CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

APPROVAL LETTER

ANDA 75-441

MAR 28 2001

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 dated August 13, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ipratropium Bromide Inhalation Solution, 0.02%, packaged in 2.5 mL plastic ampules.

Reference is also made to your amendments dated February 15, March 7, and March 22, 2001.

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 Inhalation Solution, 0.02% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Atrovent® Inhalation Solution, 0.02% 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 which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising,

and Communications (HFD-40). Please do not use Form FD-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 FD-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 is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

Gary Buehler 3/28/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

APPROVED DRAFT LABELING

Ipratropium Bromide Inhalation Solution
0.02% (0.5 mg/plastic ampule)

NDC 60505-0806-2

60 x 2.5 mL Plastic Ampules

DOSAGE: Read accompanying Prescribing Information insert for full details.

Store between 15°-30°C (59°-86°F). Protect from light.

Store unused plastic ampules in the foil pouch.

Each low density polyethylene plastic ampule contains 2.5 mL Ipratropium Bromide Inhalation Solution 0.02% preservative-free isotonic sterile aqueous solution containing sodium chloride. Adjusted to pH 3.3 - 3.5 with hydrochloric acid.

UNVARNISHED AREA

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

Manufactured for:
Apotex Corp.
Weston, FL 33326

121843

NDC 60505-0806-2

Ipratropium Bromide

Inhalation Solution

STERILE - FOR INHALATION ONLY

DOSAGE: Read accompanying Prescribing Information for full details.
Store between 15°-30°C (59°-86°F). Protect from light. Store unused plastic ampules in the foil pouch.

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from the Prescribing Information insert and dispense with solution.

℞ Only

APPROVED

60 x 2.5 mL
Plastic Ampules

APOTEX CORP.

3 60505 08062 5

Ipratropium Bromide Inhalation Solution
0.02% (0.5 mg/plastic ampule)

NDC 60505-0806-1

25 x 2.5 mL Plastic Ampules

DOSAGE: Read accompanying Prescribing Information insert for full details.

Store between 15°-30°C (59°-86°F). Protect from light.

Store unused plastic ampules in the foil pouch.

Each low density polyethylene plastic ampule contains 2.5 mL Ipratropium Bromide Inhalation Solution 0.02% preservative-free isotonic sterile aqueous solution containing sodium chloride. Adjusted to pH 3.3 - 3.5 with hydrochloric acid.

UNVARNISHED AREA

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

Manufactured for:
Apotex Corp.
Weston, FL 33326

123936

NDC 60505-0806-1

[redacted]

Ipratropium Bromide

Inhalation Solution

[redacted]

STERILE - FOR INHALATION ONLY

DOSAGE: Read accompanying Prescribing Information for full details.
Store between 15°-30°C (59°-86°F). Protect from light.
Store unused plastic ampules in the foil pouch.

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from the Prescribing Information insert and dispense with solution.

℞ Only

25 x 2.5 mL
Plastic Ampules

APOTEX CORP.

2001

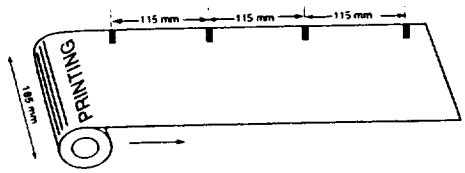
3 60505 08061 8

NOVEX PHARMA 380 Elgin Mills Rd. E., Richmond Hill, Ontario, L4C 5H2

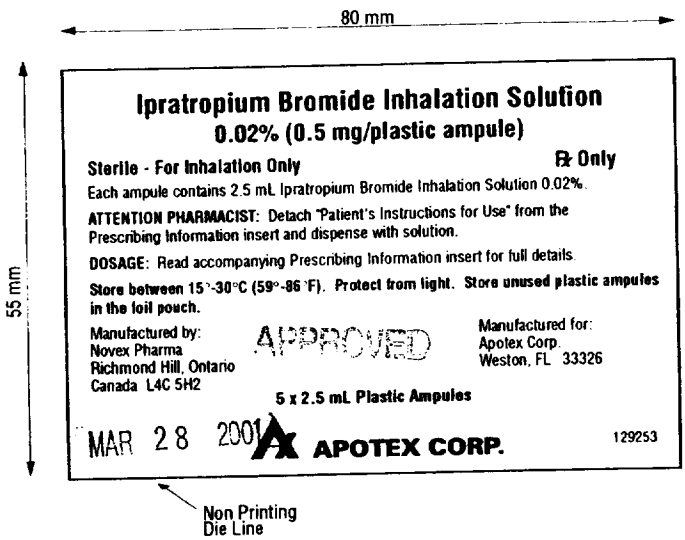
Phone: (905) 884-2050
Fax: (905) 884-9876

