CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-156

Generic Name: Ipratropium Bromide Nasal Solution, 0.03%

Sponsor: Apotex Corporation

Approval Date: April 18, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

APPROVAL LETTER

ANDA 76-156

APR 18 2003

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: Novex Pharma
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 30, 2001, 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 a 30 mL bottle fitted with a metered nasal spray pump.

Reference is also made to your amendments dated July 6, 2001; March 6, October 25, and December 20, 2002; and February 17, February 18, February 21, March 6, and March 17, 2003.

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 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.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation process has been completed. We acknowledge your commitment to cooperate with the agency to satisfactorily resolve any deficiencies that may be identified with the validation process.

Sincerely yours,

/s/

Gary Buehler 4/18/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

FINAL PRINTED LABELING(S)

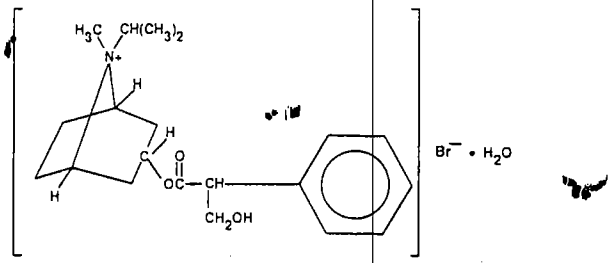
PRESCRIBING INFORMATION

IPRATROPIUM BROMIDE NASAL SOLUTION, .03%
Nasal Spray

℞ Only

DESCRIPTION

The active ingredient in ipratropium bromide nasal solution 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. Ipratropium bromide nasal solution, .03% 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. It also contains the following inactive ingredients: benzalkonium chloride, edetate disodium, purified water and sodium chloride. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH to 4.2-5.2. 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 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 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 population.

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

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

Pharmacodynamics: In two single-dose trials (n=17), doses up to 336 mcg of ipratropium bromide did not significantly affect pupillary diameter, heart rate, or systolic/diastolic blood pressure. Similarly, in patients with induced-colds, ipratropium bromide nasal solution, .06% (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 solution 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, .03% 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, .03% (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, .03% on degree of nasal congestion, sneezing or postnasal drip. The response to ipratropium bromide nasal solution, .03% 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, .03% 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, .03% does not relieve nasal congestion, sneezing or postnasal drip associated with allergic or nonallergic perennial rhinitis.

CONTRAINDICATIONS

Ipratropium bromide nasal solution, .03% 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, .03% 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, .03% comes into direct contact with the eyes. Patients should be instructed to avoid spraying ipratropium bromide nasal solution, .03% 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. Ipratropium bromide nasal solution, .03% 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/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 1,600 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

PHARMACIST TEAR AT PERFORATION AND GIVE TO PATIENT

PATIENT'S INSTRUCTIONS FOR USE

Ipratropium Bromide Nasal Solution, .03% (Nasal Spray)

Ipratropium Bromide Nasal Solution, .03% is indicated for the symptomatic relief of rhinorrhea (runny nose) associated with allergic and nonallergic perennial rhinitis in adults and children age 6 years and older. Ipratropium Bromide Nasal Solution, .03% 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.

Figure 2

2. The nasal spray pump must be primed before Ipratropium Bromide Nasal Solution, .03% 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 3

3. Before using Ipratropium Bromide Nasal Solution, .03%, 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.

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, .03% 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.

decrease the conception rate.

Pregnancy

TERATOGENIC EFFECTS Pregnancy Category B. Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1000 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/m^2 basis. Inhalation reproduction studies were conducted in rats and 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/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 2,900 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 nasal solution, .03% 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, .03% is administered to a nursing woman.

Pediatric Use

The safety of ipratropium bromide nasal solution, .03% 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, .03% for the treatment of rhinorrhea associated with allergic and nonallergic perennial rhinitis in this pediatric age group is based on an extrapolation of the demonstrated efficacy of ipratropium bromide nasal solution, .03% 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, .03% 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, .03% in patients under 6 years of age have not been established.

ADVERSE REACTIONS

Adverse reaction information on ipratropium bromide nasal solution, .03% 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, .03% three times daily, for eight weeks. In the other trial, ipratropium bromide nasal solution, .03% 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, .03%.

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, .03% 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 .03% (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 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, .03% 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 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, .03% 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, .06%) 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, .03%) 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/m^2 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/m^2 basis), and 400 mg/kg in dogs (approximately 43,000 and 25,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

The recommended dose of ipratropium bromide nasal solution, .03% 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, .03% 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 (NDC 60505-0826-1). It contains 31.1 g 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 tightly closed at 25°C (77°F); excursions permitted to 15-30°C (59-86°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.

Manufactured by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Manufactured for:
Apotex Corp.
Weston, FL
33326

129939
February 2002

Caution:
Ipratropium Bromide Nasal Solution, .03% is intended to relieve your rhinorrhea (runny nose) with regular use. It is therefore important that you use Ipratropium Bromide Nasal Solution, .03% as prescribed by your physician. For most patients, some improvement in runny nose is usually apparent during the first full day of treatment with Ipratropium Bromide Nasal Solution, .03%. Some patients may require up to two weeks of treatment to obtain maximum benefit.

Do not spray Ipratropium Bromide Nasal Solution, .03% 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, .03% 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, .03% should not be used during pregnancy or breast feeding, unless directed by a physician. It is not known whether ipratropium bromide is excreted in human milk; however, many drugs are excreted in human milk.

Storage:
Store tightly closed at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid freezing. Keep out of reach of children.

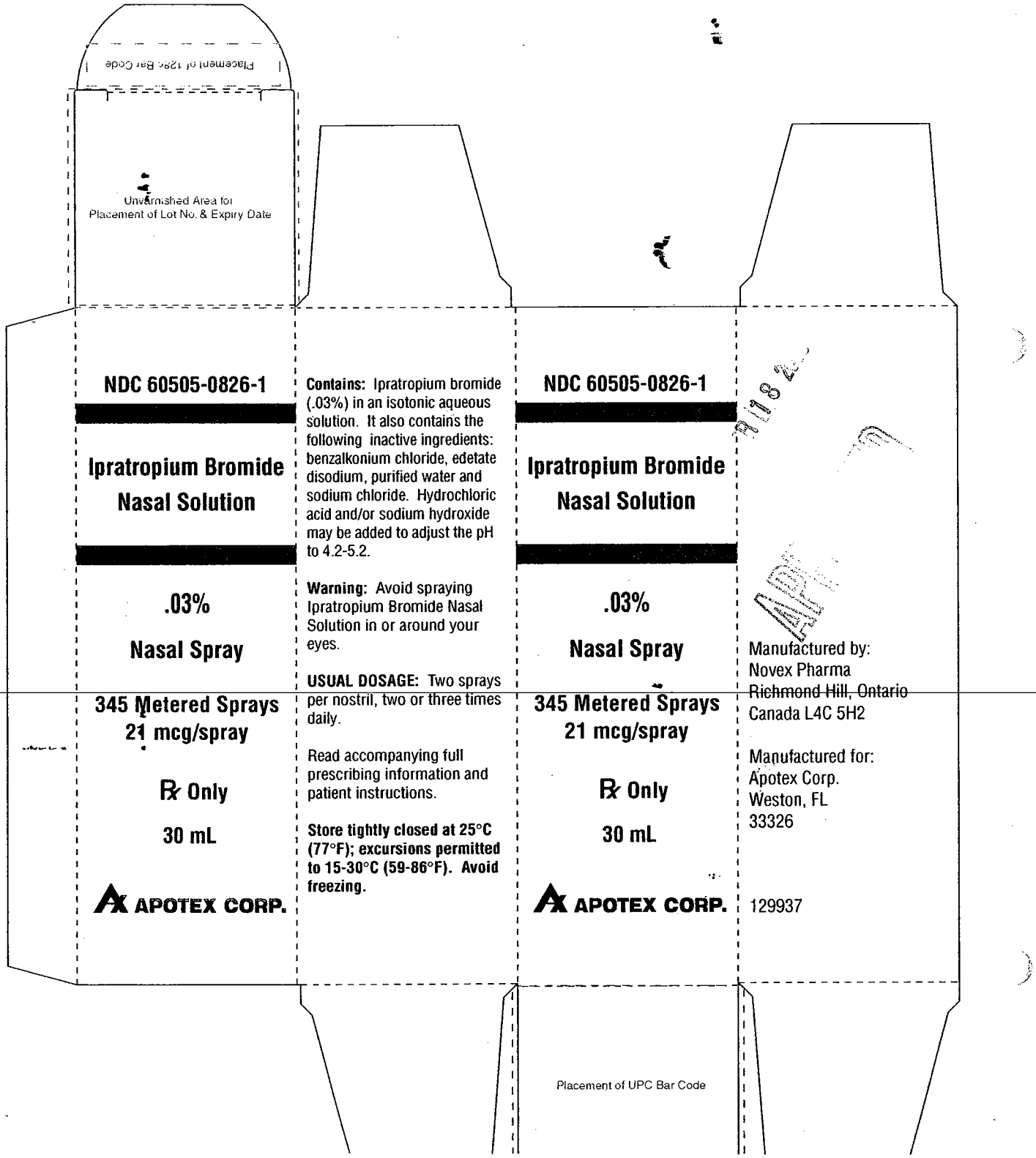
Manufactured by:
Novex Pharma
Richmond Hill, Ontario
Canada L4C 5H2

Manufactured for:
Apotex Corp.
Weston, FL 33326

129939
February 2002

NOVEX PHARMA 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIALS / LABEL STANDARD SPECIFICATIONS			Date February 05, 2002
Label Number 129937	Product Name Ipratropium Bromide Nasal Spray .03% - 30 mL Carton		Change: New
Printing	Size 40 x 40 x 122.5 mmm Van Wyck Carton Drawing # 973E, Rev. #2	Colour (s) Black Blue - 300C UV Varnish	
Caliper			
Prepared by: **Carol Vincent**	Date: **02/06/02**	Reg. Affairs Revision No.: 0	☐ AS IS ☐ NEW PROOF REQ.



NOVEX PHARMA 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIALS / LABEL STANDARD SPECIFICATIONS				Date: January 21, 2002
Label Number: 129935	Product Name: Ipratropium Bromide Nasal Spray, 0.03% - Bottle Label			Label Size: 36.3855 x 88.9 mm
Printing: Flexopress	Paper Stock: Satin Litho	Web Direction: Label on OUTSIDE of roll. Copy printed WITH the roll. Left side of label OFF FIRST. (PRINTING READS THIS WAY)	Colour (s): Black, Blue 300C, UV Varnish	Label: Novex Text Draft
Caliper: 60#	Adhesive: Permanent			Draft/Issue: Change: New Rev. 0
Prepared by: **Carol Vincent**		Date: **02/06/02**	Reg Affairs Revision No.: 0	☐ AS IS ☐ NEW PROOF REQ.

