CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-562

Generic Name: Ipratropium Bromide Inhalation Solution, 0.02%

Sponsor: Nephron Pharmaceuticals Corporation

Approval Date: September 27, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-562

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CENTER FOR DRUG
EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

APPROVAL LETTER

ANDA 75-562

SEP 27 2001

Nephron Pharmaceuticals Corporation
Attention: Steve F. Simmons
4121 34th Street
Orlando, FL 32811-6458

Dear Sir:

This is in reference to your abbreviated new drug application dated January 6, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ipratropium Bromide Inhalation Solution, 0.02%, packaged in 0.5 mg/2.5 mL unit-dose vials.

Reference is also made to your amendments dated August 13, September 5, and September 19, 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,

/S/

Gary Buehler 9/27/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

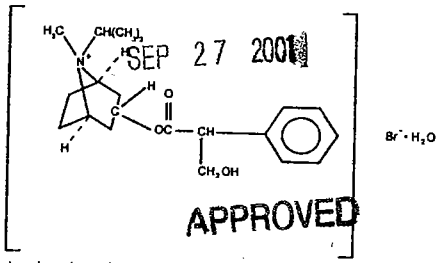
Final Printed Labeling

Ipratropium Bromide Inhalation Solution, 0.02%

Rx only

Prescribing Information

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. 430.4

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 3.4 (3 to 4) 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 inhalation solution 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 of 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 a_1-acid glycoproteins. It is partially metabolized. Autoradiographic studies in rats have shown that ipratropium bromide inhalation solution does not penetrate the blood-brain barrier. Ipratropium bromide inhalation solution 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 inhalation solution did not consistently produce significant improvement in subjective symptom scores or 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 inhalation solution 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 a mouthpiece rather than a 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 inhalation solution has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Ipratropium bromide inhalation solution 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 inhalation solution 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 inhalation solution. 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 inhalation solution should be used during pregnancy only if clearly needed.

Patient's Instructions for Use

Ipratropium Bromide Inhalation Solution , 0.02%

Read complete instructions carefully before using.

1. Twist open the top of one unit dose vial and squeeze the contents into the nebulizer reservoir (Figure 1).

Figure 1

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

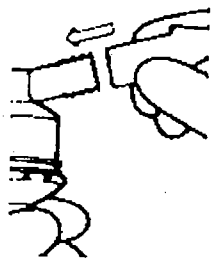


Figure 2

3. Connect the nebulizer to the compressor.

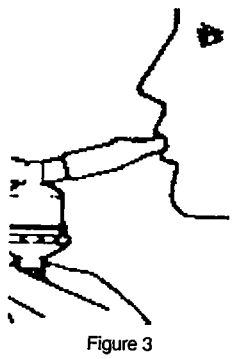


Figure 3

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° C and 30° C (59° F and 86° F). Protect from light. Store unused vials in the foil pouch.

ADDITIONAL INSTRUCTIONS: _____

Manufactured by:

nephron pharmaceuticals corporation

Orlando, FL 32811

rev. 7-21-99

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 inhalation solution 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 inhalation solution 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 inhalation solution 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 inhalation solution 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 inhalation solution 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 Unit-Dose Vial) administered three to four times a day by oral nebulization, with doses 6 to 8 hours apart. Ipratropium bromide inhalation solution Unit-Dose Vials 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 Unit-Dose Vial is supplied as a 0.02% clear, colorless solution containing 2.5 mL with 30 vials per foil pouch (NDC 0487-9801-30).

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

Store between 15° C and 30° C (59° F and 86° F).
Protect from light.
Store unused vials in the foil pouch.
ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from Package Insert and dispense with solution.

rev. 7-21-99

Manufactured by:

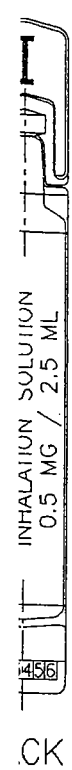
nephron pharmaceuticals corporation

Orlando, FL 32811

All Adverse Events, from a Double-blind, Parallel, 12-week Study of Patients with COPD*

	PERCENT OF PATIENTS				
	Ipratropium Bromide (500 mcg t.i.d) n=219	Metaproterenol (15 mg t.i.d) n=212	Ipratropium Bromide/ Metaproterenol (500 mcg t.i.d/15 mg t.i.d) n=108	Albuterol (2.5 mg t.i.d) n=205	Ipratropium Bromide/ 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.