PRINTED PACKAGING MATERIALS / LABEL STANDARD SPECIFICATIONS

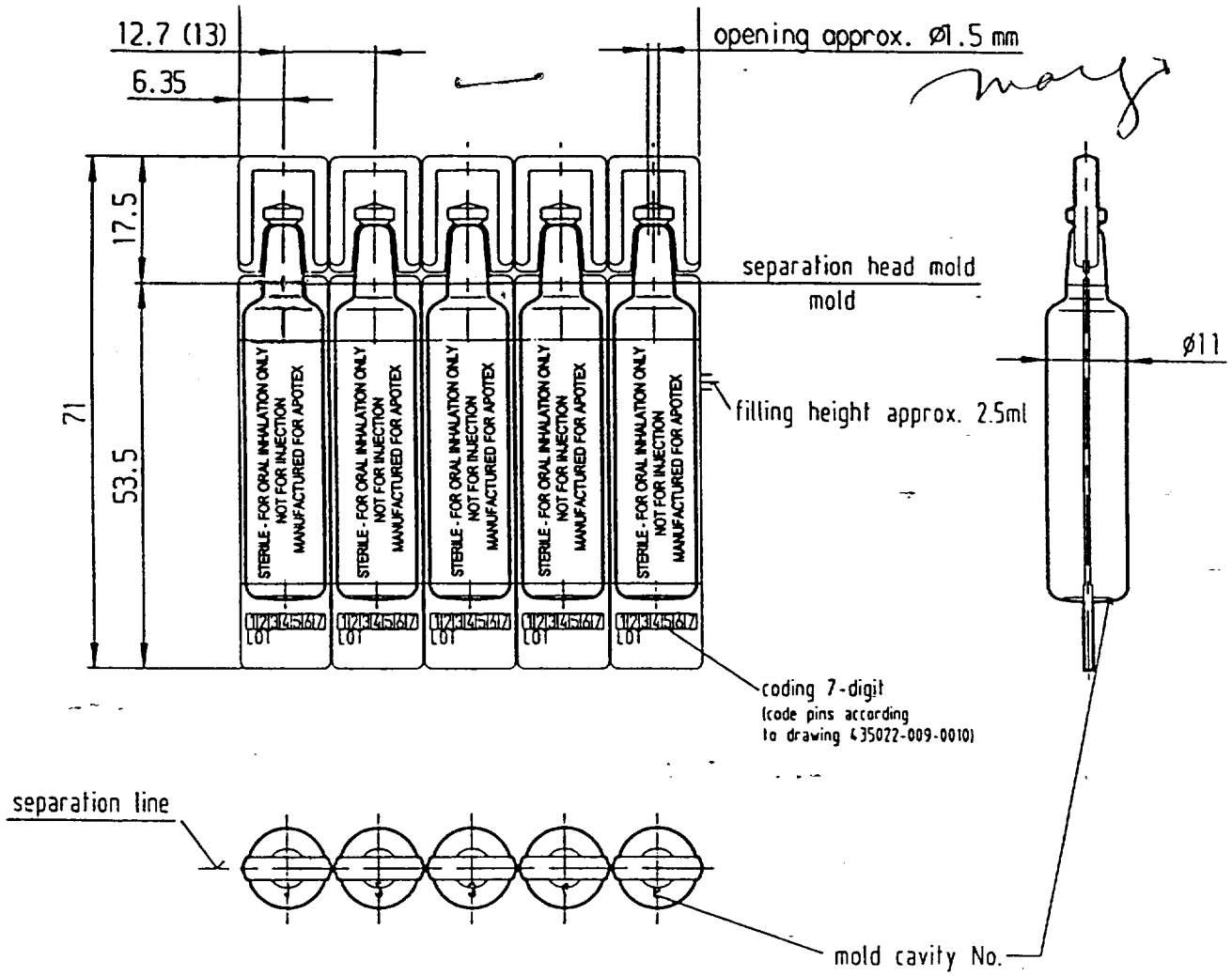
Label Number 129253	Product Name Ipratropium Bromide Inhalation Solution, 0.02% 2.5 mL ampules - Foil Pouch	Date February 12/2001
Printing	Web Direction 185 mm wide with the eye mark at 115 mm centres printed on the left hand side of a #2 unwind position roll	Label Size 80 mm x 55 mm
Caliper		Label Draft Issue Novex Draft 0
Paper Stock	Adhesive N/A	Change New
		Colour (s) Black



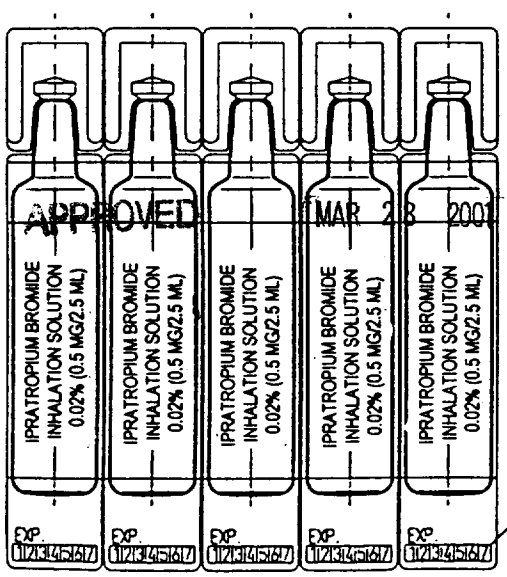
Prepared by:	Date: 02/12/01	Reg. Affairs Revision No.: 0	☐ AS IS ☐ NEW PROOF REQ.



Lot # and Expiry Date Placement N/A (LJ) 02/14/01 N/A (LJ) 02/14/01
UPC Placement N/A (LJ) 02/14/01
Unwind Position (LJ) 02/14/01
Code # Verification (LJ) 02/13/01
Colours (PMS) Verification (LJ) 02/13/01
Text Reviewed By N/A
Text Approved By 02/12/01



back side:



bottelpack -Ampullen

3 x 5-fold (block) 2.5ml on 3012

M 1:1

21. JUNI 2000

Vorschlag - Nr. 2916 m

19.06.00 Jo

PATIENT'S INSTRUCTIONS FOR USE

Ipratropium Bromide Inhalation Solution 0.02%

Read complete instructions carefully before using.

