CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-552

***Name*:** Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), 0.021 mg/spray

***Sponsor*:** Dey, L.P.

***Approval Date*:** March 31, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

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APPLICATION NUMBER:

ANDA 75-552

APPROVAL LETTER

ANDA 75-552

MAR 31 2003

Dey, L.P.
Attention: Michelle A. Carpenter
2751 Napa Valley Corporate Drive
Napa, CA 94558

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), 0.021 mg/spray, packaged in 30 mL per bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated August 9, 1999; and February 28, April 2, and November 18, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ipratropium Bromide Nasal Solution, 0.03%, (Nasal Spray), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Nasal Spray, 0.03% of Boehringer Ingelheim Pharmaceuticals, Inc.)

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/31/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-552
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-625/M.Shaikh/ 3/10/03
HFD-625/M.Smela/ 3/10/03
HFD-617/P.Chen/ 3/7/03
HFD-613/A.Payne/ 3/5/03
HFD-613/J.Grace/ 3/5/2003

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F/T by

APPROVAL PJ 3/11/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

LABELING

75-552 AP 3/31/03

DEY

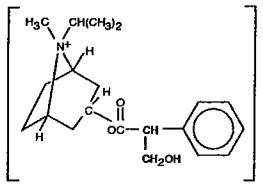
00356001

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

Rx only

Prescribing Information

DESCRIPTION The active ingredient in Ipratropium Bromide Nasal Solution (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:



$Br^- \cdot H_2O$

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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.

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is a metered-dose, manual pump spray unit which delivers 21 mcg (70 µL) ipratropium bromide per spray on an anhydrous basis in an isotonic, aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 345 sprays.

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

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 patients or perennial rhinitis patients.

Distribution: Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and α1-acid glycoprotein. Its blood/plasma concentration ratio was estimated to be about 0.89. Studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier.

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

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

Pediatrics: Following administration of 42 mcg of ipratropium bromide per nostril two or three times a day in perennial rhinitis patients 6-18 years old, the mean amounts of the total dose excreted unchanged in the urine (8.6 to 11.1%) were higher than those reported in adult volunteers or adult perennial rhinitis patients (3.7 to 5.6%). Plasma ipratropium concentrations were relatively low (ranging from undetectable up to 0.49 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 populations.

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 in patients with induced-colds, Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (84 mcg/nostril four times a day), had no significant effects on pupillary diameter, heart rate or systolic/diastolic blood pressure.

Two nasal provocation trials in perennial rhinitis patients (n=44) using ipratropium bromide nasal spray showed a dose dependent increase in inhibition of methacholine induced nasal secretion with an onset of action within 15 minutes (time of first observation).

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
The clinical trials for Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) were conducted in patients with nonallergic perennial rhinitis (NAPR) and in patients with allergic perennial rhinitis (APR). APR patients were those who experienced symptoms of nasal hypersecretion and nasal congestion or sneezing when exposed to specific perennial allergens (e.g., dust mites, molds) and were skin test positive to these allergens. NAPR patients were those who experienced symptoms of nasal hypersecretion and nasal congestion or sneezing throughout the year, but were skin test negative to common perennial allergens.

In four controlled, four and eight week comparisons of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (42 mcg per nostril, two or three times daily) with its vehicle, in patients with allergic or nonallergic perennial rhinitis, there was a statistically significant decrease in the severity and duration of rhinorrhea in the ipratropium bromide group throughout the entire study period. An effect was seen as early as the first day of therapy. There was no effect of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) on degree of nasal congestion, sneezing or postnasal drip. The response to Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) did not appear to be affected by the type of perennial rhinitis (NAPR or APR), age, or gender. No controlled clinical trials directly compared the efficacy of BID versus TID treatment.

INDICATIONS AND USAGE Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) does not relieve nasal congestion, sneezing or postnasal drip associated with allergic or nonallergic perennial rhinitis.

