury M.D., HFD-570, with whom this review was discussed.

I. Background

Atrovent 0.06% two sprays/nostril three or four times daily has been approved for treating the symptom of rhinorrhea for patients with the common cold. Atrovent 0.03% two sprays/nostril TID has been approved for the treatment of rhinorrhea in patients with PAR. This same dose was studied in patients with SAR but it failed to demonstrate efficacy at that dose level.

In a meeting with the agency on July 24, 1997, the sponsor was told that only one study would be needed to support the supplemental labeling claim (treatment of rhinorrhea in SAR) for this drug. Furthermore, the sponsor was told that it would not be necessary to do a study in children under 12 years of age.

II. Trial 244.2475

A. Study Design and Method of Analysis

This was a randomized, parallel group study with a three week treatment period after a 1-week placebo run-in period, and a 1-week washout period following the treatment period. This study compared Atrovent 0.06% Nasal Spray 84 mcg/nostril (42 mcg per spray) QID with placebo nasal spray in patients with SAR.

Patients were provided Clear Eyes as a rescue medication for severe ocular itching throughout the trial.

Both rhinorrhea severity and duration were recorded on daily diaries by the patient. (The patient also recorded the severity of congestion, itchy eyes, and sneezing and the duration

Key Words: NDA Review, Clinical Study, One Study

of the congestion. These symptoms showed no efficacy and will be minimally discussed in this review.) Both evaluations were based on rhinorrhea symptoms observed between the hours of 8 a.m. to 8 p.m. Rhinorrhea severity was assessed on a 6-point scale (0=none, 1=very mild, 2=mild, 3=moderate, 4=severe, and 5= unbearable) and rhinorrhea duration was recorded to the nearest hour (range 0-12). To enter the study, patients were required to have an average severity of rhinorrhea at least mild and an average duration of at least two hours during the run-in week.

Daily pollen counts were made at each investigative site for at least Monday through Friday and preferably for each day for the entire period of patient participation. The primary assessment time for the primary analyses was the week of highest pollen count for each patient. The average diary score was computed for rhinorrhea severity and duration. An analysis of covariance model was used in the efficacy analyses of rhinorrhea severity and duration. The model included factors for treatment group, investigator site and baseline score. The baseline was calculated by averaging the seven days of the run-in phase for that assessment. Interaction effects for treatment-by-site and treatment-by-baseline were tested in exploratory analyses. (These were not significant and will not be discussed further in this review.)

The sponsor also provided analyses over the full three weeks of treatment. Patients were included in the intent-to-treat analysis if they had at least 3 days of diary assessments.

The patient and physician made a global assessment of overall effectiveness of their study medication in controlling rhinorrhea symptoms during the previous week using a 4-point scale (1=no effect, 2=doubtful effect, 3=good effect, and 4=excellect effect).

B. Results

There were 429 patients randomized into the clinical trial at 15 investigative sites.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables. Five patients (3 Atrovent, 2 placebo) were excluded from the intent-to-treat analyses because they did not complete at least three days of diary data.

The table below provides least squares treatment means for the rhinorrhea parameters during the high pollen week (the primary endpoints).

Means (SEM) and p-values.

Variable	Atrovent (N= 215)	Placebo (N= 209)	p-values
Rhinorrhea Severity (baseline=2.95)	2.54 (0.06)	2.77 (0.06)	0.0051
Rhinorrhea Duration (hrs.) (baseline=5.19)	4.74 (0.16)	5.27 (0.16)	0.0209

The table below provides least squares treatment means for the rhinorrhea parameters during the three weeks of treatment.

	Means (SEM) and p-values.		
Variable	Atrovent (N= 215)	Placebo (N= 209)	p-values
Rhinorrhea Severity (baseline=2.95)	2.42 (0.05)	2.65 (0.05)	0.0024
Rhinorrhea Duration (hrs.) (baseline=5.19)	4.51 (0.14)	5.05 (0.15)	0.0083

No significant differences were seen in congestion severity and duration, sneezing severity or ocular itching severity either for highest pollen week or for the three weeks of treatment

Significant differences favoring Atrovent were seen in patient and physician assessments.