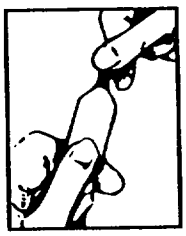


FIGURE 1

1. Twist open the top of one plastic ampule and squeeze the contents into the nebulizer reservoir (Figure 1).

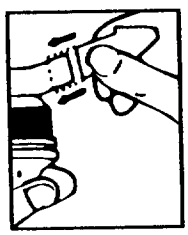


FIGURE 2

2. Connect the nebulizer reservoir to the mouthpiece or face mask (Figure 2).

3. Connect the nebulizer to the compressor.

FIGURE 3

4. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put on the face mask and turn on the compressor. If a face mask is used, care should be taken to avoid leakage around the mask as temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma, or eye pain may occur if the solution comes into direct contact with the eyes.

5. **Breathe as calmly, deeply, and evenly** as possible until no more mist is formed in the nebulizer chamber (about 5 - 15 minutes). At this point, the treatment is finished.

6. Clean the nebulizer (see manufacturer's instructions).

Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended. Ipratropium bromide inhalation solution can be mixed in the nebulizer with albuterol or metaproterenol if used within one hour but not with other drugs. Drug stability and safety of ipratropium bromide inhalation solution when mixed with other drugs in a nebulizer have not been established.

Store between 15° - 30°C (59° - 86°F). Protect from light. Store unused plastic ampules in the foil pouch.

ADDITIONAL INSTRUCTIONS: _____

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

Manufactured for:
Apotex Corp.
Weston, FL 33326

124871

May 2000

PRESCRIBING INFORMATION

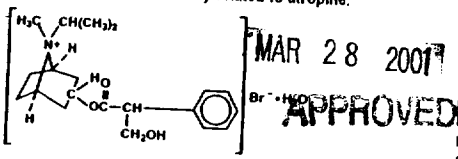
Rx Only

Ipratropium Bromide Inhalation Solution 0.02%

STERILE - FOR INHALATION ONLY

DESCRIPTION

The active ingredient in Ipratropium Bromide Inhalation Solution is ipratropium bromide monohydrate. It is an anticholinergic bronchodilator 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.



ipratropium bromide monohydrate	$C_{20}H_{30}BrNO_3 \cdot H_2O$
	Mol. Wt. 430.38

Ipratropium bromide is a white crystalline substance, freely soluble in water and lower alcohols. It is a quaternary ammonium compound and thus exists in an ionized state in aqueous solutions. It is relatively insoluble in non-polar media.

Ipratropium Bromide Inhalation Solution is administered by oral inhalation with the aid of a nebulizer. It contains ipratropium bromide 0.02% (anhydrous basis) in a sterile, preservative-free, isotonic saline solution, pH-adjusted to 3.3-3.5 with hydrochloric acid.

CLINICAL PHARMACOLOGY

Ipratropium bromide is an anticholinergic (parasympatholytic) agent that, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve.

Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) that are caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

The bronchodilation following inhalation of ipratropium bromide is primarily a local, site-specific effect, not a systemic one. Much of an administered dose is swallowed but not absorbed, as shown by fecal excretion studies. Following nebulization of a 2 mg dose, a mean 7% of the dose was absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract. The half-life of elimination is about 1.6 hours after intravenous administration. Ipratropium bromide is minimally (0 to 9% *in vitro*) bound to plasma albumin and α_1-acid glycoproteins. It is partially metabolized. Auto-radiographic studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. Ipratropium bromide has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

In controlled 12-week studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV_1 increases of 15% or more) occurred within 15 to 30 minutes, reached a peak in 1-2 hours, and persisted for periods of 4-5 hours in the majority of patients, with about 25-38% of the patients demonstrating increases of 15% or more for at least 7-8 hours. Continued effectiveness of ipratropium bromide inhalation solution was demonstrated throughout the 12-week period. In addition, significant increases in forced vital capacity (FVC) have been demonstrated. However, ipratropium bromide did not consistently produce significant improvement in subjective symptom scores nor in quality of life scores over the 12-week duration of study.

Additional controlled 12-week studies were conducted to evaluate the safety and effectiveness of ipratropium bromide inhalation solution administered concomitantly with the beta adrenergic bronchodilator solutions metaproterenol and albuterol compared with the administration of each of the beta agonists alone. Combined therapy produced significant additional improvement in FEV_1 and FVC. On combined therapy, the median duration of 15% improvement in FEV_1 was 5-7 hours, compared with 3-4 hours in patients receiving a beta agonist alone.

INDICATIONS AND USAGE

Ipratropium bromide inhalation solution administered either alone or with other bronchodilators, especially beta adrenergics, is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

Ipratropium bromide inhalation solution is contraindicated in known or suspected cases of hypersensitivity to ipratropium bromide, or to atropine and its derivatives.

WARNINGS

The use of ipratropium bromide inhalation solution as a single agent for the relief of bronchospasm in acute COPD exacerbation has not been adequately studied. Drugs with faster onset of action may be preferable as initial therapy in this situation. Combination of ipratropium bromide and beta agonists has not been shown to be more effective than either drug alone in reversing the bronchospasm associated with acute COPD exacerbation.

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 inhalation solution should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy or bladder neck obstruction.

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 the solution comes into direct contact with the eyes. Use of a nebulizer with mouthpiece rather than face mask may be preferable, to reduce the likelihood of the nebulizer solution reaching the eyes. Patients should be advised that ipratropium bromide inhalation solution can be mixed in the nebulizer with albuterol or metaproterenol if used within one hour. Drug stability and safety of ipratropium bromide inhalation solution when mixed with other drugs in a nebulizer have not been established. Patients should be reminded that ipratropium bromide inhalation solution should be used consistently as prescribed throughout the course of therapy.

Drug Interactions

Ipratropium bromide has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Ipratropium bromide has also been used with other pulmonary medications, including methylxanthines and corticosteroids, without adverse drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day of ipratropium bromide.