CONTRAINDICATIONS Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) 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 Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) 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 Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) comes into direct contact with the eyes. Patients should be instructed to avoid spraying Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in or around their 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. Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ipratropium bromide 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 190 and 95 times the maximum recommended daily intranasal dose in adults, respectively, and approximately 110 and 60 times the maximum recommended daily intranasal dose in children, respectively, on a mg/m² 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 1,600 times the maximum recommended daily intranasal dose in adults on a mg/m² basis). At an oral dose of 500 mg/kg (approximately 16,000 times the maximum recommended daily intranasal dose in adults on a mg/m² 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 160, 32,000, and 8,000 times the maximum recommended daily intranasal dose in adults on a mg/m² basis. Inhalation reproduction studies were conducted in rats and

ATTENTION PHARMACIST – DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

DEY

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)

Patient's Instructions for Use

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with allergic and nonallergic perennial rhinitis for adults and children age 6 years and older. Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) does not relieve nasal congestion, sneezing or postnasal drip associated with allergic or nonallergic perennial rhinitis. Read complete instructions carefully and use only as directed.

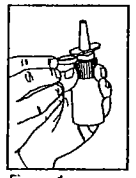

Figure 1

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.

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MAR 31 2003

2. The nasal spray pump must be primed before Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is used for the first time. To prime the pump, hold the bottle with your thumb at the base and your index and middle fingers on the white shoulder area. Make sure the bottle points upright and away from your eyes. Press your thumb firmly and quickly against the bottle seven times (Figure 2). The pump is now primed and can be used. Your pump should not have to be reprimed unless you have not used the medication for more than 24 hours; repriming the pump will only require two sprays. If you have not used your nasal spray for more than seven days, repriming the pump will require seven sprays.

Figure 2

3. Before using Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray), blow your nose gently to clear your nostrils if necessary.

Figure 3

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.

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. At some time before the medication is completely used up, you should consult your physician or pharmacist to determine whether a refill is needed. You should not take extra doses or stop using Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) without consulting your physician.

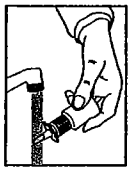


Figure 4

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:
Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) as prescribed by your physician. For most patients, some improvement in runny nose is usually apparent following the first full day of treatment with Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray). Some patients may require up to two weeks of treatment to obtain maximum benefit.

Do not spray Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in your eyes. Should this occur, immediately flush your eye with cool tap water for several minutes. If you accidentally spray Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in your eyes, you may experience a temporary blurring of vision and increased sensitivity to light, which may last a few hours. Should eye pain or blurred vision occur, contact your doctor.
Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.
You should not use this drug if you have glaucoma or difficult urination due to an enlargement of the prostate, unless directed by a physician.

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) should not be used during pregnancy or breast feeding unless directed by a physician. It is not known whether ipratropium bromide is excreted in human milk; however, many drugs are excreted in human milk.

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

DEY

Manufactured by
Dey
Napa, CA 94558

03-560-01 November 2001

rabbits at doses of 1.5 and 1.8 mg/kg, respectively, (approximately 50 and 120 times, respectively, the maximum recommended daily intranasal dose in adults on a mg/m² 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 2,900 times the maximum recommended daily intranasal dose in adults on a mg/m² 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 Nasal Solution 0.03% (Nasal Spray) 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 Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is administered to a nursing woman.

Pediatric Use The safety of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) at a dose of two sprays (42 mcg) per nostril two or three times daily (total dose 168 to 252 mcg/day) has been demonstrated in 77 pediatric patients 6-12 years of age in placebo-controlled, 4-week trials and in 55 pediatric patients in active-controlled , 6 month trials. The effectiveness of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) for the treatment of rhinorrhea associated with allergic and non allergic perennial rhinitis in this pediatric age group is based on an extrapolation of the demonstrated efficacy of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in adults with these conditions and the likelihood that the disease course, pathophysiology, and the drug's effects are substantially similar to that of the adults. The recommended dose for the pediatric population is based on within and cross-study comparisons of the efficacy of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in adults and pediatric patients and on its safety profile in both adults and pediatric patients. The safety and effectiveness of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in patients under 6 years of age have not been established.