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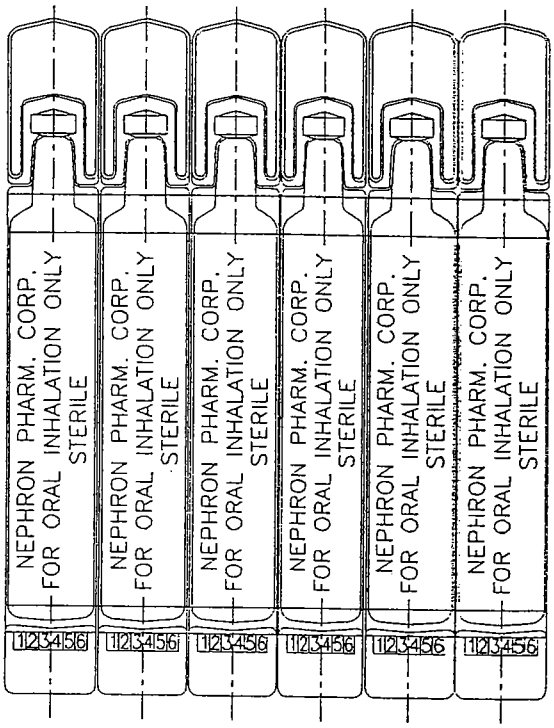
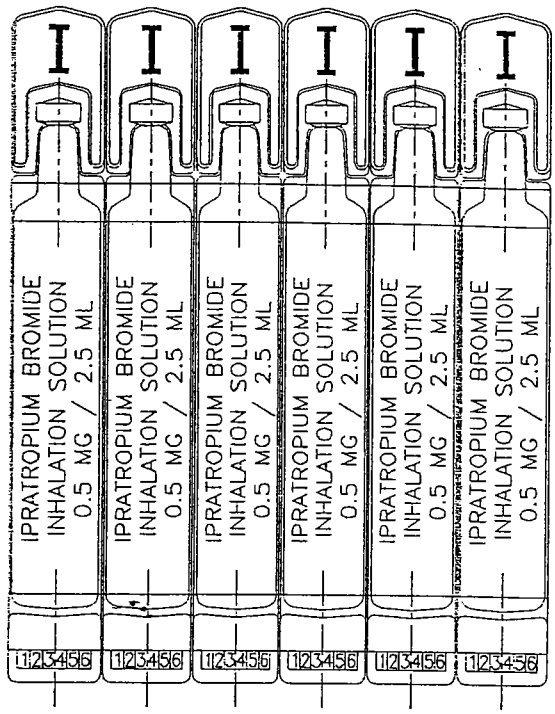


3mL VIAL CARD– FRONT



3mL VIAL CARD – BACK

REF. BOTTLE DRAWING C 301–11–2249

WEILER ENGINEERING ELK GROVE, ILLINOIS

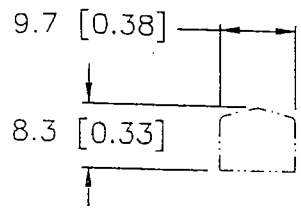
Asep-Tech® Blow/Fill/Seal Systems

			TITLE: 3mL ROUND VIAL–ENGRAVING LAYOUT "IPRATROPIUM BROMIDE"			
			DRAWN BY: L.S.	DATE: 03-02-2001	APPROVED BY	DATE
.5ML" FOR	3-7-2001	K.K.	SCALE: FULL		MATERIAL	
	DATE	BY				

FRACTIONAL DIMS ±

DECIMAL DIMS ±

DRWG. NO. B 301–11–2490



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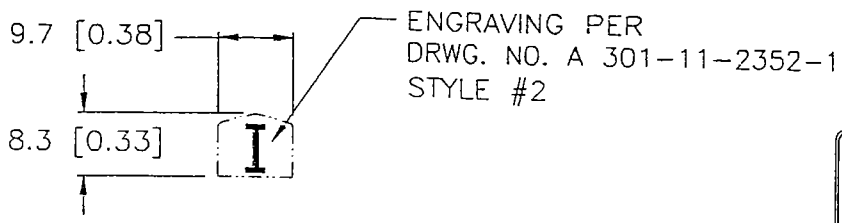
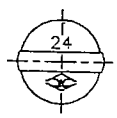


BACK

ENGRAVING HEIGHT 6.3mm [0.250]

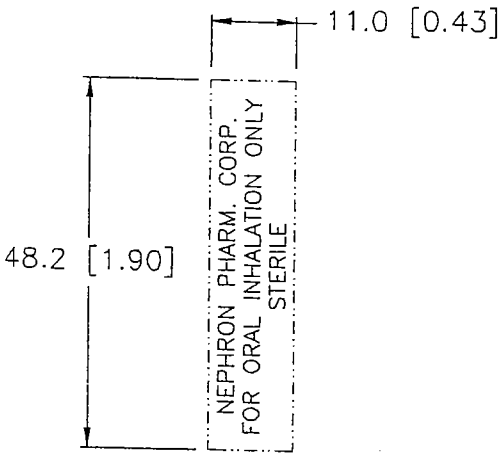
FRONT



SEAL MOLD

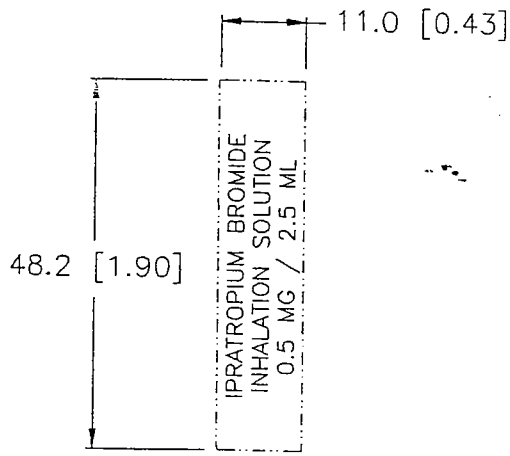
SEP 27 2001

APPROVED



FRONT

ENGRAVING HEIGHT 2.0mm [0.080]