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 at oral doses up to 50 mg/kg/day was unaffected by ipratropium bromide administration. At doses above 90 mg/kg, increased resorption and decreased conception rates were observed.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Oral reproduction studies performed in mice, rats and rabbits at doses of 10, 100, and 125 mg/kg respectively, and inhalation reproduction studies in rats and rabbits at doses of 1.5 and 1.8 mg/kg (or approximately 38 and 45 times the recommended human daily dose) respectively, have demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. However, no adequate or well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether ipratropium bromide is excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to a significant extent, especially when taken by inhalation since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. However, because many drugs are

excreted in human milk, caution should be exercised when ipratropium bromide is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population below the age of 12 have not been established.

ADVERSE REACTIONS

Adverse reaction information concerning ipratropium bromide inhalation solution is derived from 12-week active-controlled clinical trials. Additional information is derived from foreign post-marketing experience and the published literature.

All adverse events, regardless of drug relationship, reported by three percent or more patients in the 12-week controlled clinical trials appear in the table below.

Additional adverse reactions reported in less than three percent of the patients treated with ipratropium bromide include tachycardia, palpitations, eye pain, urinary retention, urinary tract infection and urticaria. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported.

Lower respiratory adverse reactions (bronchitis, dyspnea and bronchospasm) were the most common events leading to discontinuation of ipratropium bromide therapy in the 12-week trials. Headache, mouth dryness and aggravation of COPD symptoms are more common when the total daily dose of ipratropium bromide equals or exceeds 2,000 mcg.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria, laryngospasm and anaphylactic reaction have been reported. Many of the patients had a history of allergies to other drugs and/or foods.

OVERDOSAGE

Acute systemic overdosage by inhalation is unlikely since ipratropium bromide is not well absorbed after inhalation at up to four-fold the recommended dose, or after oral administration at up to forty-fold the recommended dose. The oral LD_{50} of ipratropium bromide ranged between 1001 and 2010 mg/kg in mice; between 1667 and 4000 mg/kg in rats; and between 400 and 1300 mg/kg in dogs.

DOSAGE AND ADMINISTRATION

The usual dosage of ipratropium bromide inhalation solution is 500 mcg (1 plastic ampule) administered three to four times a day by oral nebulization, with doses 6 to 8 hours apart. Ipratropium bromide inhalation solution plastic ampules contain 500 mcg ipratropium bromide anhydrous in 2.5 mL normal saline. Ipratropium bromide inhalation solution can be mixed in the nebulizer with albuterol or metaproterenol if used within one hour. Drug stability and safety of ipratropium bromide inhalation solution when mixed with other drugs in a nebulizer have not been established.

HOW SUPPLIED

Ipratropium Bromide Inhalation Solution plastic ampule is supplied as a 0.02% clear, colorless solution containing 2.5 mL with 25 plastic ampules per carton (NDC 60505-0806-1) or 60 ampules per carton (NDC 60505-0806-2).

Each plastic ampule is made from a low density polyethylene (LDPE) resin.

Store between 15° - 30°C (59° - 86°F). Protect from light. Store unused plastic ampules in the foil pouch.

ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from the Prescribing Information insert and dispense with solution.

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

Manufactured for:
Apotex Corp.
Weston, FL 33326

124871

May 2000

ALL ADVERSE EVENTS, FROM A DOUBLE-BLIND, PARALLEL, 12-WEEK STUDY OF PATIENTS WITH COPD*

	PERCENT OF PATIENTS				
	Ipratropium (500 mcg t.i.d) n = 219	Metaproterenol (15 mg t.i.d) n = 212	Ipratropium/ Metaproterenol (500 mcg t.i.d/ 15 mg t.i.d) n = 108	Albuterol (2.5 mg t.i.d) n = 205	Ipratropium/ Albuterol (500 mcg t.i.d/ 2.5 mg t.i.d) n = 100
Body as a Whole - General Disorders					
Headache	6.4	5.2	6.5	6.3	9.0
Pain	4.1	3.3	0.9	2.9	5.0
Influenza-like Symptoms	3.7	4.7	6.5	0.5	1.0
Back Pain	3.2	1.9	1.9	2.4	0.0
Chest Pain	3.2	4.2	5.6	2.0	1.0
Cardiovascular Disorders					
Hypertension/Hypertension Aggravated	0.9	1.9	0.9	1.5	4.0
Central & Peripheral Nervous System					
Dizziness	2.3	3.3	1.9	3.9	4.0
Insomnia	0.9	0.5	4.6	1.0	1.0
Tremor	0.9	7.1	8.3	1.0	0.0
Nervousness	0.5	4.7	6.5	1.0	1.0
Gastrointestinal System Disorders					
Mouth Dryness	3.2	0.0	1.9	2.0	3.0
Nausea	4.1	3.8	1.9	2.9	2.0
Constipation	0.9	0.0	3.7	1.0	1.0
Musculo-Skeletal System Disorders					
Arthritis	0.9	1.4	0.9	0.5	3.0
Respiratory System Disorders (Lower)					
Coughing	4.6	8.0	6.5	5.4	6.0
Dyspnea	9.6	13.2	16.7	12.7	9.0
Bronchitis	14.6	24.5	15.7	16.6	20.0
Bronchospasm	2.3	2.8	4.6	5.4	5.0
Sputum Increased	1.4	1.4	4.6	3.4	0.0
Respiratory Disorder	0.0	6.1	6.5	2.0	4.0
Respiratory System Disorders (Upper)					
Upper Respiratory Tract Infection	13.2	11.3	9.3	12.2	16.0
Pharyngitis	3.7	4.2	5.6	2.9	4.0
Rhinitis	2.3	4.2	1.9	2.4	0.0
Sinusitis	2.3	2.8	0.9	5.4	4.0

* All adverse events, regardless of drug relationship, reported by three percent or more patients in the 12-week controlled clinical trials.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75441

3. NAME AND ADDRESS OF APPLICANT

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

U.S. Representative:
Apotex Corporation
50 Lakeview Parkway
Suite 127
Vernon Hills, Illinois 60061

4. LEGAL BASIS FOR SUBMISSION

The applicant stated that the listed drug product, Atrovent® Inhalation Solution 0.02% held by Boehringer Ingelheim (NDA 20-228), currently is not entitled to patents and marketing exclusivity.