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APR 18 2003

APPROVED
APR 18 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

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76-156

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-156 Date of Submission: March 30, 2001
Applicant's Name: Novex Pharma : US agent Apotex
Established Name: Ipratropium Bromide Nasal solution, 0.03% (Nasal Spray)

Labeling Deficiencies:

1. GENERAL COMMENTS: Please revise the name of the product to read as follows: Ipratropium Bromide Nasal Solution, .03% (Nasal Spray)
2. CONTAINER - 345 metered sprays, 30 mL - 5.2. It also contains the following inactive ingredients benzalkonium... In addition, your listing of inactives is incomplete. You did not add the pH adjustors. Please be consistent with your composition statement. Please alphabetized your inactive ingredients.
3. CARTON – see comment under CONTAINER. In addition, the product name and strength should also appear of the top panel.
4. INSERT –DESCRIPTION, 2nd paragraph – 5.2. It also contains the following inactive ingredients benzalkonium... In addition, please alphabetized your inactive ingredients.
5. PATIENT INFORMATION sheet – See General Comment above.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

/S/

Wm. Peter Rickman
Acting 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: 345 metered sprays (30 mL)
Carton Labeling: 345 metered sprays (30 mL)
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA 20-393

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4385048	May 24, 2000	u-119	Treatment of nasal hypersection	P-II	Use in labeling

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling Impact
I-223	April 01, 2001	Symptomatic relief of rhinorrhea associated with allergic and nonallergic perennial rhinitis in children age 6 – 11 yrs	Indication in labeling

Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form: Atrovent
NDA Number: 20-393
NDA Drug Name: Ipratropium bromide nasal spray 0.03%
NDA Firm: Boehringer Ingelheim
Date of Approval of NDA Insert and supplement #: S-01, approved Oct. 8, 1998.
Has this been verified by the MIS system for the NDA? Yes No
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: sample in jackets
Basis of Approval for the Carton Labeling: sample in jackets
Other Comments:

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	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?			
Packaging			X
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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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: The RLD pH is 4.7 were as the generic applicant as a range which covers 4.7 but is a range ok (4.2-5.2).

FOR THE RECORD:

1. Review based on the labeling of Atrovent (NDA 20-393; boehring; revised 4/98 ; approved Oct 8, 1998 .
2. Patent/ Exclusivities3. Paragraph II filed by applicant. See details above.
3. Storage Conditions:

   NDA – Store tightly closed between 15- 30C avoid freezing, keep out of reach of children. Do not spray in eyes.

   ANDA - same. Store tightly closed at 25C, excursion premitted to 15-30. Avoid freezing. Keep out of reach of children. Do not spray in eyes.

   USP -
4. Dispensing Recommendations:

   NDA – dispensed patient instruction sheet with product.

ANDA – same.
USP -

5. Scoring: Not applicable
NDA -
ANDA -
USP -

6. Product Line:
The innovator markets their product in in white HDPE bottle nasal spray with green safety clip., 345 sprays, 30 mL.
The applicant proposes to market their product in same

7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3583 red (Volume 1.1) .

9. Manufactured by Novex in Canada for Apotex Corp in Weston, Fl.

Date of Review: June 11, 2001 **Date of Submission: March 30, 2001**

cc: ANDA: 76-156
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V: firmsnz/Novex/lets&rev/76156na1.L
Review

/S/ 6/11/01
/S/ 6/11/2001

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 76-156

3. NAME AND ADDRESS OF APPLICANT

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Ipratropium Bromide

13. DOSAGE FORM

Metered Nasal Spray

14. STRENGTH(s)

0.03%, 0.021 mg/70 µL spray

10. PHARMACOLOGICAL CATEGORY

Anticholinergic agent for symptomatic relief of rhinorrhea associated with the common cold

11. Rx or OTC Rx

4. LEGAL BASIS FOR SUBMISSION

Atrovent® Nasal Spray 0.03%, NDA 20-393, Boehringer Ingelheim Pharmaceuticals, Inc.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to A1.9 (1.2 to 1.7 are Bio only.):

03/30/01 Original submission
04/26/01 Acknowledgement - acceptable for filing 4/4/01

Vol. A2.1

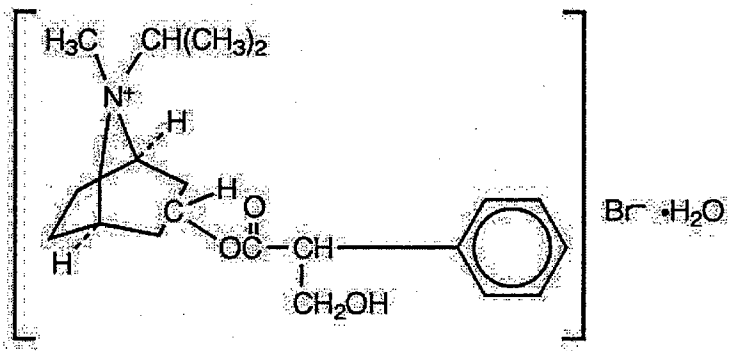
Bio amendment (Received 07/17/01)

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

I have reviewed 76-155, Ipratropium Bromide Nasal Spray, 0.06%, Novex Pharma.

15. CHEMICAL NAME AND STRUCTURE

The active ingredient is 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

16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

23.A, 23.B, 25, 26, 28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Novex Pharma commits to the resolution of any issues identified in the methods validation process after approval. We will schedule the study after the test method issues are resolved.

32. LABELING

The labeling was found **deficient** by Angela Payne 6/11/01.

33. ESTABLISHMENT INSPECTION

The EER is pending, as of 8/7/01.

34. BIOEQUIVALENCE STATUS

COMIS shows the assignment open, as of 8/7/01.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-155 is **NOT APPROVED - MAJOR AMENDMENT requested.**

19. REVIEWER: DATE COMPLETED:

Eugene L. Schaefer, Ph.D. 8/7/01

Revised on 8/8/01, based on comments from Dr. Paul Schwartz, Deputy Division Director.

Redacted 29

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 76-156

3. NAME AND ADDRESS OF APPLICANT

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. LEGAL BASIS FOR SUBMISSION

Atrovent® Nasal Spray 0.03%, NDA 20-393, Boehringer Ingelheim Pharmaceuticals, Inc.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Ipratropium Bromide

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to A1.9 (1.2 to 1.7 are Bio only.):
03/30/01 Original submission
04/26/01 Acknowledgement - acceptable for filing 4/4/01
08/13/01 NA-Major

Vol. A2.1
07/06/01 Bio amendment

Vol. B3.1
03/06/02 Bio amendment

Vol. A4.1 and A4.2
03/11/02 Major amendment (**the subject of this review**)

10. PHARMACOLOGICAL CATEGORY

Anticholinergic agent for symptomatic relief of rhinorrhea associated with the common cold

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

76-155, Ipratropium Bromide Nasal Spray, 0.06%, Novex Pharma.

13. DOSAGE FORM

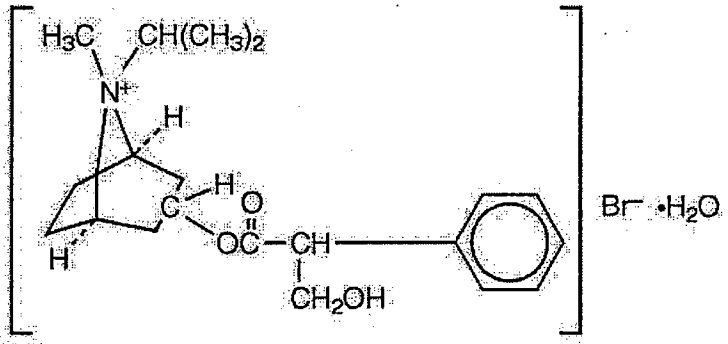
Metered Nasal Spray

14. STRENGTH(s)

0.03%, 0.021 mg/70 µL spray

15. CHEMICAL NAME AND STRUCTURE

The active ingredient is 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

16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Novex Pharma commits to the resolution of any issues identified in the methods validation process after approval. We will schedule the study after the test method issues are resolved.

32. LABELING

The labeling was found **satisfactory** by Angela Payne 4/10/02.

33. ESTABLISHMENT INSPECTION

The facilities were found to be **acceptable** 11/06/01.

34. BIOEQUIVALENCE STATUS

The review of the NC of 3/6/02 is pending, as of 7/22/02.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-155 is **NOT APPROVED - MINOR AMENDMENT requested.**

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	7/23/02	7/26/02

Redacted 29

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 76-156

3. NAME AND ADDRESS OF APPLICANT

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. LEGAL BASIS FOR SUBMISSION

Atrovent® Nasal Spray 0.03%, NDA 20-393, Boehringer Ingelheim Pharmaceuticals, Inc.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Ipratropium Bromide

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to A1.9 (1.2 to 1.7 are Bio only.):
03/30/01 Original submission
04/26/01 Acknowledgement - acceptable for filing 4/4/01
08/13/01 NA-Major

Vol. A2.1
07/06/01 Bio amendment

Vol. A3.1
03/06/02 Bio amendment

Vol. A4.1 and A4.2
03/11/02 Major amendment
08/08/02 NA-Minor
09/09/02 Minor amendment (**the subject of this review**)

10. PHARMACOLOGICAL CATEGORY

Anticholinergic agent for symptomatic relief of rhinorrhea associated with the common cold

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

76-155, Ipratropium Bromide Nasal Spray, 0.06%, Novex Pharma.

13. DOSAGE FORM

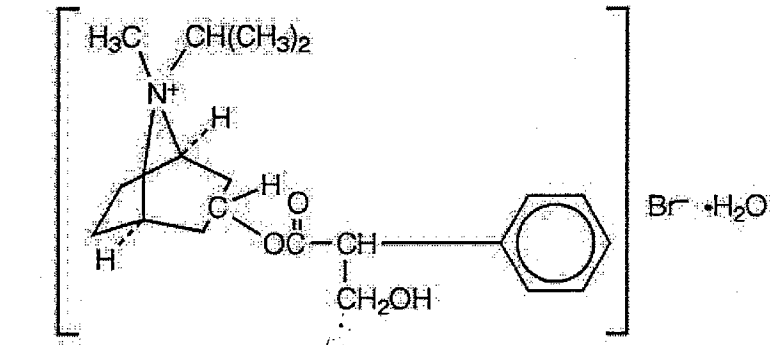
Metered Nasal Spray

14. STRENGTH(s)

0.03%, 0.021 mg/70 µL spray

15. CHEMICAL NAME AND STRUCTURE

The active ingredient is 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

16. RECORDS AND REPORTS N/A

17. COMMENTS

There are **deficiencies** in the following Review Points:

28.B, 29

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Novex Pharma commits to the resolution of any issues identified in the methods validation process after approval. We will schedule the study after the test method issues are resolved.

32. LABELING

The labeling was found **satisfactory** by Angela Payne 4/10/02.