ADVERSE REACTIONS Adverse reaction information on Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) in patients with perennial rhinitis was derived from four multicenter, vehicle-controlled clinical trials involving 703 patients (356 patients on ipratropium bromide and 347 patients on vehicle), and a one-year, open-label, follow-up trial. In three of the trials, patients received Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) three times daily, for eight weeks. In the other trial, Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) was given to patients two times daily for four weeks. Of the 285 patients who entered the open-label, follow-up trial, 232 were treated for 3 months, 200 for 6 months, and 159 up to one year. The majority (>86%) of patients treated for one year were maintained on 42 mcg per nostril, two or three times daily, of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray).

The following table shows adverse events, and the frequency that these adverse events led to the discontinuation of treatment, reported for patients who received Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) at the recommended dose of 42 mcg per nostril, or vehicle two or three times daily for four or eight weeks. Only adverse events reported with an incidence of at least 2.0% in the ipratropium bromide group and higher in the ipratropium bromide group than in the vehicle group are shown.

	% of Patients Reporting Events+			
	Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) (N=356)		Vehicle Control (N=347)	
	Incidence%	Discontinued%	Incidence%	Discontinued%
Headache	9.8	0.6	9.2	0
Upper respiratory tract infection	9.8	1.4	7.2	1.4
Epistaxis[1]	9.0	0.3	4.6	0.3
Rhinitis*				
Nasal dryness	5.1	0	0.9	0.3
Nasal irritation[2]	2.0	0	1.7	0.6
Other nasal symptoms[3]	3.1	1.1	1.7	0.3
Pharyngitis	8.1	0.3	4.6	0
Nausea	2.2	0.3	0.9	0

+ This table includes adverse events which occurred at an incidence rate of at least 2.0% in the ipratropium bromide group and more frequently in the ipratropium bromide group than in the vehicle group.
[1] Epistaxis reported by 7.0% of Ipratropium bromide patients and 2.3% of vehicle patients, blood tinged nasal mucus by 2.0% of ipratropium bromide patients and 2.3% of vehicle patients.
[2] Nasal irritation includes reports of nasal itching, nasal burning, nasal irritation and ulcerative rhinitis.
[3] Other nasal symptoms include reports of nasal congestion, increased rhinorrhea, increased rhinitis, posterior nasal drip, sneezing, nasal polyps and nasal edema.
* All events are listed by their WHO term; rhinitis has been presented by descriptive terms for clarification.

Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) was well tolerated by most patients. The most frequently reported nasal adverse events were transient episodes of nasal dryness or epistaxis. These adverse events were mild or moderate in nature, none was considered serious, none resulted in hospitalization and most resolved spontaneously or following a dose reduction. Treatment for nasal dryness and epistaxis was required infrequently (2% or less) and consisted of local application of pressure or a moisturizing agent (e.g., petroleum jelly or saline nasal spray). Patient discontinuation for epistaxis or nasal dryness was infrequent in both the controlled (0.3% or less) and one-year, open-label (2% or less) trials. There was no evidence of nasal rebound (i.e., a clinically significant increase in rhinorrhea, posterior nasal drip, sneezing or nasal congestion severity compared to baseline) upon discontinuation of double-blind therapy in these trials.

Adverse events reported by less than 2% of the patients receiving Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) during the controlled clinical trials or during the open-label follow-up trial, which are potentially related to ipratropium bromide's local effects or systemic anticholinergic effects include: dry mouth/throat, dizziness, ocular irritation, blurred vision, conjunctivitis, hoarseness, cough and taste perversion. Additional anticholinergic effects noted with other ipratropium bromide dosage forms (Ipratropium bromide inhalation solution, Ipratropium bromide inhalation aerosol and Ipratropium Bromide Nasal Solution 0.06% (Nasal Spray)) include: precipitation or worsening of narrow angle glaucoma, urinary retention, prostatic disorders, tachycardia, constipation, and bowel obstruction.

There were infrequent reports of skin rash in both the controlled and uncontrolled clinical studies. Other allergic-type reactions such as angioedema of the throat, tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported with other ipratropium bromide products.