There was no indication of rebound in rhinorrhea symptoms during the washout week.

The Atrovent patients used more rescue medication (Clear Eyes) than did the placebo group although the difference was not very large. Since Atrovent is an anticholinergic, such increase is not unexpected.

C. Reviewer's Comments

This reviewer duplicated the sponsor's analyses from the programs and datasets provided.

This study has demonstrated efficacy of Atrovent for rhinorrhea severity and duration in SAR both during the week of highest pollen count and the full three weeks of treatment.

James R. Gebert, Ph.D.
Mathematical Statistician

Concur: Dr. Wilson 9/13/00
This review contains 3 pages of text.
cc:
Archival NDA 20-394/SE1-004
HFD-570
HFD-570/Dr. Chowdhury
HFD-570/Ms. Jafari
HFD-715/Div. File
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-394/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13.0 PATENT INFORMATION

Patent Number and Expiration Date:	US Patent No. 4,385,048 - May 24, 2000
Type of Patent:	Method of Use
Name of the Patent Owner:	Boehringer Ingelheim GmbH D-55216 Ingelheim am Rhein Germany
US Agent for Patent Owner:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road Ridgefield, CT 06877

Declaration:

The undersigned declares that Patent No. 4,385,048 covers the method of use of ATROVENT® Nasal Spray, 0.06%. This product is the subject of this application for which approval is being sought.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By _____
Alan Stempel

Capacity: ☐ Applicant's Agent (Representative)
☒ Applicant's Attorney

Date February 24, 2000

EXCLUSIVITY SUMMARY for NDA # 20-394 SUPPL #004
Trade Name Atrovent Nasal Spray Generic Name ipratropium bromide
Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.
HFD-570
Approval Date

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 questions 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 /_X__/ NO /___/

      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 /___/ NO /_X__/

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

_____

_____

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

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X__/ NO /___/

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

NDA # 20-394 Atrovent Nasal Spray 0.03%

NDA # 20-291 Combivent Inhalation Aerosol

NDA # _____ _____

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 /_X__/

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 /___/

   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 9:**

   _____

   _____

   (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 /___/ NO /_X__/

(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:

Investigation #1, Study # 244.2475

Investigation #2, Study # 244.2435 NJ

Investigation #3, Study # 244.2405 NJ

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.

(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 /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X__/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # 244.2475

Investigation #__, Study # 244.2435

Investigation #__, Study # 244.2405

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.

(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 # (b) (4) YES /_X__/ 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 /_X__/

If yes, explain: _____

_____

_____

Ladan Jafari
Signature of Preparer
Title: Project Manager

10.25.00
Date

Signature of Office of Division Director

10/26/00
Date

cc:
Archival NDA 20-394
HFD-570/Division File
HFD-570/Jafari
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020394	**Trade Name:**	ATROVENT (IPRATROPIUM BROMIDE) NASAL SPR
Supplement Number:	004	**Generic Name:**	IPRATROPIUM BROMIDE (0.06%)
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF COMMON COLD
Action Date:	12/30/99		

Indication # 1 Sesonal Allergic Rhinitis

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
5 years	Adult	Deferred	12/31/01

Comments: Applicant has not requested for a defferal yet, but have asked for a waiver which was denied.

This page was last edited on 10/4/00

Signature - Date

CERTIFICATION REQUIREMENT

SECTION 306(k)(1) OF THE ACT
21 U.S.C. 355a(k)(1)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it 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) of the Federal Food, Drug and Cosmetic Act in connection with ATROVENT® Nasal Spray 0.06% (ipratropium bromide).