33. ESTABLISHMENT INSPECTION

The facilities were found to be **acceptable** 11/06/01.

34. BIOEQUIVALENCE STATUS

The review of the Bio amendment dated 3/6/02 is pending, as of 10/28/02.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-156 is **NOT APPROVED - MINOR AMENDMENT requested.**

19. REVIEWER:	DATE COMPLETED:	REVISED:
Eugene L. Schaefer, Ph.D.	10/29/02	11/5/02

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-156

CHEMISTRY CLOSE

3. NAME AND ADDRESS OF APPLICANT

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. LEGAL BASIS FOR SUBMISSION

Atrovent® Nasal Spray 0.03%, NDA 20-393, Boehringer Ingelheim Pharmaceuticals, Inc.

5. SUPPLEMENT(s)
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to A1.9 (1.2 to 1.7 are Bio only.):
03/30/01 Original submission
04/26/01 Acknowledgement - acceptable for filing 4/4/01
08/13/01 NA-Major

Vol. A2.1
07/06/01 Bio amendment
08/08/01 Bio deficiencies were faxed to Apotex

Vol. A3.1
03/06/02 Bio amendment

Vol. A4.1 and A4.2:

03/11/02 Major amendment
08/08/02 NA-Minor

09/09/02 Minor amendment
11/26/02 NA-Minor

12/20/02 Minor amendment **(a subject of this review)**

02/04/03 Telecon re Spray Pattern limits
02/06/03 Telecon re GM-155 Spray Droplet Size Distribution
02/14/03 Telephone amendment in response to telecons of 02/04/03 and 02/06/03 (**a subject of this review**)
2/18/03 Bioequivalence Amendment
2/21/03 NC Updated 356h

10. PHARMACOLOGICAL CATEGORY

Anticholinergic agent for symptomatic relief of rhinorrhea associated with the common cold

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s) See DMF Checklist.

76-155, Ipratropium Bromide Nasal Spray, 0.06%, Novex Pharma.

13. DOSAGE FORM

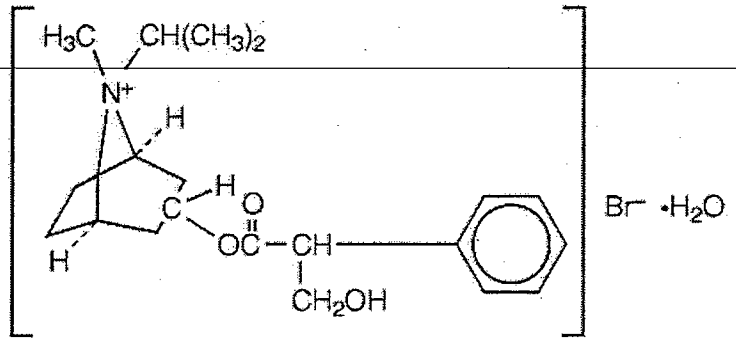
Metered Nasal Spray

14. STRENGTH(s)

0.03%, 0.021 mg/70 µL spray

15. CHEMICAL NAME AND STRUCTURE

The active ingredient is 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

16. RECORDS AND REPORTS N/A

17. COMMENTS

The chemistry issues have been resolved.

The conditions of the **other disciplines** are as follows:

25. MANUFACTURING AND PROCESSING (Microbiology)

A nasal spray is not required to be sterile.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Novex Pharma has committed to the resolution of any issues identified in the methods validation process after approval. The test method issues have been resolved and we are scheduling the study.

32. LABELING

The labeling was found **satisfactory** by Angela Payne 4/10/02.

33. ESTABLISHMENT INSPECTION

The facilities were found to be **acceptable** 11/06/01.

34. BIOEQUIVALENCE STATUS

The review of the Bio amendment dated 2/18/03 is pending.

18. CONCLUSIONS AND RECOMMENDATIONS

ANDA 76-156 is ready for approval except for methods validation and bioequivalence. Therefore, I recommend a **CHEMISTRY CLOSE**.

19. REVIEWER: DATE COMPLETED: REVISED:

Eugene L. Schaefer, Ph.D. 2/21/03

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 76-156

ADDENDUM

3. NAME AND ADDRESS OF APPLICANT
Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy MacDonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

4. LEGAL BASIS FOR SUBMISSION
Atrovent® Nasal Spray 0.03%, NDA 20-393, Boehringer Ingelheim Pharmaceuticals, Inc.

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Ipratropium Bromide

9. AMENDMENTS AND OTHER DATES:

Vol. A1.1 to A1.9 (1.2 to 1.7 are Bio only.):
03/30/01 Original submission

Vol. A4.1 and A4.2:
06/25/01 Bio telecon
10/25/02 Bio amendment
12/20/02 Minor amendment
01/15/03 Bio telecon
01/29/03 Bio telecon
02/04/03 Telecon re Spray Pattern limits
02/06/03 Telecon re GM-155 Spray Droplet Size Distribution
02/20/03 Bio deficiencies were faxed to firm.
02/21/03 NC Updated 356h: No longer in jacket.

Vol. A5.1:
02/17/03 Telephone amendment in response to telecons of 02/04/03 and 02/06/03: Transferred from A4.1
02/18/03 Bioequivalence Amendment: Transferred from A4.1

Vol. A6.1:
03/06/03 Bio amendment
03/17/03 Bio telephone amendment

12. RELATED IND/NDA/DMF(s)
76-155, Ipratropium Bromide Nasal Spray, 0.06%, Novex Pharma.

13. DOSAGE FORM
Metered Nasal Spray

14. STRENGTH(s)
0.03%, 0.021 mg/70 µL spray

17. COMMENTS

22. SYNTHESIS

I found DMF —— to be adequate on 2/4/03. There have been no further submissions, as of 4/9/03.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

Novex Pharma has committed to the resolution of any issues identified in the methods validation process after approval. A MV request was sent to Diane O'Brien on 2/28/03.

34. BIOEQUIVALENCE STATUS

Acceptable by Lin-Whei Chuang, 4/7/03.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA 76-156 is ready for approval. Methods validation is pending.

19. REVIEWER:
Eugene L. Schaefer, Ph.D.

DATE COMPLETED:
4/10/03

cc: ANDA 76-156
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/ELSchaefer, Chemist/ ES 4/10/03

HFD-625/MSmela, Team Leader/ /S/ 4/11/03

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F/T by:

CHEMISTRY REVIEW - APPROVED, methods validation pending.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

BIOEQUIVALENCE REVIEW(S)

Ipratropium Bromide

Nasal Spray, 0.03% (21 µg/spray)
ANDA # 76-156
Reviewer: Gur J.P. Singh
W. 76156SW.301

Novex Pharma

Richmond Hill, Canada
Submission Date:
March 30, and July 6, 2001

Review of Comparative Formulation and In Vitro Performance Data

Ipratropium Bromide Nasal Spray (IPBR NS) 0.03% is indicated for the relief of rhinorrhea associated with the common cold for adults and children age 12 years and older. The active drug is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The reference listed drug (RLD) is Atrovent[R] Nasal Spray, 0.03% (21 µg/spray) manufactured by Boehringer Ingelheim.

The RLD recommended dose is two sprays (42 µg) per nostril three or four times daily. The drug is supplied as solution in a ——— bottle fitted with a *metered nasal spray pump*. Each bottle is designed to deliver 345 metered sprays of 0.07 mL each (21 µg/spray of ipratropium bromide).

Division of Bioequivalence (DBE) evaluates equivalence of solution nasal sprays based on Q1 and Q2 sameness of formulations and comparable in vitro performance in drug delivery. The firm submitted supporting data on March 30, 2001. Based on a preliminary review of this application, the firm was requested to provide additional supporting data. The sponsor submitted the requested information on July 6, 2001. The following review is based on the data submitted on March 30 and July 6, 20001.

FORMULATION COMPARISON (not for release under FOI)

	mg/mL		
Ingredient	Test	Ref	Test/Ref
Ipratropium bromide*	0.3	0.3	1.00
Edetate disodium USP	—	—	—
Sodium chloride USP	—	—	—
Benzalkonium chloride NF	—	—	—
Sodium hydroxide NF	To adjust pH*	To adjust pH*	-
Hydrochloric acid NF	To adjust pH*	To adjust pH*	-
Purified water USP	q.s.	q.s.	

pH = — (Test) and —(Ref)

IN VITRO TESTING RECOMMENDATIONS

This application contains in vitro performance data for the lower of the two marketed strengths (0.03% and 0.06%) of IPBR NS. Novex uses same models of pumps and actuators for its IPBR NS, 0.03% and 0.06%. The firm has submitted full in vitro testing on its IPBR NS 0.06% (ANDA #76-155) and abbreviated testing on the 0.03% product.

Based on the Draft Nasal BA/BE guidance, only abbreviated testing is required for the lower strength, provided the sponsor uses the same pump and actuator for the lower- and higher-strength products. The testing recommendations for the multiple-strength solution nasal sprays in the Agency's draft Guidance are as follows:

TEST	STRENGTH	
	HIGHER	LOWER
Unit Dose Content	At Beg. & End	At Beg. & End
Priming	Recommended	Recommended
Tail Off	Recommended	Recommended
Laser Diffraction Analysis	At Beg. , Mid. & End	At Beg. Only
Cascade Impaction	At Beg. & End	Not Necessary
Spray Pattern	At Beg. & End	At Beg. Only
Plume Geometry	At Beg. Only	Not Necessary

Beg. and Mid. = Beginning and middle sectors of the product use life.

DRUG PRODUCTS

Test: Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03%, consisted of one lot of the drug solution formulation (Lot #0X210, Lot size [redacted] divided into three sublots using three separate batches of pumps (Novex Pharma QC Nos. 5633, 5634 and 5635).

Reference: Boehringer Ingelheim's Atrovent[R] Nasal Spray, 0.03%; Lots 819013B, 819014A and 819014B. The expiry dates for all three batches was 8/01.

COMPARABILITY OF SPRAY DEVICES

The pump supplier [redacted], has confirmed that the metered dose pump supplied for Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03% is identical to that used in Atrovent[R] Nasal Spray (also supplied by [redacted]. Physical comparative data with the test and reference metering devices were provided. Based on the July 6 amendment, comparative dimension of the test and reference product actuators are as follows:

Parameter	Dimension	
	Test	REF
Height	34.44 mm	33.87 mm
Outer Width	8.25 mm	8.37 mm
Inner Width	4.27 mm	4.97 mm
Orifice Diameter	260 μ	264 μ

IN VITRO PERFORMANCE TESTING

Procedures and Information Applicable to All Tests

All actuations of the nasal spray products were made using an automated actuator to actuate the nasal sprays in a reproducible manner. The actuator used designed by [redacted] for nasal spray actuation. The procedure used for operation of the actuator is described in SOP# GM-143 (pp. 121, vol. 1.1). The actuator operating conditions were as follows:

Dose time:	20 msec
Return Time:	30 msec
Hold Time:	0.5 sec
Actuation Force:	6.0 kg

Unit dose (Unit spray content) and uniformity of unit dose

Novex Pharma submitted data for the above-mentioned testing. The firm performed the uniformity of unit dose test using a stability-indicating method [Test Method No. TM-1132, vol. 1.1, pp. 139]. Since the labeled number of full medication doses per bottle is 345 sprays, the unit dose test was carried out on the entire bottle to determine the priming, re-priming and tail-off characteristics. According to *the Patient's Instructions for Use leaflet* for reference listed drug, each unit is primed by wasting seven actuations, and the unit should be re-primed by actuating the pump twice after 24 hours of non-use and by 7 actuations after 7 days of non-use.