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

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 four bottles of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray)) 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 mmHg 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 16,000 and 9,500 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis), 1,700 mg/kg in rats (approximately 55,000 and 32,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis); and 400 mg/kg in dogs (approximately 43,000 times and 25,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m² basis).

DOSAGE AND ADMINISTRATION The recommended dose of Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is two sprays (42 mcg) per nostril two or three times daily (total dose 168 to 252 mcg/day) for the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Optimum dosage varies with the response of the individual patient.

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 Ipratropium Bromide Nasal Solution 0.03% (Nasal Spray) is supplied in a white high density polyethylene (HDPE) bottle fitted with a white and clear metered nasal spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. It contains 31.1g of product formulation, 345 sprays, each delivering 21 mcg (70 µL) of ipratropium per spray, or 28 days of therapy at the maximum recommended dose (two sprays per nostril three times a day).

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

Do not spray in the eyes.

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

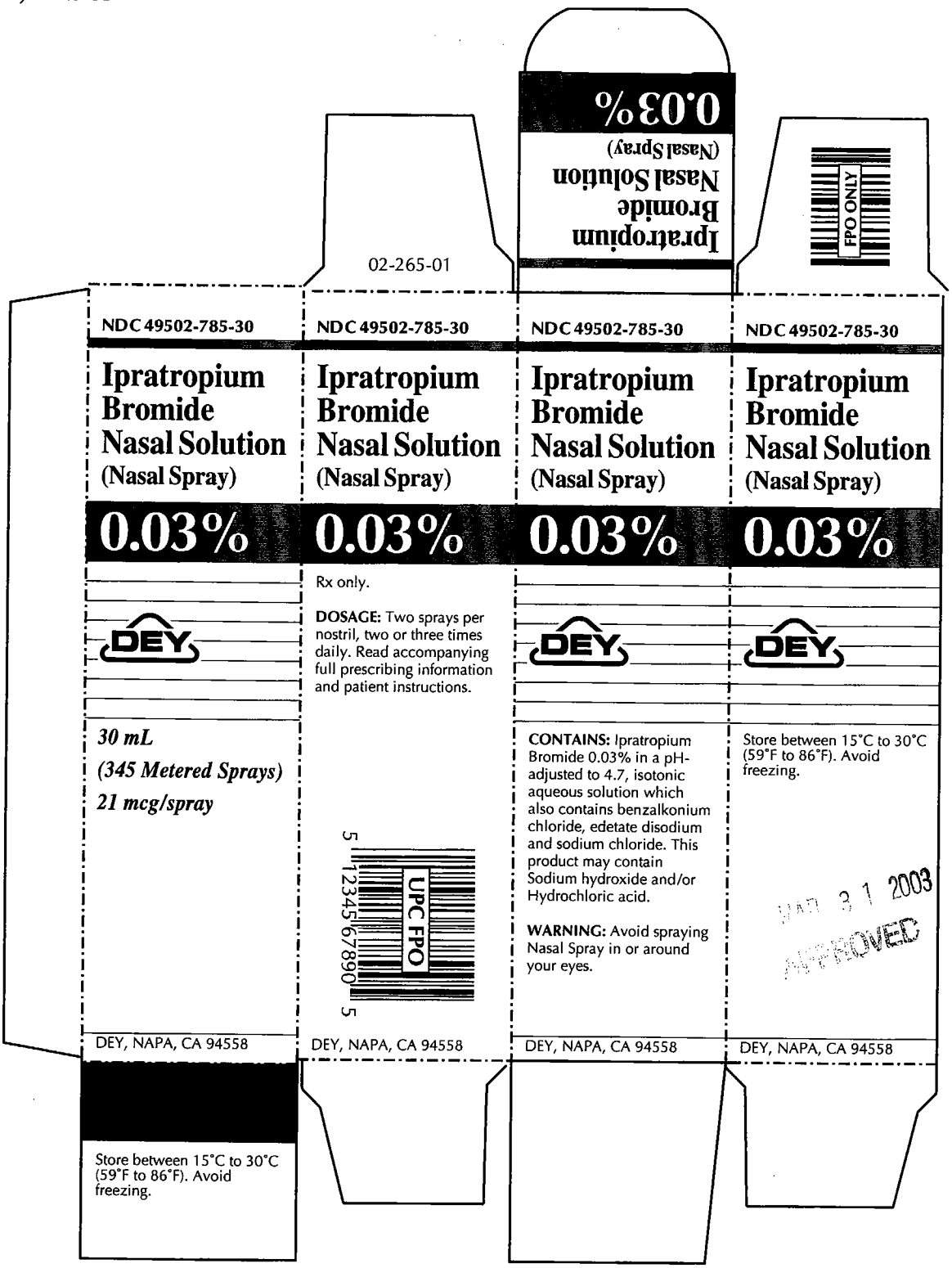
Rx only.