Signature:

Name of the Applicant: Martin Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: February 23, 2000

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please see attached list of investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Martin Kaplan, M.D., J.D.	Vice President, Drug Regulatory Affairs
FIRM/ORGANIZATION: Boehringer Ingelheim Pharmaceuticals, Inc.	
SIGNATURE: Martin M Kaplan	DATE: Feb 18, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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ORIGINAL

Telefax

Boehringer Ingelheim

NDA SUPP AMEND

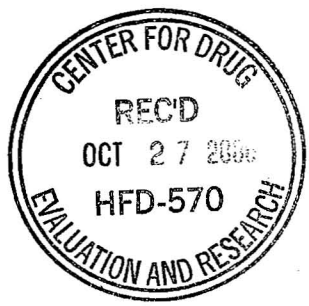
LJ
N ATT. 10.31.00

SE1 | BL 004

Ms. Ladan Jafari
FDA
(tel) 301-827-5584
(fax) 301-827-1271

Boehringer Ingelheim
Pharmaceuticals Inc.

October 26, 2000



ATROVENT Nasal Spray 0.06%
NDA 20-394, S-04

Dr. C. R. Tamorria
Telephone 203-798-4344
Telefax 203-791-6262
E-Mail

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Jafari,

As you requested by telephone this afternoon, I am faxing to you the latest version of the package insert, including all revisions requested by the Agency. Please let me know if you have further questions or comments.

Sincerely,

C.R. Tamorria

ORIGINAL

Telefax

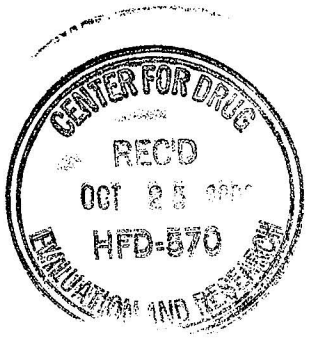
Boehringer Ingelheim

NDA SUPP AMEND
SE1-004-BL

NAS1 hJ
10,2600

Boehringer Ingelheim
Pharmaceuticals, Inc.

Ms. Ladan Jafari
Food and Drug Administration, Division of Pulmonary and Allergy Drug Products
Telephone:(301) 827-5584
Fax: (301) 827-1271



October 24, 2000

C. Richard Tamorria, Ph.D.
Telephone (203) 798-4344
Telefax (203) 791-6262
E-Mail
rtamorri@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

ATROVENT® Nasal Spray 0.06%
(ipratropium bromide)

NDA 20-394/S-004

RESPONSE TO REQUEST FOR INFORMATION

Dear Ms. Jafari,

We are sending herewith the requested final DRAFT labeling for the above supplement. (one black/white, one color)

Please contact me or Ms. Tacy Pack at (203) 798-5545, should there be any additional requests. I plan to be back in the office on Thurs. Oct. 26, 2000.

Sincerely,

C. R. Tamorria

C. Richard Tamorria, Ph. D.
Sr. Associate Director
Drug Regulatory Affairs

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

N 20394/S-004-C

R.J
NAT
10.24.00

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC
900 RIDGEBURY ROAD
P.O.BOX 368
RIDGEFIELD, CT 06877

TELEFAX

NO. OF PAGES: 4
(Including Cover Page)

Date: October 23, 2000

TO: Ms. Ladan Jafari
FDA

FAX: (301) 827-1271

FROM: Dr. C. R. Tamorria

TEL: (203) 798-4344

FAX: (203) 791-6262

SUBJECT: NDA 20-394 (S-04)
Final Revisions for Labeling for SAR Indication

Dear Ms. Jafari

I am sending revised wording in accord with your request on Friday Afternoon (10/20/00) for several changes within the Pediatric Use section and the Clinical Trials section.

We have accepted all of your requested revisions and have added the words "of age" after "12 years" in two places. Both of these are readily discernable on the attached sheets (see pages ① and ③.

If you have any questions or comments, please call me as soon as possible. We can also discuss any follow-up you may want in terms of hard-copy of labeling, etc.