The number of sprays required to prime the pump was determined by assaying the first ten sprays of each unit. A re-priming study was performed by leaving the bottle for 24 hours in upright position, and drug content of the next spray (No. 177) was then analyzed immediately. Additional studies to evaluate the performance of the pump after 7 days of non-use were also performed. Repriming studies included units stored in both horizontal and vertical positions.

For each test, ten (10) units from each of the three sub-lots of the test product and each of the three lots of the reference product were tested. Therefore, for each test a total of 30 units of the test product and 30 units of the reference product were tested.

The weight of individual sprays was also determined by weighing bottles before and after each spray collection, and the amount of drug per spray was determined by a validated —— analysis (LOQ= ——

The unit spray content data were reported for the beginning (actuation 8) and end of unit life (actuation 345). The following table provides a summary based on the reviewer's calculations.

Product	Sector	Mean		Variability (%CV)			T/R	p
		Arith.	Geo.	Intra-lot	Inter-lot	Total		
Test	Beg.	99.99	99.98	0.99-1.55	0.21	1.22	0.98 0.98	0.0004
	End	99.83	99.83	1.06-1.70	0.51	1.41	0.98 0.98	0.0008
Ref	Beg.	102.37	102.35	0.93-2.18	2.17	2.3		
	End	102.33	102.28	1.24-4.19	1.94	3.03		

The mean unit spray content data are expressed % of label claim based on arithmetic means. Outcome of the statistical analysis remains the same whether the data are expressed as % LC or amount spray.

Comments on the Unit Dose Data

1. For Novex's product, the geometric mean values at actuations 8 and 345 values are 2% lower than the corresponding reference product values. The test product exhibited slightly lower variability (%CV) than the reference product with regard to the unit dose data. The test/ref ratios are within the 90-111% limits employed hitherto by DBE for acceptance of nasal solution sprays.

2. The quantity of the drug assayed is based on each single spray. The minimum and maximum values for the test product show that the delivered doses fall within 95.5.3-106.3% of the labeled dose. The draft guidance recommends that based on the 'first tier' of testing (10 units), not more than one unit be outside 80-120% of the label claim, and none should be outside the 75-125%, and mean values should not outside 85-115%.

3. Based on the mean values, there was no change in the unit dose determined at the beginning and end sectors. Furthermore, the data did not show a particular trend in changes in variability through the container life.

4. Based on the data obtained, the test product is fully primed at the 6th spray (Figure 1, attachment). Prime retention was determined on the 177th spray by allowing the product to rest for a period of 24 hours or 7 days, followed by collecting the next spray without priming. Based on the data submitted, the test and reference products have the same prime retention characteristics.

5. The unit spray content data are based on both the [redacted] assay and gravimetric measurements. There is a good correlation between the quantity of the drug delivered per spray obtained by weight and that obtained by assay using an [redacted] method.

6. The tail off profile characterizes the decrease in emitted dose following delivery of the labeled number of actuations) based on the [redacted] assay (up to actuations 360) and by tabulating the spray weights up to actuation 460 (corresponding to full spray No. 165) to product exhaustion. Data given in Figure 2 (attachment) indicate that the test product delivers the labeled numbers of doses and its tail off is no more erratic than that of the reference product.

Droplet size distribution

a. Laser Diffraction

Droplet size determination was performed based on the Test Methods GM 155 (vol. 1.1) on 10 units from each of the 3 unit lots of test and reference products. Each unit was tested only at the beginning sector of unit life. Each unit was actuated at three distances relative to the [redacted] (3 cm, 6 cm, and 9 cm). At each distance, measurements were taken at different delay times. The three delay times characterize three regions in the plume life based on % transmission:

Plume Region	*Transmission Characteristic*
Plume formation (Initial)	Drops
Fully formed plume (Intermediate)	Stable
Plume dissipation (End)	Rises

The three separate regions constitute the sampling areas on which the droplet size distribution data are based. The delay times representing these regions vary with the actuation distance. In the July 6 amendment (vol. 2.1), the firm has submitted representative time history plots indicative of the three plume regions. Based on these graphs, the firm's selection of the three plume regions is acceptable.

The firm submitted D10, D50, D90 and SPAN data. Equivalence evaluation is based on D50 and SPAN data. A summary of these data based on the reviewer's calculations is as follows:

D50

Prod.	Distance (cm)	Plume Form.	Mean (N = 30) Arith.	Mean (N = 30) Geo.	Variability (%CV) Intra-lot (N=10)	Variability (%CV) Inter-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith.	TEST/REF Geo	*p*
		Initial	30.02	29.95	6.8-7.5	0.81	7.07	0.98	0.98	0.259
	3	Intermed.	25.22	25.21	2.2-3.9	0.93	3.37	0.95	0.95	0.002
		Dissip.	30.13	30.10	3.2-5.6	1.48	4.64	0.99	0.99	0.475
		Initial	37.25	37.18	3.4-8.1	0.93	5.91	1.00	1.00	0.819
TEST	6	Intermed.	33.49	33.46	3.7-4.3	1.84	4.20	0.99	0.99	0.300
		Dissip.	34.96	34.93	3.2-4.7	1.48	4.23	0.98	0.98	0.068
		Initial	42.01	41.83	5.5-12.6	3.81	9.27	1.00	0.99	0.847
	9	Intermed.	39.78	39.74	2.8-5.3	1.82	4.69	1.00	1.00	0.816
		Dissip.	41.12	41.11	2.2-2.6	0.78	2.55	0.98	0.98	0.011
		Initial	30.56	30.52	4.4-4.8	3.55	5.05			
	3	Intermed.	26.45	26.43	2.3-4.1	2.53	3.79			
		Dissip.	30.37	30.35	3.1-3.9	2.51	3.91			
		Initial	37.36	37.31	4.5-5.4	2.30	5.10			
REF	6	Intermed.	33.87	33.84	3.2-4.6	1.29	3.80			
		Dissip.	35.68	35.65	3.3-4.4	3.38	4.53			
		Initial	42.22	42.11	5.8-5.9	5.98	7.36			
	9	Intermed.	39.91	39.86	3.6-5.8	2.25	5.14			
		Dissip.	41.88	41.87	1.7-2.1	1.56	2.22			

SPAN

Prod.	Distance (cm)	Plume Form.	Mean (N = 30) Arith.	Mean (N = 30) Geo.	Variability (%CV) Intra-lot (N=10)	Variability (%CV) Inter-lot (N=3)	Variability (%CV) Total (N=30)	TEST/REF Arith.	TEST/REF Geo	*p*
		Initial	1.41	1.40	9.8-15.5	1.86	12.31	1.02	1.02	0.914
	3	Intermed.	1.26	1.26	7.4-11.5	3.63	9.63	0.96	0.96	0.080
		Dissip.	2.18	2.17	5.1-11.9	2.70	8.65	1.02	1.01	0.399
		Initial	1.04	1.04	8.1-10.6	2.52	8.96	0.95	0.95	0.016
TEST	6	Intermed.	0.95	0.94	7.5-10.0	4.24	9.11	0.94	0.94	0.013
		Dissip.	0.94	0.94	7.7-12.8	2.20	9.77	1.03	1.03	0.135
		Initial	1.12	1.11	6.8-13.6	4.90	10.22	0.90	0.90	0.003
	9	Intermed.	1.01	1.01	5.2-7.9	1.87	6.62	0.94	0.94	0.002

		Dissip.	0.82	0.82	5.5-7.6	0.70	6.40	1.02	1.02	0.174
		Initial	1.38	1.37	4.0-12.3	2.53	10.00			
	3	Intermed.	1.32	1.31	5.8-11.2	3.79	8.90			
		Dissip.	2.15	2.14	5.3-6.6	2.31	6.11			
		Initial	1.10	1.09	7.2-8.8	1.64	8.55			
REF	6	Intermed.	1.01	1.00	6.3-8.6	2.05	8.91			
		Dissip.	0.91	0.91	6.4-9.9	3.51	8.45			
		Initial	1.24	1.24	4.4-9.7	1.56	9.24			
	9	Intermed.	1.08	1.08	4.7-9.1	2.25	6.77			
		Dissip.	0.80	0.80	2.5-8.6	1.60	5.51			

Comments on Droplet Size Distribution by laser diffraction

1. The test/reference ratios of the geometric means of D50 at initial, middle and end of plume formation for the three distances are in the range of 0.95-1.00. For most comparisons the P values were insignificant.

2. The ratios of the test geometric means to the reference geometric means for SPAN at initial, middle and end of plume formation for the three distances are in the range of 0.94-1.02. For most of the comparisons the P values were insignificant.

3. For D50 and SPAN, the within-lot variability, between lot variability and total variability at the initial, middle, and end of plume formation for the test product are comparable to that of reference product.

4. Based on the mean values:

   - The D50 values were greater at the end of plume formation than at the onset and middle of plume formation.
   - Total variability was generally low at the middle of plume formation for both D50 and SPAN.
   - For the test and the reference products, total variability of D50 was generally less than that of the SPAN.

5. Based on these data, distribution of droplets in the test product spray is similar to that of the reference product spray.

The sponsor was requested to provide the plume duration data used in the laser diffraction analyses. These data were requested for information purpose only, and they are not evaluated for product approval/disapproval. A summary of those data based on the reviewer's calculations is as follows:

Product	Distance	Plume Portion	Duration (msec)			Test/Ref
			Mean	%CV	Range	
	3	Intermediate	57.33	18.54	[redacted]	1.07
		Entire	100.67	7.98	[redacted]	1.12
Test	6	Intermediate	54.67	16.46	[redacted]	1.33
		Entire	128.00	17.94	[redacted]	1.02
	9	Intermediate	48.22	27.21	[redacted]	1.37
		Entire	173.33	20.81	[redacted]	0.97
	3	Intermediate	53.78	8.16	[redacted]	
		Entire	90.22	6.84	[redacted]	
Ref	6	Intermediate	41.11	18.22	[redacted]	
		Entire	125.11	16.55	[redacted]	
	9	Intermediate	35.11	26.95	[redacted]	
		Entire	178.22	18.17	[redacted]	

b. Cascade impaction: This test is not required for the lower strength products.