DEY

DEY
Napa, CA 94558

03-560-01 Printed: November 2001

A (round #12) 11-15-01



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-552

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-552 **Date of Submission: February 22, 1999**

Applicant's Name: Dey Labs

Established Name: Ipratropium Bromide Nasal Solution, 0.03%

Labeling Deficiencies:

1. GENERAL COMMENT

   a. The established name for this product is Ipratropium Bromide Nasal Solution. Revise all labels and labeling accordingly. Note: "Spray" may appear on labels and labeling separate and away from the established name.

2. CONTAINER (30 mL bottle)

   a. Revise "CAUTION: Federal law…" statement to read "Rx only".

   b. Include the following statement:

      This product may contain Sodium hydroxide and/or Hydrochloric acid.

   c. Revise your storage recommendation to read as follows:

      Store between 15°C to 30°C (59°F to 86°F).

   d. See comment (a) under GENERAL COMMENTS.

3. CARTON (1 X 30 mL)

   a. See comments under CONTAINER.

4. PHYSICIAN'S INSERT

   a. TITLE

      We encourage the inclusion of "Rx only" in this section.

b. Please note, the most recent labeling for the reference listed drug, ATROVENT® Nasal Spray, 0.03%, was approved April 1, 1998. Please revise your insert labeling to be in accord.

c. See comment (a) under GENERAL COMMENTS.

5. PATIENT PACKAGE INSERT

a. Revise your storage recommendation to read as follows:

Store between 15°C to 30°C (59°F to 86°F).

b. See comment (a) under GENERAL COMMENTS.

Please revise your container labels and carton, physician's insert and patient package insert labeling, as instructed above, and submit 12 copies of final printed container labels, along with 12 copies of carton labeling. Submit 4 copies of draft physician's insert and patient package insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels: (30 mL)

Carton Labeling: (1 x 30 mL, shrink wrapped in trays of 12)

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ATROVENT® Nasal Spray, 0.03%

NDA Number: 20-393/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.03%
NDA Firm: Boerhinger Ingelheim

Date of Approval of NDA Insert and supplement #: April 1, 1998
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:

Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is ATROVENT® Nasal Spray (Boerhinger Ingelheim; NDA#20-393/S-001; Approved April 1, 1998.

2. Patents/Exclusivities

   Patent#438504 - U-119 (Treatment of Nasal Hypersecretion)
   Expires May 24, 2000
   Exclusivity- New Drug Formulation
   Expired October 20, 1998
   Exclusivity- I-223 (Use in the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 to 11)
   Expires April 1, 2001.

   The applicant certifies that it will not market until after the expiration dates of both the patent and exclusivity. See Vol. 1.1, page 3.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 253.

4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 264.

5. Container/Closure

   A high-density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be ——— stamped with lot number and expiration date. See Vol. 1.2, page 455.

6. Finished Product

   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. See Vol. 1.1, page 26A.

7. Product Line

Supplied as 30 mL of solution in a HDPE bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. The 30 mL bottle of ipratropium bromide nasal spray is designed to deliver 345 sprays of 0.07 mL each (21 mcg), or 28 days of therapy at the maximum recommended dose (two sprays in each nostril three times a day). See Vol. 1.1, page 26A.

8. Components/compositon

Innovator:
Active: Ipratropium Bromide, 0.03%
Inactive: benzalkonium chloride
Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water
pH adjusted to 4.7

Applicant:
Active: Ipratropium Bromide, 0.03%
Inactive: Benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid

See Vol. 1.1, page 6 and page 40.