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Ipratropium Bromide Inhalation Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR:

None

9. AMENDMENTS AND OTHER DATES:

Firm:

Original Submission:	8/13/98	
NC:	6/1/00	
Major Amendment:	7/31/00	
Fax Amendment:	2/16/01	(Response to NA letter dated 1/16/01-Subject of this review).
Telephone Amendment:	3/6/01	(provides updated information to support this review)

FDA:

Accepted for Filing	8/17/98	(Acknowledgment letter: 9/3/98)
NA Letter:	2/17/99	
Dunner Letter:	5/10/00	(Inquiry into Novex's failure to respond to NA letter)
NA Letter:	1/16/01	

10. PHARMACOLOGICAL CATEGORY

Bronchodilator

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF	LOA
Ipratropium Bromide	Lusochimica S.p.A.	8979(II)	V1.1, p92
			....., p643

13. DOSAGE FORM

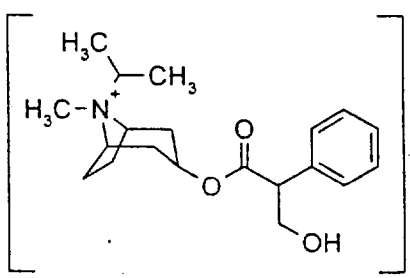
Solution

14. POTENCY

0.02%

15. CHEMICAL NAME AND STRUCTURE:

Ipratropium Bromide: 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-
oxo-2-phenylpopoxy)-8-methyl-(1-methylethyl)-, bromide, monohydrate-
(*endo, syn*)-, (±)-.
$C_{20}H_{30}BrNO_3 \cdot H_2O$.



$Br^{(-)} \cdot H_2O$

16. RECORDS AND REPORTS

None

17. COMMENTS

1. The Microbiology review finds the ANDA acceptable on January 22, 2001.
2. The Labeling review finds the ANDA acceptable on March 2, 2001.
3. EER was found satisfactory on December 22, 2000.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved

19. REVIEWER: Steven Adah

DATE COMPLETED: March 20, 2001

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Chem Rev
3/20/01

FEB 17 1999

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	75-441
APPLICANT:	Apotex Corp.
DRUG PRODUCT:	Ipratropium Bromide Inhalation Solution, 0.02%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please note that the quantity of Ipratropium Bromide in the composition table on page 84 is incorrect.

2. Please note that you incorrectly stated in your cover letter that this drug product is a USP drug product by using the term "USP" in the drug name.

3. Please establish a limit of total unknown impurities in the specification for the drug substance, Ipratropium Bromide.

4. The testing results of the impurities in Ipratropium Bromide are much lower than their limits. Please reduce the limits of individual and total impurities accordingly.

5. Please provide schedules and the tests for retesting of the drug substance and inactive ingredients.

6. The inhalation product packaged in containers for which you are seeking approval should employ a secondary overwrap such as a laminated foil or a pouch to ensure the identity, strength, quality, and purity of the product, unless you can demonstrate that such an overwrap is unnecessary via comparative studies. Please give particular attention to the use of the overwrap to control water vapor permeation, gas permeation, extractables and leachables (including heavy metals, adhesives and ink from the labeling). Studies assessing levels of vanillin and heavy metals

were not provided to justify the lack of an overwrap. You should compare vials that have been protected with an overwrap with vials that have not. The vials should be filled with drug product or purified water and stored at 40°C for at least 3 months. Testing should be conducted for the full range of potential volatile and semi-volatile contaminants at sensitivities in the 100 ppb range. The vehicle should be fully tested at the start of the study to serve as the control. The vials that do not have a protective overwrap must be packaged identically as proposed for market (same inks, same adhesive, same labels, same cartons).

7. Please add the impurities/degradation products test (individual and total) in the finished product specification.

8. Please provide a justification for not monitoring the impurities Ipratropium Bromide , and in Ipratropium Bromide in the finished product and the stability samples.

9. Please note that the assay limit for Ipratropium Bromide in the finished product specifications should be tightened.

10. According to the USP 23, a deliverable volume test should be performed for releasing the finished product. You had a similar test, net content test, in your finished product specification issue No. 2, but not in the current finished product specification issue No. 3. Please clarify.

11. You have stated the sample and standard solutions used in methods, TM-68, TM-70, TM-607, and TM-624 are not stable for a period of time. However, the given time ranges varied from 1 week to 6 weeks for the stock solution A and 2 hours to 6 days at room temperature for the sample solutions. Please clarify and provide the stability data of these solutions.

12. Please note that the final pH adjustment for mobile phases used in the analytical methods, TM-68, TM-70, and TM-624, is not appropriate since pH can not be measured reliably in organic/aqueous mixed systems.

13. Please establish limits for individual and total unknown impurities in the stability specifications.

14. Please note that a weight loss test should be included in the stability specification since the plastic ampule is made from

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Upon the resolution of the deficiencies of method validations indicated above, the assay methods for finished product will need to be validated by a FDA laboratory.