Thank you,

R. C. Tamorria

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

ORIGINAL

SE1/004
NC

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Robert Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products, (HFD-570)
Food and Drug Administration
Ctr. For Drug Evaluation & Research II
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

July 10, 2000

Response to FDA Request for Information

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

C. Richard Tamorria, Ph.D.
Sr. Associate Director
Telephone (203) 798-4344
Telefax (203) 791-6262
E-Mail rtamorri@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Meyer:

As requested by Ms. Ladan Jafari on July 7, 2000, Boehringer Ingelheim Pharmaceuticals, Inc. is submitting herewith two (2) copies of the container label and the carton for ATROVENT® Nasal Spray 0.06% (ipratropium bromide).

If there are further questions, please contact the undersigned.

Sincerely,

C. R. Tamorria

C. Richard Tamorria, Ph. D.
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Ladan Jafari

Dctm\DRA Submissions\ipratropium bromide nasal spray\US\NDA\Correspondence to FDA\FDA Request for Info ltr (10July00)

ORIGINAL
SNC 004

NEW CORRESP

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Robert Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products, (HFD-570)
Food and Drug Administration
Ctr. For Drug Evaluation & Research II
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

June 29, 2000

FDA Request for Information

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

C. Richard Tamorria, Ph.D.
Sr. Associate Director
Telephone (203) 798-4344
Telefax (203) 791-6262
E-Mail rtamorri@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Meyer:

As requested by Ms. Ladan Jafari on June 26, 2000, Boehringer Ingelheim Pharmaceuticals, Inc. is hereby submitting an electronic copy of the revised Package Insert for ATROVENT® Nasal Spray 0.06%. The original submission dated December 29, 1999/S004 did not include this diskette.

If there are further questions, please contact the undersigned.

Sincerely,

Marilyn Maxwell
for C. Richard Tamorria, Ph. D.
Sr. Associate Director
Drug Regulatory Affairs

Desk Copy: Ms. Ladan Jafari (w/diskette)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Jafari

NDA 20-394/S-004

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

MAR 13 2000

Attention: C.R. Tamorria, Ph.D.
DRA Sr. Associate Director

Dear Dr. Tamorria:

Reference is made to your supplemental new drug application dated December 29, 1999, received December 30, 1999, submitted under section 505 (b) of the Federal Food, Drug and Cosmetic Act for Atrovent (ipratropium bromide) Nasal Spray.

We also refer to your correspondence dated February11, 2000, requesting FDA to issue a waiver for pediatric studies.

On December 2, 1998, the FDA published a final rule requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients (63 *FR* 66632). This became effective on April 1, 1999. Under this regulation, any application approved after April 1, 1999, must contain the appropriate pediatric studies or contain a waiver or deferral for pediatric studies (21 CFR 314.55 or 601.27).

We have reviewed your request for a waiver for pediatric studies and are unable to issue a waiver. We believe your drug product has the potential for providing a meaningful therapeutic benefit for the pediatric population (see 21 CFR 314.55(c)(5)). You must submit pediatric studies or other information on the following indications and age groups to fulfill the requirements of 21 CFR 314.55.

- Symptomatic relief of rhinorrhea associated with perenial rhinitis in pediatric population between 2 to 6 years of age.

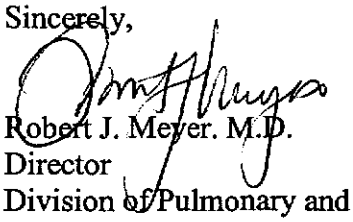
- Symptomatic relief of rhinorrhea associated with common cold in pediatric population between 2 to 5 years of age.

A deferral will be considered if specifically requested and justified (see 21 CFR 314.55 (b)(1)).

Please note that submission of the above studies alone may not qualify for pediatric exclusivity under section 505A of the Act. This letter does not constitute a Written Request under section 505A of the Act. To qualify for pediatric exclusivity or to obtain a Written Request, please refer to the *Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.*

If you have questions, please contact Ms. Ladan Jafari, Regulatory Project Manager, at (301) 827-5584.