Spray Pattern

The firm submitted spray pattern data at three distances (2.5, 3 and 4 cm) from [redacted] plate at beginning and end life sectors for the test product and the reference products. It provided individual results of spray pattern determination in term of D_{max}, D_{min} and ovality ratio (D_{max}/D_{min}).

The firm provided color photocopies of corresponding [redacted] plates with markings indicating D_{max} and D_{min} (Vol.1.1). The staining agents ([redacted] hat react with drug was used to highlight the pattern of the [redacted] plate. Test Method No. TM-1254 (Spray Pattern Determination for ~~Ipratropium Bromide Nasal Spray 0.03% (21 ug/spray)) can be found in Vol. 1.1, page~~ 156, along with its corresponding validation report.

Comments on the Spray Pattern Data. Reviewer's analysis of the spray pattern data are not presented because these data are unacceptable due to the following reasons:

- Spray patterns in many color photographs submitted by the firm are difficult to visualize. In some cases no patterns were distinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).
- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper visualization quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

Plume Geometry: Not required for the lower strength products

DEFICIENCY

Novex Pharma's testing of in vitro performance of its ipratropium bromide (0.03%) nasal spray is incomplete due to following deficiency:

The spray pattern testing is unacceptable because:

- Spray patterns in many color photographs submitted by the firm are difficult to visualize. In some cases no patterns were indistinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).

- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.

- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

The firm should submit revised spray pattern data after proper visualization and quantitation. The sponsor may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

The firm used [redacted] technology to compare plume geometry of the test and reference product. The same laser-based technology may be used for determination of spray pattern. It eliminates the need for impaction surface and chromogenic reagents. However, the firm should note that quantitation of spray patterns by [redacted] methodology warrants modification.

[redacted] measures spray pattern dimensions based on fitting of "ellipse" to the observed pattern, regardless of true shape of the pattern. The Agency requests spray patterns quantitation in terms of longest diameter (D_{max}), shortest diameter (D_{min}) and Ovality ratio. If spray pattern analyses use [redacted] technology, a geometric center of mass (unweighted for density) or a moment of inertia center (weighted for density) may be computed for each pattern shape. The computer software should then determine the D_{max} and D_{min} axes (the longest and shortest line passing through the center) meeting the computer defined boundaries of the spray pattern.

The appropriate quantitation of spray patterns by [redacted] has not been determined. It warrants further exploratory studies to determine the appropriateness of weighted versus unweighted centers. However, until such studies are performed, spray pattern images produced by [redacted] may be manually quantified. For spray pattern analyses based on the [redacted] methodology, the firm is recommended to use the time -averaged images. These images are produced using the "Sum tool", with the default automatic mode. The true pattern shape is visualized using the "[redacted]" option. D_{max} and D_{min} axes may be manually drawn using the line tool. The sponsors should submit representative (≥ 20%) color prints or electronic files of images based on "rainbow" or "gradient" palette. The images should exhibit the manually drawn lines as well as the computer defined boundaries of spray patterns.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

The in vitro performance data submitted by Novex Pharma comparing its ipartropium bromide nasal spray (0.03%) with the reference product, Atrovent® nasal spray (0.03%) have been found to be incomplete due to the above deficiency.

The firm should be informed of the above deficiency. It should also note that approval of the lower strength of a nasal spray product based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing of the higher strength product.

/S/

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR /S/ Date 7/25/2001

Concur: /S/ Date 8/2/01

Dale P. Conner, Pharm.D
Director, Division of Bioequivalence

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APPEARS THIS WAY
ON ORIGINAL

AUG - 8 2001

BIOEQUIVALENCY DEFICIENCY

ANDA: 76-156 APPLICANT: Novex

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The spray pattern testing is unacceptable because:

- Spray patterns in many color photographs are difficult to visualize. In some cases no patterns were indistinguishable from the background (e.g., vol. 1.1, pp. 307, 322, and 336).

- In most cases (where visualized), spray patterns are reddish-orange against yellow background. However, in some cases the patterns are yellow on white background. It is not clear what represents spray patterns.

- Spray patterns are expected to be more intense at shorter distances, which is not always the case.

Acceptable spray pattern quantitation should accurately reflect the true shape (e.g., circular, oval, spoked) and size of spray patterns. The diameters (D_{max} and D_{min}) by definition should intersect the center of the spray pattern.

Please submit revised spray pattern data after proper visualization and quantitation. You may wish to use an automated image analysis technique in order to reduce subjectivity and improve accuracy and precision. The revised data should be accompanied by representative color photographs/photocopies clearly indicative of the quantitation (including marking for spray pattern perimeter, D_{max} and D_{min}) along with identity of distance, product, and lot number.

You have used [redacted] technology to compare plume geometry of the test and reference product. The same laser-based technology may be used for determination of spray pattern. It eliminates the need for impaction surface and chromogenic reagents. However,

please note that quantitation of spray patterns by _____ methodology warrants modification.

_____ measures spray pattern dimensions based on fitting of "ellipse" to the observed pattern, regardless of true shape of the pattern. The Agency requests spray patterns quantitation in terms of longest diameter (D_{max}), shortest diameter (D_{min}) and Ovality ratio. If spray pattern analyses use _____ technology, a geometric center of mass (unweighted for density) or a moment of inertia center (weighted for density) may be computed for each pattern shape. The computer software should then determine the D_{max} and D_{min} axes (the longest and shortest line passing through the center) meeting the computer defined boundaries of the spray pattern.

The appropriate quantitation of spray patterns by _____ has not been determined. It warrants further exploratory studies to determine the appropriateness of weighted versus unweighted centers. However, until such studies are performed, spray pattern images produced by _____ may be manually quantified. For spray pattern analyses based on the _____ methodology, the time -averaged images should be used. These images are produced using the "Sum tool", with the default automatic mode. The true pattern shape is visualized using the "_____ _____ option. D_{max} and D_{min} axes may be manually drawn using the line tool. Please submit representative (≥ 20%) color prints or electronic files of images based on "rainbow" or "gradient" palette. The images should exhibit the manually drawn lines as well as the computer defined boundaries of spray patterns.

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Please note that approval of the lower strength of a nasal spray product based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing of the higher strength product.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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CC: ANDA #76-156
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Bio team Leader

Endorsements: (Final with Dates)
HFD-655/ Reviewer CTOS 7/24/01
HFD-655/ Bio team 7/25/01
HFD-650/ D. Conner 8/2/01

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BIOEQUIVALENCY - DEFICIENCIES Submission Date:3/30/01

1. **In Vitro STUDY** (ST)
Strengths: ~~10 mg/mL~~ 0.037.
✓ **Outcome: IC**

BIOEQUIVALENCY - DEFICIENCIES Submission Date:7/6/01

2. **STUDY AMENDMENT** (STA) 6/29/00
Strengths: ~~10 mg/mL~~ 0.037.
✓ **Outcome: AC**

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ON ORIGINAL

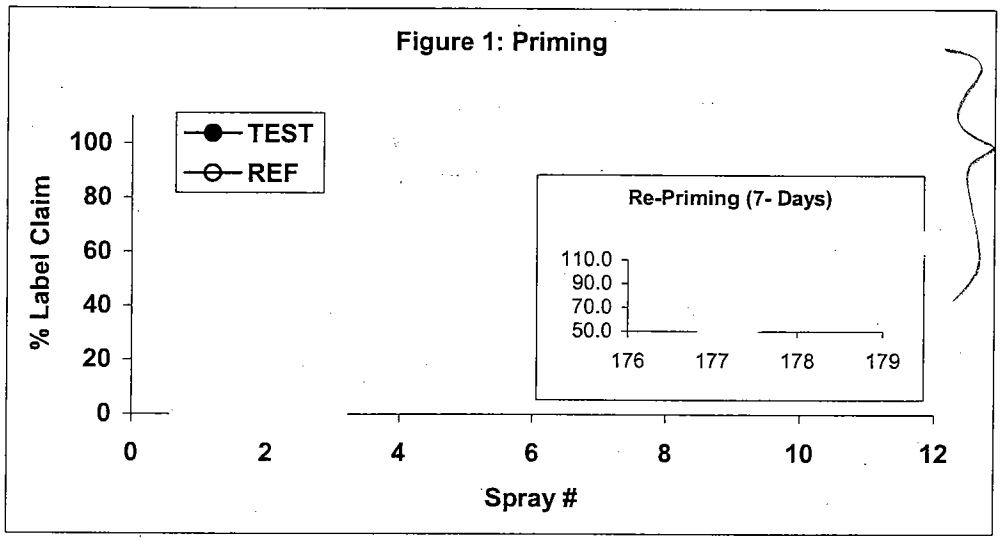
Figure 1: Priming
TEST
REF
% Label Claim
100
80
60
40
20
0
0
2
4
6
8
10
12
Spray #
Re-Priming (7- Days)
110.0
90.0
70.0
50.0
176
177
178
179

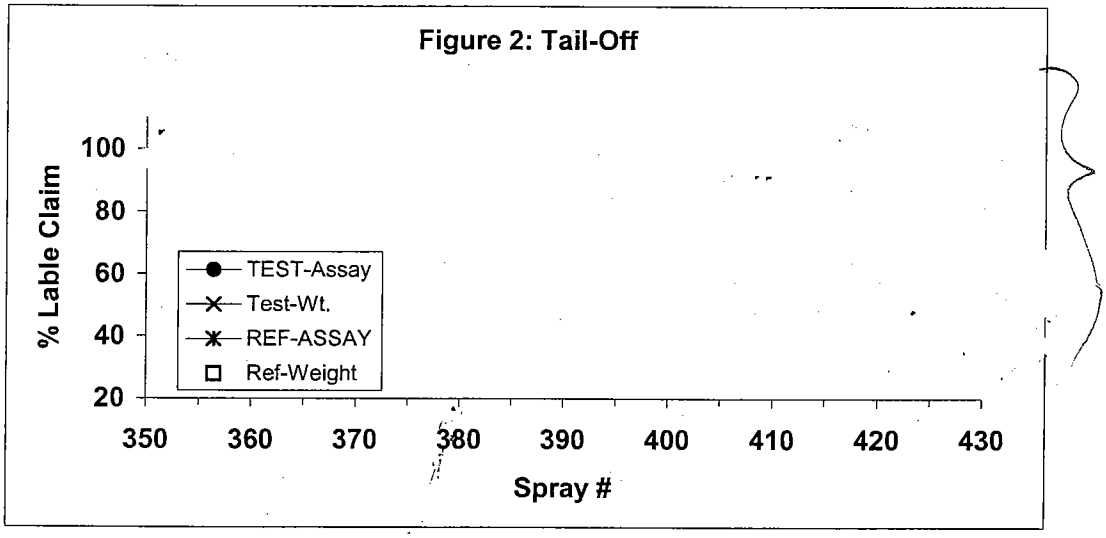
Figure 2: Tail-Off
% Lable Claim
100
80
60
40
20
TEST-Assay
Test-Wt.
REF-ASSAY
Ref-Weight
350
360
370
380
390
400
410
420
430
Spray #

FEB 12 2003

Ipratropium Bromide Solution
0.03% Nasal Spray, 42 µg/spray
ANDA #76-156
Reviewer: Mamata S. Gokhale
v:\firmsam\apotex\ltrs&rev\76156A1002.doc

Apotex Corporation
50 Lakeview Parkway
Suite 127
Vernon Hills IL 60061
Submission Date: October 25, 2002

3/6/02

Review of an Amendment

Background

1) The firm submitted original ANDA for its drug product, Ipratropium Bromide Nasal Spray, 0.03% on 3/30/01 and amendments on 7/6/01 and 3/6/02. The reference-listed drug (RLD) is Atrovent® Nasal Spray, 0.03% (42 µg/spray, NDA #20-394), manufactured by Boehringer Ingelheim Pharmaceuticals Ltd.