2. A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the applications is necessary at the time of the approval of the applications.

3. The microbiology information that you have provided is under review. After this review is completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #2

January 22, 2001

A. 1. ANDA: 75-441

APPLICANT: Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario CANADA

2. PRODUCT NAME: Ipratropium Bromide Inhalation Solution, 0.02%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5 mg/2.5 mL, single-dose clear plastic ampoule; Inhalation solution

4. METHOD OF STERILIZATION:
[redacted]nology

5. PHARMACOLOGICAL CATEGORY: Bronchodialator

B. 1. DATE OF INITIAL SUBMISSION: August 13, 1998

2. DATE OF AMENDMENT: July 28, 2000
Subject of this review (Received August 02, 2000)

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: January 19, 2001

C. REMARKS: The subject drug is manufactured at the Novex Pharma facility in Ontario, CANADA for Apotex Corp. of Vernon Hills, IL. The subject amendment provides for the response to microbiology deficiencies in the correspondence dated January 11, 2000.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes".

Nrapendra Nath 1/24/01
Nrapendra Nath, Ph. D.

cc:

1/24/01

[redacted]00; V:\MICROREV\75441a2.DOC

Page(s) 6

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Micro Review 2

1/22/01

JAN 16 2004

ANDA: 75441 APPLICANT: Novex Pharma

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution 0.02%

The deficiencies below represent FAX deficiencies.

1. The specifications for individual and total impurities for the drug substance are still too broad. Please tighten these specifications further except for the APO compound which may be separately limited and not included in the Total Impurities.

2. Please add a quantitative color test (e.g. APHA) to the drug product Release and Stability specifications and provide test data at the next station.

3. The drug product Identification test is unsatisfactory. Please use a specific (e.g. IR) ID test or add a second non-specific test (e.g. UV)to the current test.

4. These are questions regarding the degradation products of Ipratropium Bromide. In your studies, at least one peak in the unstressed and stressed chromatograms could be the Ipratropium Bromide Isomer. However, you did not determine what the identity of this peak is and if the relative area under the peak changes after each degradation study. Moreover in the text, on page 65, you refer to Ipratropium Bromide isomer as a known degradation product. This last statement causes significant confusion.

   Is this peak residual from the raw material as opposed to a degradation product? Is this peak Ipratropium Bromide Isomer or another side product? Please comment on your statement contained on page 65.

   Please set limits for
   and Ipratropium Bromide Isomer in the drug product Release and Stability specifications or provide convincing data that these compounds are not degradants as well as process impurities.

5. Two minor mistakes are found in TM-68. In section 5.4.4.1 on page 53, the addition of is not mentioned in the preparation of the solution but a final concentration for is given. In section 6.8 on page 55,five impurities/degradation products are given but there are six retention times. Please comment on this.

6. The degradation product stability specifications for Individual Unknowns and Total Unknowns are too broad. Please tighten these specifications.

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

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

1. We recommend that the protective pouches should be controlled to be pinhole free or have a validated limited number of pinholes that will not compromise its protective capacity.

2. Please submit all available long term stability data.

3. You sterility information is pending review.

4. Your response must also address the labeling deficiencies.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #1

January 6, 2000

A. 1. **ANDA:** **75-441**

APPLICANT: Novex Pharma
380 Elgin Mills Road East
Richmond Hill, Ontario
CANADA L4C 5H2

2. PRODUCT NAME: Ipratropium Bromide Inhalation Solution, 0.02%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5 mg/2.5 mL, single-dose clear plastic (LDPE) ampoule; Inhalation solution

4. METHOD OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Bronchodialator

B. 1. DATE OF INITIAL SUBMISSION: August 13, 1998
Subject of this review (Received August 17, 1998)

2. DATE OF AMENDMENT: none

3. RELATED DOCUMENTS:

4. ASSIGNED FOR REVIEW: September 23, 1999

C. REMARKS:
The U.S. agent for the applicant is: Apotex Corp.
50 Lakeview Parkway, Suite 127
Vernon Hills, IL 60061

The subject drug is manufactured and aseptically filled at the Novex Pharma facility in Richmond Hill, Ontario, CANADA.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments regarding the aseptic filling process are provided in "E. Review Notes" and "Microbiology Comments to be Provided to the Applicant" found at the end of this review.

Paul C. DeLeo 1/6/2000

Paul C. DeLeo, Ph. D.

1/6/00

c:

Page(s) 5

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

Micro Review
1/6/00

Microbiology Comments to be Provided to the Applicant

ANDA: **75-441** APPLICANT: **Novex Pharma**

DRUG PRODUCT: **Ipratropium Bromide Inhalation Solution, 0.02%**

A. Microbiology Deficiencies:

1. Please report the pressures among the rooms in the classified areas of the plant relative to ambient pressure.

2. Please specify holding times for the bulk drug solution and provide validation data for holding times exceeding 72 hours.

3. With regard to environmental monitoring of air:

   a. Please specify the frequency of air monitoring for viable organisms in the Class area.

   b. Please clarify the action limit for viable organisms in air. You stated that the action limit for air monitoring in the Class rea is ne system would always exceeds the action limit. In addition, since f air is collected during monitoring of the Class area, the limit of detection is

4. With regard to environmental monitoring of surfaces, the action limit for surface monitoring of the by swabs seem very high and should be reduced.

5. With regard to personnel monitoring:

   a. You should monitor personnel more frequently, especially those involved in the filling process.

   b. You should analyze the data trends from your personnel monitor.

   c. You should test the gloves of all personnel involved in the filling process.

   d. You should lower the action limit for glove

   e. You should monitor the gowns of personnel.