Sincerely,



Robert J. Meyer. M.D.
Director
Division of Pulmonary and Allergy Drug Products
HFD-570
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original 1 Archival NDA 20-394
HFD-570/division file
HFD-570/Jafari L.J. 3-10-00
HFD-570/Chowdhury
HFD-570/Meyer
HFD-570/Nashed
HFD-570/Poochikian
HFD-570/McGovern
HFD-570/Sun
HFD-570/Wilson
HFD-570/Choi
HFD-570/Uppoor

HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-002/T.Crescenzi

Drafted by: L.Jafari/3-7-2000
Initialed by: Trout/3-7-00
Chowdhury/3-10-00
Meyer/3-10-00

3-13-00

filename:NDA 20-394/pedref

PEDIATRIC STUDY REQUIREMENT
GENERAL CORRESPONDENCE (GC)

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Robert Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products, (HFD-570)
Food and Drug Administration
Ctr. For Drug Evaluation & Research II
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

February 11, 2000

C. R. Tamorria, Ph.D.
DRA Sr. Associate Director
Telephone (203) 798-4344
Telefax (203) 791-6262
E-Mail rtamorri@rdg.boehringer-ingelheim.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

REQUEST FOR WAIVER

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

Dear Dr. Meyer

This is in reference to our NDA 20-394 Supplement Number 004 dated December 29, 1999. Your notice of receipt letter, dated January 11, 2000, noted that submissions made after April 1, 1999 are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless the requirement is waived or deferred (63FR66632).

After discussions with Ms. Ladan Jafari, during which we explained that this product has been approved for pediatric use, that we were not being granted exclusivity and we had been advised at a meeting with the Agency that a study of the type submitted would suffice for a Seasonal Allergic Rhinitis (SAR) indication in adults and in children, she requested that we submit a request for a waiver.

We hereby request a waiver from conducting further pediatric studies for this drug product. This product was approved for pediatric patients age five years and above on November 9, 1998. A lower strength, ATROVENT® Nasal Spray 0.03%, NDA 20-393, was also approved for pediatric patients age six years and above on April 1, 1998.

We were advised by the Agency that neither of these pediatric approvals qualified for exclusivity.

Boehringer Ingelheim

In a meeting with the Agency on July 24, 1997, the indication SAR was discussed for ATROVENT® Nasal Spray 0.06% and it was noted by the Agency that one trial would be adequate and that no additional pediatric patients needed to be studied. This was explained in detail in our Supplement S-004, dated December 29, 1999 (Volume 1, Pages 10-17).

We continue to believe that no further pediatric studies are required for this indication. The mechanism of disease for seasonal allergic rhinitis is identical to that of perennial allergic rhinitis, in which pediatric trials have been conducted and the safety of ATROVENT® Nasal Spray 0.03% has been demonstrated. ATROVENT® Nasal Spray 0.06% has been demonstrated to be safe in pediatric common cold patients as well. There is no clinical reason to expect that the safety of ATROVENT® Nasal Spray will be any different in pediatric seasonal allergic rhinitis patients. Therefore further clinical trials would provide no pertinent new information.

If further information or discussion regarding this request for a waiver is necessary, please contact me.

Sincerely,

C. R. Damarria

C. Richard Tamorria, Ph.D.
Sr. Associate Director
Drug Regulatory Affairs

Jafari

NDA 20-394/s-004

PRIOR APPROVAL SUPPLEMENT

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

JAN 1 1 2000

Attention: C. Richard Tamorria, Ph.D.
Sr. Associate Director, Drug Regulatory Affairs

Dear Dr. Tamorria:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following Atrovent (ipratropium bromide) Nasal Spray 0.06%.