2) The spray pattern testing in the original submission was unacceptable because:

- Spray patterns in many color photographs were difficult to visualize. In some cases the patterns were indistinguishable from the background.
- In most case (where visualized), spray patterns were yellow on white background. It was not clear what represented spray patterns.
- Spray patterns were expected to be more intense at shorter distances, which was not always the case.

The firm was asked to submit revised spray pattern data with proper visualization and quantitation using [redacted] Technology. The firm was also informed that "approval of the lower strength based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing on the higher strength of the product", i.e. Ipratropium Bromide Nasal Spray, 0.06% submitted to ANDA 76-155.

Firm's response to deficiencies

The firm submitted spray pattern data from the [redacted] output in a tabulated format for 120 values both hard copies (attachments #1, 5 and 6) and electronic copies (attachment 7, data diskette). In the same amendment the firm submitted similar data on the higher strength (attachments #1, 2, 3 and 4). The spray pattern analysis was repeated at 3 and 5 cm distances on both the strengths, i.e. 0.03% and 0.06%.

Deficiency Comment on the firm's response

After reviewing the data on the higher strength, the DBE encouraged the firm to repeat spray pattern analysis using the [redacted] technique at different forces, i.e. actuator settings and increasing the dose time to 22 msec (teleconferences on 1/15/03 and 1/29/03). Since approval of the lower strength, based on abbreviated in vitro testing, is contingent upon the acceptance of complete in vitro testing on the higher strength of the product, the firm has been asked to repeat the

abbreviated spray pattern testing on the lower strength, using the — method. Therefore the spray pattern data submitted in this amendment does not warrant regulatory evaluation.

Recommendation

The in vitro performance testing conducted by Apotex on its Ipratropium Bromide Nasal Spray, 0.03%, Lots #5633, 5634 and 5635 comparing it with the reference product, Atrovent® Nasal Spray, 0.03%, Lots #157479A, 057080A and 156431A has been found incomplete due to the deficiency mentioned above.

The firm should be informed of the recommendation.

/S/ 2/11/03
Mamata S. Gokhale, Ph.D.
Division of Bioequivalence

RD INITIALED GJP SINGH, Ph.D.
FT INITIALED GJP SINGH, Ph.D. /S/ Date 2-11-03

Concur: /S/ Date 2/12/03
Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-156 (original), Gokhale, HFD-658, Drug File, Division File

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANTS

ANDA:76-156 APPLICANT: Apotex Corporation

DRUG PRODUCT: Ipratropium Bromide Nasal Spray 0.03%

The Division of Bioequivalence has completed its review of your application acknowledged on the cover sheet. The following deficiency have been identified:

The approval of the lower strength, 0.03% based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing on the higher strength, 0.06, submitted to ANDA 76-155. The spray pattern data on the higher strength has been found to be incomplete. Therefore, the data submitted on the 0.03% strength does not warrant a review at this time.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA # 76-156
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: Gur J.P. Singh

V:\FIRMSAM\APOTEX\LTRS&REV\76156W1002.DOC
Printed in final on 2/11/2003

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale MSK 2/11/03
HFD-658/ Gur J.P. Singh GJPS 2-11-03
HFD-650/ D. Conner
HFD-617/ S. Mazzella 2/12/03

BIOEQUIVALENCY – Incomplete

3/6/02 (NC)
Submission Date: 10/23/2002

Biowaiver (WAI)

Strength: 0.03%
Outcome: IC

Outcome Decisions:

IC – Incomplete

WinBio Comments: Biowaiver request is incomplete

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :76-156 SPONSOR : Novex Pharma

DRUG AND DOSAGE FORM : Ipratropium Bromide Nasal Spray

STRENGTH(S) : 0.03%

TYPES OF STUDIES : In Vitro Studies

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : Novex Pharma,

STUDY SUMMARY : In Vitro Studies are acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status:	Inspection results:
First Generic __No___ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Lin-Whei Chuang .BRANCH : I

INITIAL : LWC DATE : 4/1/03

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : YHH DATE : 4/3/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 4/9/03

APR - 9 2003

Ipratropium Bromide Solution
0.03% Nasal Spray, 42 µg/spray
ANDA #76-156/BE Amendment
Reviewer: Lin-Whei Chuang
V:\FIRMSNZ\NOVEX\LTRS&REV\76156A0203.doc

Novex Pharma
Richmond Hill, Ontario
Canada
Submission Date:
February 18, 2003
March 14, 2003

Review of an Amendment

Background

This is the lower strength of the firm's ipratropium bromide solutions. The application for the higher strength (0.06%) is through ANDA #76-155.

Chronology for ANDA #76-156:

3/30/2001 & 7/6/2001: Comparative Formulations and results of the abbreviated *in vitro* testing results were submitted. The spray pattern testing was found to be unacceptable by the DBE.

10/23/2002: An amendment was submitted to report spray pattern data which was found to be incomplete due to the following deficiency:

> *"After reviewing the data on the higher strength, the DBE encouraged the firm to repeat spray pattern analysis using the — technique at different forces, i.e. actuator settings and increasing the dose time to 22 msec (teleconferences on 1/15/03 and 1/29/03). Since approval of the lower strength, based on abbreviated in vitro testing, is contingent upon the acceptance of complete in vitro testing on the higher strength of the product, the firm has been asked to repeat the abbreviated spray pattern testing on the lower strength, using the — method. Therefore the spray pattern data submitted in this amendment does not warrant regulatory evaluation."*

Review

The firm has conducted spray pattern test using the — technique at two distances —— and —, from — plate at the beginning life sector for the test product and the reference products. It provided individual results of spray pattern determination in term of longest diameter (D_{max}), shortest diameter (D_{min}) and ovality ratio (D_{max}/D_{min}).

The firm also provided color photocopies of corresponding — plates with markings indicating D_{max} and D_{min} (pages 18-30, Vol. 5.1) for 20% of samples. The staining agents (———— and ————) that react with drug was used to highlight the pattern of the — plate. Test Method No. TM-1254 (Issue No.2) can be found in Vol. 5.1, pages 9-11.

Drug Products:

Test: Novex Pharma's Ipratropium Bromide Nasal Spray, 0.03%, Lot #0X400, using 3 batches of pumps (Novex Pharma QC Nos. 5630, 5631 and 5632).

Reference: Boehringer Ingelheim's Atrovent^{R} Nasal Spray, 0.03%; Lots 158413A, 256881A and 256181A, expire 11/2003, 05/2004 and 03/2004, respectively.

A summary of the spray pattern data based on the reviewer's calculations is presented in Table 1.

Table 1: Spray Pattern at the Beginning of Product Life

Dist (cm)	Parameter	Mean (Geometric Mean) for N=30	Variability (%CV)			Test Mean/ Ref. Mean (*)	P Value (1-tail ttest)
			Within-lot (N=10)	Between-lot (N=3)	Total (N=30)		
TEST PRODUCT – NOVEX							
3	Dmax (cm)	4.02 (4.01)	4.2 – 9.1	0.173	8.25	0.92 (0.92)	0.00157
3	Dmin (cm)	2.93 (2.92)	6.3 – 11.0	0.058	8.46	0.88 (0.88)	0.00005
3	Ovality	1.39 (1.37)	8.6 – 17.1	0.098	14.44	1.04 (1.04)	0.12097
5	Dmax (cm)	6.34 (6.33)	6.2 – 9.8	0.153	7.80	0.95 (0.96)	0.05596
5	Dmin (cm)	4.43 (4.41)	5.9 – 10.9	0.208	9.61	0.90 (0.92)	0.01854
5	Ovality	1.44 (1.43)	8.4 – 15.7	0.100	13.44	1.04 (1.05)	0.24311
REFERENCE PRODUCT – BOEHRINGER INGELHEIM							
3	Dmax (cm)	4.39 (4.36)	7.7 – 17.4	0.058	12.35		
3	Dmin (cm)	3.33 (3.31)	7.7 – 14.6	0.153	11.38		
3	Ovality	1.33 (1.32)	7.6 – 13.3	0.085	11.17		
5	Dmax (cm)	6.65 (6.60)	6.0 – 19.1	0.231	13.35		
5	Dmin (cm)	4.91 (4.82)	10.1 – 21.2	0.551	20.76		
5	Ovality	1.39 (1.37)	7.0 – 32.1	0.124	21.32		

*** = Ratio of Geometric means**

Comments:

1. As shown in Table 1, the ratios of the test geometric means to the reference geometric means for D_{max}, D_{min} and Ovality were within 0.92-1.05 except for Dmin at 3 cm (0.88) which is deemed acceptable because the Dmax at the same distance was 0.92 and the test product is the lower strength of the acceptable product of ANDA #76-155 (per G. Singh of DBE).
2. Total variability in the three parameters was similar between the test and reference product.
3. The spray pattern data are acceptable.
4. The test and reference formulations were found to be equivalent based on Q1 and Q2 sameness (see the review for the submission of 3/30/2001).
5. The spray devices of the test and reference products have been found to be comparable (see the review for the submission of 3/30/2001).
6. Other required in vitro tests were found to be acceptable (see the review for the submission of 3/30/2001).

Recommendation:

The *in vitro* performance data submitted by Novex Pharma comparing its ipratropium bromide nasal spray (0.03%) with the reference product, Atrovent® nasal spray (0.03%) have been found to be acceptable by the Division of Bioequivalence. The studies demonstrate equivalent *in vitro* performance of Novex's ipratropium bromide Nasal Spray, 0.03%, and the reference listed drug product Atrovent®, Nasal Solution, 0.03%, manufactured by Boehringer Ingelheim.

From the bioequivalence viewpoint, the firm has met the requirements of formulation sameness, device comparability and *in vitro* performance testing.

The firm should be informed of the above recommendation.