6. Please specify the alert and/or action limit for bioburden and endotoxin in WFI.

7 With regard to in-process validation of the
please indicate the re-validation frequency for the process.

8. Please submit data demonstrating the sterility of the container/closure assembly or validate the sterilization efficacy of the as part of this data, it would be appropriate to determine the bioburden of the container resin.

9. Please submit a summary of the sterile filtration validation data for the bulk drug solution filters; the application is not complete without it. Please describe the filter integrity testing conducted prior to and following sterile filtration, including acceptance criteria such as minimum bubble point.

10. Please provide validation data for the sterility test including a bacteriostasis/ fungistasis test of the drug product.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The minimum incubation times for the selective media may not be sufficient for the recovery of aerobic bacteria and fungi.

2. You reported data showing that non-viable particles in the air of classified areas regularly exceeded the action limits; you may want to consider evaluating operating procedures within the aseptic area in order to determine how to reduce the incidence of exceeding the action limits.

3. You should specify a bulk solution bioburden limit appropriate for the subject drug based on trends in data observed at the facility.

4. You should consider conducting testing prior to if it is not conducted presently.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Mary Fanning, M.D., Ph.D.
Associate Director of Medical Affairs
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS

ANDA: #75-441 APPLICANT: Apotex Corp.

DRUG PRODUCT: Ipratropium Bromide inhalation Solution, 0.02% (0.5 mg/ 2.5 mL).

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,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS

ANDA: #75-441 APPLICANT: Apotex Corp.

DRUG PRODUCT: Ipratropium Bromide inhalation Solution, 0.02% (0.5 mg/ 2.5 mL).

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,

Dale P. Conner

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

Ipratropium Bromide Inhalation Solution 0.02% (0.5 mg/2.5ml) Unit dose vial; ANDA # 75-441
Reviewer: Patrick E. Nwakama
x:\new\firmsam\apotex\ltr&rev\75441w.898.doc

Apotex Corp.
Vernon Hills, Illinois
Submission Date:
August 13, 1998

Review of a Bioequivalence Waiver Request

BACKGROUND

1. The firm has requested a waiver of *in vivo* bioequivalence study requirements for its drug product, Ipratropium Bromide Inhalation Solution 0.02% (0.5mg/2.5ml). The referenced listed drug (RLD) is Atrovent[R] (Ipratropium Bromide) Inhalation Solution 0.02% (Boehringer-Ingelheim, NDA #20228, approved 9/93).

2. The drug is indicated for use as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

FORMULATION COMPARISON

Comparative compositions of the test and the reference products are as follows:

Formulation Comparison		
Ingredient	**Test Product**	**RLD**
Ipratropium Br 0.02%		
Sodium Chloride,		
Hydrochloric Acid		
Purified Water,	[illegible]	QS

COMMENTS

1. The drug product is classified "AN" in the list of "Approved Drug Products with Therapeutic Equivalence Evaluation."

2. The test drug product contains the same active and inactive ingredients in the same concentrations as the currently approved reference listed product, Atrovent[R].

3. The waiver of *in vivo* bioequivalent study requirement may be granted based 21 CFR 320.22 (b)(3)of the Bioavailability/ Bioequivalence Regulations.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Apotex Corp. demonstrates that its Ipratropium Bromide Inhalation Solution 0.02% (0.5 mg/2.5 ml), falls under 21 CFR Section 320.22 (b)(3) of Bioavailability/Bioequivalence regulations. The waiver of *in vivo* Bioequivalence study for Ipratropium Bromide inhalation Solution 0.02% of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems Apotex's Ipratropium Bromide inhalation Solution, 0.02% (0.5 mg/2.5 ml)to be bioequivalent to the reference listed product, Boehringer-Ingelheim's Atrovent[R], 0.02%.

Patrick E. Nwakama, Pharm.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR Date: 10/21/1998

Concur Date: 10/27/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-441

FIRM: Novex Pharma

DOSAGE FORM: Solution

STRENGTH: 0.02%

DRUG: Ipratropium Bromide Inhalation Solution

cGMP STATEMENT/EIR UPDATED STATUS:
EER is acceptable per 12/22/00.

BIO STUDY:
Bio waiver was granted on 10/27/98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Methods Validation package was submitted on 03/08/01. Validation Report is pending.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.

Expiration dating period of 18 months for the drug product is acceptable per CR # 3 completed by S. Adah.

LABELING:
Satisfactory per A. Payne's review completed on 03/02/01.

STERILIZATION VALIDATION (IF APPLICABLE):
Acceptable per N. Nath's review dated 01/22/01.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
N/A.
Bio waiver is requested.

NDS Source: Referenced for . is adequate per review completed on 02/07/01.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Size of stability Batch liters
(50% of the full scale production batch size)

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Production batch size post-approval of the application is
The production batch manufacturing process is the same as the bio/stability batch with allowances made for modifications due to the increased batch size (i.e. larger vats, etc.).

Steven Adah
Review Chemist
Division of Chemistry I
OGD/CDER
03/20/01

cc:

Endorsements:
HFD
P
V

3/27/01

3/27/01

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

ANDA Number: 75-441 Date of Submission: August 13, 1998

Applicant's Name: Apotex Corp.

Established Name: Ipratropium Bromide Inhalation Solution, 0.02%

Labeling Deficiencies:

1. GENERAL COMMENTS

2. CONTAINER (2.5 mL)

   Satisfactory in draft.

3. CARTON (250)

   Front Panel

   Revise the storage statement to read as follows:

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

4. INSERT

   a. TITLE

      Enhance the prominence of the established name.

   b. HOW SUPPLIED

      Revise the storage statement to read as follows:

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

5. PATIENT'S INSTRUCTIONS FOR USE

   Revise the storage statement to read as follows:

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

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels along with 12 copies of final printed carton, physician's insert and patient's instructions for use labeling.