9. Storage/Dispensing

NDA: 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 eyes.

ANDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.
See Vol. 1.1, page 26A.

Date of Review: March 24, 1999
Date of Submission: February 22, 1999

Reviewer: J Watkins Date: 4/14/99

Team Leader: Date:

John J. Grace 4-15-1999

cc:

ANDA: 75-552
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSAM\DEY\LTRS&REV\75552na1.l
Review

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-552 **Date of Submission: April 27, 2001**
Applicant's Name: Dey Labs
Established Name: Ipratropium Bromide Nasal Solution, 0.03%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (30 mL)
Carton Labeling: (1 x 30 mL, shrink wrapped in trays of 12)
Professional Package Insert Labeling: # 03-560-01 r/Mar.2001 satisfactory in FPL submitted April 27, 2001 vol. 2.1 page 01316
Patient Package Insert Labeling: attached to Insert satisfactory in FPL submitted April 27, 2001
Revisions needed post-approval: Need to revise name to Ipratropium Bromide Nasal Solution, 0.03% (Nasal Spray). Firm elected not to revise their product name. April 27, 2001 cover letter.
BASIS OF APPROVAL:
No Unexpired patent or exclusivity issues.
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: ATROVENT® Nasal Spray, 0.03%
NDA Number: 20-393/S-001
NDA Drug Name: Ipratropium Bromide Nasal Spray, 0.03%
NDA Firm: Boerhinger Ingelheim
Date of Approval of NDA Insert and supplement #: April 1, 1998
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator carton labeling in jacket.
REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X

Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is ATROVENT® Nasal Spray (Boerhinger Ingelheim; NDA#20-393/S-001; Approved April 1, 1998.
2. Patents/Exclusivities
   Patent#438504 – U-119 (Treatment of Nasal Hypersecretion)
   Expires May 24, 2000

Exclusivity- New Drug Formulation
Expired October 20, 1998

Exclusivity- I-223 (Use in the symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 to 11)
Expires April 1, 2001.

The applicant certifies that it will not market until after the expiration dates of both the patent and exclusivity. See Vol. 1.1, page 3.

3. The product is manufactured by Dey, 2751 Napa Valley Corporate Drive, Napa, CA 94558. See Vol. 1.1, page 253.
4. Outside firms are utilized for testing purposes only. See Vol. 1.2, page 264.
5. Container/Closure
A high-density polyethylene bottle and nasal pump assembly. The bottle has a pre-printed pressure sensitive label that will be ——— stamped with lot number and expiration date. See Vol. 1.2, page 455.
6. Finished Product
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. See Vol. 1.1, page 26A.
7. Product Line
Supplied as 30 mL of solution in a HDPE bottle fitted with a metered nasal spray pump, a safety clip to prevent accidental discharge of the spray, and a clear plastic dust cap. The 30 mL bottle of ipratropium bromide nasal spray is designed to deliver 345 sprays of 0.07 mL each (21 mcg), or 28 days of therapy at the maximum recommended dose (two sprays in each nostril three times a day). See Vol. 1.1, page 26A.
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Innovator:
Active: Ipratropium Bromide, 0.03%
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Edetate disodium
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Purified water
pH adjusted to 4.7

Applicant:
Active: Ipratropium Bromide, 0.03%
Inactive: Benzalkonium chloride
Edetate disodium
Sodium chloride
Purified water
Sodium hydroxide
Hydrochloric acid
See Vol. 1.1, page 6 and page 40.
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NDA: 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 eyes.
ANDA: Store tightly closed between 59°F (15°C) and 86°F (30°C). Avoid freezing. Keep out of reach of children. Avoid spraying in or around the eyes.
See Vol. 1.1, page 26A.

Date of Review: August 2, 2001 **Date of Submission: April 27, 2001**

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cc:
ANDA: 75-552
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:/firmsam/dey/let&rev/75552ap.L
Review

APayne 8/2/01
JGrace 9/17/2001