/S/ 4/7/2003

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ 4/7/2003

Concur: /S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-156 APPLICANT: Novex Pharma

DRUG PRODUCT: Ipratropium Bromide Nasal Spray, 0.03%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76-156
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer L. Chuang
HFD-652/ Bio team Leader YC Huang

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Last printed 04/07/03 2:38 PM

Endorsements: (Final with Dates)
HFD-652/ Reviewer L. Chuang LWC 4/7/03
HFD-652/ Bio team Leader YC Huang YH 4/7/2003
HFD-650/ D. Conner DB 4/9/03
HFD-617/ A. Sigler

BIOEQUIVALENCY - ACCEPTABLE submission date: 2-18-03

1. **STUDY AMENDMENT** (STA) OTC Strengths: 0.03%
Outcome: AC

2. **STUDY AMENDMENT** (STA) Strengths: 0.03%
(3-14-03 for expiration date of RLD) **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

I (Gene Schaefer) called Ms. Culp and asked her to include a copy of "GM-155 Spray Droplet Size Distribution" in each of the telephone amendments she will be submitting in response to our request of two days ago. She said she will do this.

She said she will fax the chemistry portions of the telephone amendments to us, and send the Bio response by courier. Thus the Bio response should arrive within a couple days after the faxed chemistry responses.

APPEARS THIS WAY
ON ORIGINAL

DATE
February 6, 2003

ANDA NUMBER
76-155 & 76-156

TELECON

INITIATED BY MADE

_ APPLICANT/ SPONSOR BY X TELE.

X FDA _ IN PERSON

PRODUCT NAME
Ipratropium Bromide Nasal Spray 0.06% & 0.03%

FIRM NAME
Novex Pharma

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ms. Dawn Culp, B.Sc., Director, Regulatory Affairs

TELEPHONE NUMBER
905-508-2562

SIGNATURE ES 2/6/03
ELSchaefer, Chemist, Br II;

MSmela, TL, Br II

V:\FIRMSNZ\NOVEX\TELECONS\76-155f.doc

RECORD OF TELEPHONE CONVERSATION/MEETING

Mr. Smela and I called Ms. Culp regarding the firm's proposed limits for the Spray Pattern test for the drug products. We had sent them a deficiency which said "*Your proposed limits for the Spray Pattern test are not adequately supported by the data you have provided. Please tighten the limits significantly or provide further data and justification for them.*" They had responded by saying that they wished to base the limits for both products on data for both strengths of their product, plus data from samples of the innovator's products.

I told Ms. Culp that I had calculated means and standard deviations, means ± two standard deviations, and means ± three standard deviations from their submitted data. Based on my calculations, Mr. Smela and I asked the firm to tighten their proposed lower limit for D_{max} from ~~——~~ and their proposed upper limit for Ovality from ~~——~~.

Ms. Culp said she would share our comments with her lab people, and they would submit tightened limits in ~~telephone amendments to the two ANDAs~~ if they agreed with our request.

We also asked when they anticipated submitting the Bioequivalence amendment for 76-155. She said they should have it to us by the end of February, but would try to get it done sooner.

DATE
February 4, 2003

ANDA NUMBER
76-155 & 76-156

TELECON

INITIATED BY — **MADE BY**
_ APPLICANT/SPONSOR — X TELE.
X FDA — _ IN PERSON

PRODUCT NAME
Ipratropium Bromide Nasal Spray 0.06% & 0.03%

FIRM NAME
Novex Pharma

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Ms. Dawn Culp, B.Sc., Director, Regulatory Affairs

TELEPHONE NUMBER
~~905-508-2562~~

SIGNATURE ES 2/4/03
ELSchaefer, Chemist, Br II;
2/4/03
MSmela, TL, Br II

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76-156

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 16, 2001

TO: C.T. Viswanathan, Ph.D.
Associate Director, Division of Scientific Investigations
MPN I, HFD-48

THROUGH: Dale P. Conner, Pharm. D. /S/
Director, Division of Bioequivalence, HFD-650

FROM: DBE/GBIB Liaison
Division of Bioequivalence, Office of Generic Drugs, HFD-617, MPN II

SUBJECT: Biopharmaceutics Compliance Program 7348.001

Request for Inspection

References:

ANDA# 76-155/156
Product Ipratropium Bromide Nasal Spray 0.06% 0.03%
Sponsor Novex Pharma US Agent Apotex
(full address, phone, fax, contact) 50 Lakeview Parkway Suite 127
Vernon Hills, IL 60061
847-573-9999 fax 847-573-1001 Mercy Macdonald
Submission Date March 30, 2001

Priority C

A (highest) = ready for approval, outstanding issues
B = Bio review complete, pending chemistry
C (routine) = Bio under review

Due Date Oct 2001

1. Studies

In vitro Sites

~~Study #1~~

Number PD-087

Title Determination of Aerodynamic Particle Size distribution in Ipratropium Bromide Nasal Solution 0.03% & 0.06% using andersen cascade impactor and Innove automatic spray pump actuation station

Clinical Site (full address, phone, fax) Novex Pharma
3120 Flying mills Rd East
Richmond Hill, Ontario
L4C 5H2

Investigator/Contact Phyllis Tseng / Dawn Culp 905-884-2050 fax 905-884-9876

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

Study #2

Number

Title

Clinical Site (full address, phone fax)

Investigator/Contact

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

Study #3

Number

Title

Clinical Site (full address, phone, fax)

Investigator/Contact

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

1. Reason for Inspection Request

_____ Not inspected in the last three years
_____ For Cause/Violative history
__X__ New Site
_____ Other

COMMENTS:

2. Bio-study Status

__X__ Study under review
_____ Study review completed
  _____ study incomplete pending additional information from sponsor
  _____ study unacceptable with questionable data pending inspection verification
  _____ study acceptable pending satisfactory inspection results
_____ Other:

CC:

HFD-617 (DBE/GBIB Liaison)
HFD-48 (Viswanathan)
HFD-65_ (Bio Reviewer)
HFD-65_ (PM)
HFD-630 (ANDA# 76-155)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-156

CORRESPONDENCE

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 17, 2003

Dr. Aaron Sigler, Project Manager
Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
Nc/Bio

TELEPHONE AMENDMENT

RE: Ipratropium Bromide Nasal Solution
0.06% and 0.03% (Nasal Spray)
ANDA No. 76-155 and 76-156

To Whom It May Concern:

Apotex Corp. as the U.S. agent for Novex Pharma of Canada, is hereby forwarding in duplicate the following telephone amendment in response to the Aaron Sigler,FDA communication with Marcy Macdonald dated March 14, 2003.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
MAR 19 2003
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

March 14, 2003

NEW CORRESP
NC/Bio

Dr. Aaron Sigler
Project Manager
Office of Generic Drugs, CDER, FDA, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Sigler:

Re: TELEPHONE AMENDMENT
Ipratropium Bromide Nasal Solution, .03% and .06% (Nasal Spray)
ANDA Nos. 76-156 (.03%) and 76-155 (.06%)

Further to the telephone conversation between yourself and Marcy Macdonald on March 14, 2003, we are pleased to provide you with our response to your request in duplicate (Archival and Review copies). For ease of review, we have prepared our responses in a question-and-answer format. An Application Form FDA 356h for each strength has been prepared and enclosed in Attachment No. 1.

1. *Provide the Expiry dates for the three lots of the RLD recently submitted for ANDA Nos. 76-155 and 76-156.*

Response: The expiry dates for the lots of RLD, most recently submitted, are as follows:

.03% Strength	
Lot No.	**Expiry Date**
(L) 158431A	Nov/03
(L) 256881A	May/04
(L) 256181C	Mar/04

.../cont'd

.06% Strength	
Lot No.	**Expiry Date**
(L) 256644A	May/04
(L) 256930A	Jun/04
(L) 257306C	Jul/04

2. *Regarding ANDA 76-156, why are the Novex Pharma Lot Nos. different from the original submission?*

   Response: The Lot Nos. for the Novex Pharma product are actually the same as those for the original submission (i.e. Lot No. 0X400, packaged with Pump QC Nos. 5633, 5634, and 5635). However, in the Summary of Spray Pattern Test for Ipratropium Bromide Nasal Spray, .03%, which was provided in the Bioequivalency Amendment submitted on February 17, 2003, the QC Nos. for the pumps used for the .06% strength were provided instead of those for the .03% strength. This typographical error has been corrected, and a revised summary is included as Attachment No. 2.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:kf

Encl.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 6, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

N/AB

NDA ORIG [illegible]

BIOEQUIVALENCY AMENDMENT

RE: Ipratropium Bromide Nasal Solution
.03% (Nasal Spray)
ANDA No. 76-156

Apotex Corp. as the U.S. agent for Novex Pharma of Canada, is hereby forwarding in duplicate the following bioequivalency amendment in response to the FDA bioequivalency deficiency letter dated February 20, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Mary Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
MAR 10 2003
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

March 05, 2003

Mr. Steven Mazzella
Project Manager
Office of Generic Drugs - HFD 600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Mazzella:

Re: BIOEQUIVALENCY AMENDMENT
Ipratropium Bromide Nasal Solution, .03% (Nasal Spray), ANDA No. 76-156

Further to your Bioequivalency Amendment letter dated February 20, 2003, we are pleased to provide you with our response in duplicate (Archival and Review copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our response in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2.

1. *The approval of the lower strength, 0.03% based on abbreviated in vitro testing is contingent upon the acceptance of complete in vitro testing on the higher strength, 0.06, submitted to ANDA 76-155. The spray pattern data on the higher strength has been found to be incomplete. Therefore, the data submitted on the 0.03% strength does not warrant a review at this time.*

Response: Novex Pharma hereby acknowledges that approval of the lower strength, .03% based on abbreviated *in vitro* testing is contingent upon acceptance of complete *in vitro* testing on the higher strength .06% (ANDA 76-155). In order to complete the submission requirements for the Ipratropium Bromide Nasal Solution, .06% (ANDA 76-155), Novex Pharma resubmitted electronic files for droplet size distribution by cascade impactor and spray pattern tests in an archival format (SAS transport V5), on March 05, 2003.

Please note, a Bioequivalency Amendment was submitted for Ipratropium Bromide Nasal Solution, .03% on February 17, 2003. The Amendment provided spray pattern data for the lower strength that was collected using the same methodology employed for the most recently submitted spray pattern data for the higher strength (Amendment dated February 14, 2003 and Resubmission of Electronic Files dated March 05, 2003). To ensure compliance with

.../cont'd

the electronic ANDA guidance for Ipratropium Bromide Nasal Solution, .03% please find electronic data files for spray pattern tests which have been resubmitted in an archival format (SAS transport V5). With the exception of the blinding codes, the SAS file contains the same data set that was previously sent in Excel format with the Bioequivalency Amendment dated February 17, 2003. The electronic file is enclosed in Attachment No. 3.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:kf

cc: Apotex Corp.