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

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

John L. Smith for

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-441

CORRESPONDENCE

APOTEX CORP.

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

March 23, 2001

ORIG AMENDMENT

N/FA

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

TELEPHONE AMENDMENT

RE: Ipratropium Bromide Inhalation Solution 0.02%
ANDA 75-441

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate this telephone amendment in response to the FDA telephone request to Marcy Macdonald on March 21, 2000. A field copy is also enclosed.

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

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG
RECD
MAR 26 2001
OGD
EVALUATION AND RESEARCH

APOTEX CORP.

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

March 07, 2001

N/FA

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

TELEPHONE AMENDMENT

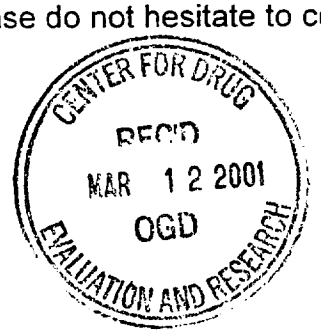
RE: ANDA No.75-441
Ipratropium Bromide Inhalation Solution, 0.02%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate this telephone amendment in response to the FDA telephone request by Steve Adah to Marcy Macdonald on February 27, 2001. A field copy is also enclosed.

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

Sincerely,



Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

APOTEX CORP.

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

February 16, 2001

NEW CORRESP

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

FAX AMENDMENT

RE: ANDA No.75-441
Ipratropium Bromide Inhalation Solution, 0.02%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate this fax amendment in response to the FDA fax deficiency letter dated January 16, 2001. A field copy is also enclosed.

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

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG
RECD
FEB 20 2001
OGD
EVALUATION AND RESEARCH

Hard copy of N/FA

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

ANDA Number: 75-441 **Date of Submission: July 31, 2000**
Applicant's Name: Apotex Corp.(U.S. Agent for Novex)
Established Name: Ipratropium Bromide Inhalation Solution, 0.02%
Labeling Deficiencies:

1. CONTAINER (2.5 mL) - Satisfactory in draft.
2. FOIL OVERWRAP - (5 x 2.5 mL)
   a. Include an "Each vial contains..." statement on your foil pouch.
   b. Include a "Usual Dosage" statement on your foil pouch.
   c. Include the following:
   ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from Package insert and dispense with solution.
3. CARTON (25's and 60's) - [Side Panel] Revise "DESCRIPTION: Each low density..." to read "Each low density..."

4. INSERT- Satisfactory in draft.
5. PATIENT'S INSTRUCTIONS FOR USE- Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels along with 12 copies of final printed carton, physician's insert and patient's instructions for use 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.

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

APOTEX CORP.

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

July 31, 2000

NDA ORIG AMENDMENT
N/AC FPL

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

MAJOR AMENDMENT

RE: ANDA 75-441
Ipratropium Bromide Inhalation Solution, 0.02%

To Whom It May Concern:

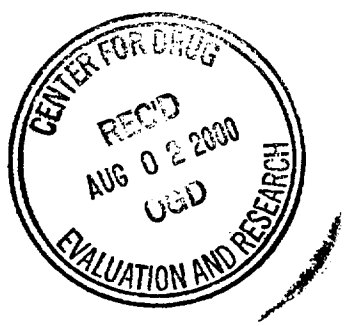
Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate a response to the major amendment letter dated February 17, 1999. A field copy is also enclosed.

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

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223



APOTEX CORP.

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

Faxed will amend by 7/3/00 Check Status then - Marcy Macdonald 6/7/00

June 1, 2000

NEW CORRESP

NC

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

RESPONSE TO "NOT APPROVABLE" LETTER

RE: ANDA 75-441
Ipratropium Bromide Inhalation Solution, 0.02%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding in duplicate a response to the "Not Approvable" letter dated February 17, 1999.

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

Sincerely,

Marcy Macdonald (KK)

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 05 2000
OGD

ANDA 75-441

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

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

MAY 10 2000

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated August 13, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Ipratropium Bromide Inhalation Solution 0.02%.

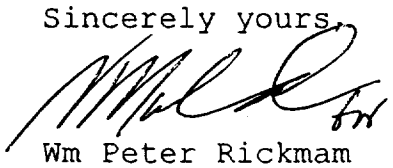
We refer you to our "Not Approvable" letter dated February 17, 1999, which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

Please send all correspondence to the following address:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Sincerely yours,



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

ANDA 75-441

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

SEP 3 1998

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 Inhalation Solution, 0.02%

DATE OF APPLICATION: August 13, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 17, 1998

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:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

9/3/98

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APOTEX CORP.

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

August 13, 1998

505(j)(2)(a) OK
8/27/98

Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Ipratropium Bromide Inhalation Solution USP 0.02%
Original Submission

Dear Mr. Sporn,

Apotex Corp., as the U.S. agent for Novex Pharma, a Division of Apotex, Inc., is submitting, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act as amended September 24, 1984, an abbreviated new drug application for Ipratropium Bromide Inhalation Solution USP 0.02%.

We are submitting an archival copy under a blue cover, a chemistry review copy under red cover, and the bioavailability/bioequivalence review section under an orange cover.

A field copy is also being submitted under a burgundy cover as this abbreviated new drug application is being submitted by a foreign applicant.

We appreciate your review of this application. Please direct any inquiries regarding this application to me at the address listed.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director, Regulatory Affairs

RECEIVED
AUG 17 1998
DRUGS

J:\ANDA\ipraltr.wpd