NDA Number: 20-394

Supplement Number: S-004

Therapeutic Classification: Standard (S)

Date of Supplement: December 29, 1999

Date of Receipt: December 30, 1999

This supplement provides support for an expansion of the approved indication to include seasonal allergic rhinitis (SAR).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 1 ,2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 30, 2000, and the secondary user fee goal date will be December 30, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a

waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the supplemental application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Ms. Ladan Jafari, Project Manager, at (301) 827-5584.

Sincerely,

Parinda Jani

Parinda Jani.
Acting Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

1-11-00

cc:
Archival NDA 20-394
HFD-570/Div. Files
HFD-570/L.Jafari
HFD-570/Div. Files
HFD-570/Jani

DISTRICT OFFICE

Drafted by: LJ/January 7, 2000
Initialed by: PJ/January 10, 2000
final: CY/January 10, 2000
filename: N20394S0

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT (AC)

14034

Memorandum of Telephone Facsimile Correspondence

Date: October 17, 1997

To: C. Richard Tamorria, Ph.D.
Senior Associate Director, Regulatory Affairs

From: Denise P. Toyer
Project Manager

Subject: Minutes for (b) (4) for NDA 20-394

(b) (4)

[redacted]

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 827-1050 and return it to us at 5600 Fishers Lane, HFD-570, DPDP, Rockville, MD 20857.

Thank you.

Denise P. Toyer

Denise P. Toyer
Project Manager
Division of Pulmonary Drug Products

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-394 /SE 1 - 004

Drug Atrovent Nasal Spray Applicant Boehringer Ingelheim Pharmaceuticals Inc. (BIPI)

RPM Ladan Jafari Phone 301-827-5584

X505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s)

Application classifications:
Chem Class 3S
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary Oct 30, 2000
Secondary Dec 30, 2000

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☑ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption
- Action Letter..... ☑AP ☐ AE ☐NA
- Labeling & Labels
  FDA revised labeling and reviews.....
  Original proposed labeling (package insert, patient package insert) .....
  Other labeling in class (most recent 3) or class labeling.....
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels ..... No change
  Nomenclature review ..... N/A
- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☑ is not on the AIP.
  Exception for review (Center Director's memo).....
  OC Clearance for approval.....

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) N A ☐ Materials requested in AP letter

- Post-marketing Commitments — None
  - Agency request for Phase 4 Commitments ....
  - Copy of Applicant's commitments ....

- Was Press Office notified of action (for approval action only)? .... ☐ Yes ☑ No
  - Copy of Press Release or Talk Paper .... NA

- Patent
  - Information [505(b)(1)] .... ✓
  - Patent Certification [505(b)(2)] ....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ....

- Exclusivity Summary ....

- Debarment Statement .... ✓

- Financial Disclosure
  - No disclosable information .... ✓
  - Disclosable information – indicate where review is located ....

- Correspondence/Memoranda/Faxes .... ✓

- Minutes of Meetings .... ✓
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting .... NA
  - Date of Meeting ....
  - Questions considered by the committee ....
  - Minutes or 48-hour alert or pertinent section of transcript ....

- Federal Register Notices, DESI documents .... NA

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ....

- Clinical review(s) and memoranda ....

Continued ⇨

- Safety Update review(s) ..... _____

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☑ Deferred
  Pediatric Page..... _____
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda ..... ✓

- Biopharmaceutical review(s) and memoranda..... NA

- Abuse Liability review(s) ..... NA
  Recommendation for scheduling ..... _____

- Microbiology (efficacy) review(s) and memoranda ..... NA

- DSI Audits ..... NA
  ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda ..... _____

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... NA

- DMF review(s) ..... NA

- Environmental Assessment review/FONSI/Categorical exemption Categorical exclusion.. ✓

- Micro (validation of sterilization) review(s) and memoranda ..... NA

- Facilities Inspection (include EES report)
  Date completed _____ NA ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... NA ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... NA

- Memo from DSI regarding GLP inspection (if any) ..... NA

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... NA
- CAC/ECAC report ..... NA