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

ORIG AMENDMENT

N/AB

February 18, 2003

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

BIOEQUIVALENCY AMENDMENT

RE: Ipratropium Bromide Nasal Solution
.03% (Nasal Spray)
ANDA No. 76-156

Apotex Corp. as the U.S. agent for Novex Pharma of Canada, is hereby forwarding in duplicate the following bioequivalency amendment in response to the FDA bioequivalency deficiency letter dated December 18, 2002.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
FEB 20 2003
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

February 17, 2003

Mr. Aaron Sigler
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sigler:

Re: BIOEQUIVALENCY AMENDMENT
Ipratropium Bromide Nasal Solution, .03%, ANDA No. 76-156

We are pleased to provide you with an amendment to our Ipratropium Bromide Nasal Solution, .03% (Nasal Spray) based on the Bioequivalency Amendment letter dated December 18, 2002 for Ipratropium Bromide Nasal Solution, .06% (Nasal Spray), ANDA No. 76-155. For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. Duplicate copies (Archival and Review copies) of this amendment are provided.

1. *In the Droplet Size Distribution by Cascade Impaction:*

   Based on the Division of Scientific Investigations report, the [redacted] assay used for determination of the drug levels is not accurate because:

   A. *Majority of the concentrations in Groups 2 and 3 were below the LOQ.*
   B. *The analytical runs were performed without calibration standards. Furthermore these runs used only single QC.*

   You are requested to repeat the Cascade Impaction test. The analytical runs should include proper calibration standards and at least three QCs.

   Please note that in the Agency's experience, use of a [redacted] in combination with multiple actuations provides measurable concentrations in Groups 2 and 3.

.../cont'd

Response: According to the Draft Guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action" droplet size distribution by cascade impactor is not required for the low strength of a solution formulation nasal spray provided Beginning and End studies have been performed on the high strength. For data on high strength, please refer to response to Bioequivalency Amendment for Ipratropium Bromide Nasal Solution, .06% (Nasal Spray), ANDA No. 76-155, which was submitted on February 14, 2003.

2. *The spray pattern testing is unacceptable because:*

The ratios of the test geometric means to the reference geometric means for D_{max}, D_{min} and the area of the spray patterns at beginning and end life sectors at 2, 3 and 4 cm distances are outside the 0.90-1.11 range, used by the Division of Bioequivalence for acceptance in vitro performance data on solution nasal sprays. You may repeat spray pattern testing using the conventional thin layer chromatography technique.

Response: The spray pattern test has been repeated using the conventional thin layer chromatography procedure as suggested by the agency. Based on our experimental data and discussions with Dr. Singh of the Division of Bioequivalence, the spray pattern was obtained at two distances from the [redacted] plate (3 and 5 cm). A copy of the spray pattern method (TM-1254) is enclosed in Attachment No. 3. Summary tables of the spray pattern test are included in Attachment No. 4 and individual spray pattern results are included in Attachment No. 5. Also enclosed in Attachment No. 6 are 20% of the representative color copies of the spray patterns from the [redacted] plates.

As required, the samples were blinded for the study. A copy of the blinding codes is enclosed in Attachment No. 7.

For ease of review, electronic data files for the test and blinding codes are enclosed for your reference in Attachment No. 8.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:cd

cc: Apotex Corp.

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

December 20, 2002

ORIG AMENDMENT
NJ/AM

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: Ipratropium Bromide Nasal Solution
.03% (Nasal Spray)
ANDA No. 76-156

Apotex Corp. as the U.S. agent for Novex Pharma, in Canada is hereby forwarding in duplicate the following minor amendment in response to the FDA minor deficiency letter dated November 26, 2002. A field copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED
DEC 26 2002
OGD / CDER

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

December 18, 2002

Peter Chen
Project Manager
Office of Generic Drugs, HFD-600
CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Chen:

Re: MINOR AMENDMENT
Ipratropium Bromide Nasal Solution, .03% (Nasal Spray), ANDA #76-156

Further to your Minor Amendment letter dated November 26, 2002, we are pleased to provide you with our responses in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included as Attachment No. 3.

1. *For the revised finished product specifications on pages 11 to 16, and the revised stability specifications on pages 17 to 20:*

   a. *Your proposed limits for the Spray Pattern test are not adequately supported by the data you have provided. Please tighten the limits significantly or provide further data and justification for them.*

   Response: In the last deficiency response (dated September 06 2002), only the applicable summary table for the individual strength was submitted to the agency in support of the proposed limit for the Spray Pattern test. However, the proposed limit was set up based on data obtained from both the .03% and .06% spray pattern data summary. This is because both products used the same pump configuration so the limits are set up based on the BA/BE spray pattern analysis as the nature of the spray pattern is governed largely by the mechanics of the pump. Enclosed in Attachment No. 4 please find spray pattern summaries of Ipratropium Bromide Nasal Solution manufactured by Novex for both the .03% (beginning of product life) and the .06% (beginning and end of product life).

.../cont'd

As can be seen from the enclosed data, the minimum value of Dmin obtained is [redacted] and the maximum value is [redacted] whereas the minimum value of Dmax obtained is [redacted] and the maximum value is [redacted] In addition, [redacted] the [redacted] had indicated that they [redacted] the same pump and insert to the RLD (Reference Listed Drug) manufacturer and therefore, we had to take consideration into the Innovator's data when setting up the specification in order to provide us with added assurance to cover batch to batch variation of the pumps. Therefore the limit set by Novex is not unreasonable given the great variability of the nature of the test and that of the pump, a parameter which we have no control over. We would like to retain our proposed limit as we do not want to fail a batch over a test which we do not have control of.

b. Further clarification is needed regarding the structure and name of Impurity V.

i. Your Response A.1.f says the structure of Impurity V in Response 4.m.iii (of the amendment of March 8, 2002) is correct. However, there are two structures in Response 4.m.iii, one on page 5 and one on page 6. Which of these is correct?

Response: The correct structure of Impurity V is identified on page 5 (Response 4.m.iii of the amendment dated March 08, 2002).

ii. The structure in Response 4.m.v appears to be the same as you have given in your revised scheme, but you say there was a mistake in the structure in Response 4.m.v. Please clarify.

Response: There was a typo in our response to A.1.f. (of the amendment dated September 06, 2002). The correct statement should read: "The structure of Impurity V in Response 4.m.iii (page 5) is correct, there was a mistake in the structure of Impurity V in Response 4.m.iii (page 6). The scheme in Response 4.m.iii (page 6) should be identified as..." Again we apologize for any confusion this may have caused.

---

2. You have explained that the Resolution/Peak Identification test tubes, used in test methods TM-70, TM-624 and TM-1130, are prepared at Novex by research chemists. However, a regulatory analytical method must be able to be run by an FDA laboratory when necessary. Please add the preparation procedure to these three methods. You may include an instruction to retrieve a tube from the freezer if available, along with instructions for making the peak ID solution if a freezer tube is not available.

Response: As requested, we have added the procedure for preparing Resolution/Peak Identification test tubes to test methods TM-70, TM-624 and TM-1130. Copies of the revised test methods are included in Attachment No. 5.

.../cont'd

3. *Regarding your updated stability data:*

   a. *Please provide 24 month data, or reduce your proposed expiration dating to 22 months.*

   Response: As requested, 24 month stability data to support a 24 month expiry dating for the product has been included in Attachment No. 6.

   b. *Please provide an investigation report or explanation for the Out of Specification initial Droplet Size Dv (90) value of 113 µm.*

   Response: The observed Out of Specification initial Droplet size data was previously explained on page 4161 of the original submission. The initial and one month accelerated study data and initial shelf-life study data was obtained based on initial machine set up parameters when we first acquired the [redacted]. The artificially higher Dv (90) results were due to the [redacted]. The instrument's set up parameters were revised during discussion with the agency on another submitted nasal product. The initial and one-month time points were re-analyzed using the revised parameters and a table with the revised droplet size data was also provided on page 4161 of the original submission. For ease of review a table with the revised droplet size data is provided below:

Revised Droplet Size Stability Data for Ipratropium Bromide Nasal Solution, .03%
Storage Condition: 40°C/75% RH

Lot # 0X400	Specification	Initial*	1 Month*		2 Months		3 Months	
Droplet Size			Horizontal	Vertical	Horizontal	Vertical	Horizontal	Vertical
Dv(10)	NLT [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dv(50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dv(90)	NMT [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Revised droplet size data

In addition to responding to the these deficiencies, please note and acknowledge the following in your response:

1. *Your bioequivalence information is pending review.*

   Response: Novex hereby acknowledges that the bioequivalence information is pending review.

.../cont'd

2. *We will schedule the Method Validation study after the methods issues are resolved.*

Response: Novex hereby acknowledges that a Method Validation study will be scheduled after the test method issues are resolved.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Director, Regulatory Affairs

DC:ia

Encl.

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

September 9, 2002

ORIG AMENDMENT

N/Am

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

RE: Ipratropium Bromide Nasal Solution
.03%
ANDA No. 76-156

To Whom It May Concern:

Apotex Corp., as the US agent for Novex Pharma, is hereby forwarding a minor amendment in duplicate in response to the FDA major deficiency letter dated August 08, 2002. A Field Copy is also included.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Director, Regulatory Affairs
Ext. 223

RECEIVED

SEP 13 2002

OGD / CDER

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

July 06, 2001

ORIG AMENDMENT
N/AB

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

BIOEQUIVALENCE TELEPHONE AMENDMENT

RE: ANDA [redacted] and 76-155
Ipratropium Bromide Nasal Spray
0.03% and 0.06%

To Whom It May Concern:

As per the telephone conversation with Division of Bioequivalence on 06/25/01, Apotex Corp. as the U.S. agent for Novex Pharma, is hereby forwarding the following in duplicate.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald /MM

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

ANDA 76-156

APR 26 2001

Apotex Corp.
U.S. Agent for: Novex Pharma
Attention: Marcy Macdonald
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Ipratropium Bromide Nasal Solution, 0.03%

DATE OF APPLICATION: March 30, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 4, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

4/25/01 for filing
ACK for S. Middleton 505(j)(2)(A)

Concur.
26-APR-2001
Gregory S. Davis

March 30, 2001

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

Re: Abbreviated New Drug Application for
<u>Ipratropium Bromide Nasal Spray 0.03%</u>

We are pleased at this time to submit Volumes 1 to 9 of an original Abbreviated New Drug Application (ANDA) seeking approval to market our product Ipratropium Bromide Nasal Spray 0.03%.

This ANDA is submitted by Apotex Corp. as the US agent for Novex Pharma. Accordingly, a Letter of Authorization is enclosed in Section XX of this application.

The drug product described herein is equivalent to Atrovent® Nasal Spray marketed by Boehringer Ingelheim Pharmaceuticals Inc. A request for a waiver of evidence of *in vivo* bioavailability or bioequivalence is enclosed as the drug product is a solution.

We trust that the information submitted is sufficient for the evaluation of this ANDA and commit to the resolution of any issues identified in the methods validation process after approval.

Should you have any questions or comments regarding the enclosed, please do not hesitate to contact Apotex Corp. or myself at (905) 508-2562 or FAX (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC/mt

Encl.

cc: Apotex Corp.