BACK

ENGRAVING HEIGHT 2.0mm [0.080]

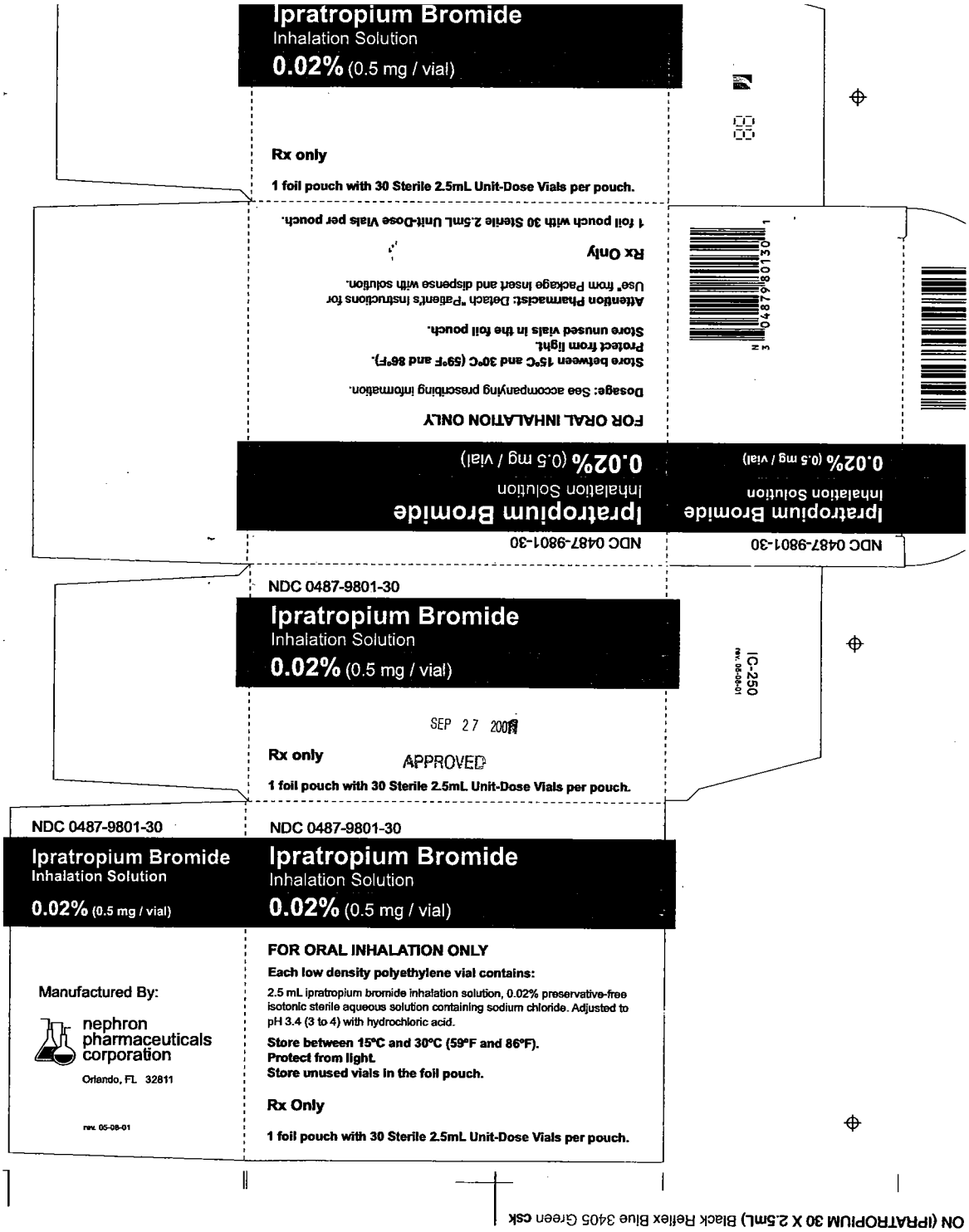
MAIN MOLD

LEFT SIDE OF MOLD
ENGRAVING DEPTH 0.4mm [0.016]

RIGHT SIDE OF MOLD
ENGRAVING DEPTH 0.4mm [0.016]

ENGRAVING PANELS

A	REVISED ENGRAVING "0.
EQUAL SPACING
LET.	REVISIC


Ipratropium Bromide
Inhalation Solution
0.02% (0.5 mg / vial)
Rx only
1 foil pouch with 30 Sterile 2.5mL Unit-Dose Vials per pouch.
NDC 0487-9801-30
Ipratropium Bromide
Inhalation Solution
0.02% (0.5 mg / vial)
SEP 27 2007
APPROVED
Rx only
1 foil pouch with 30 Sterile 2.5mL Unit-Dose Vials per pouch.
IC-250
rev. 05-08-01
NDC 0487-9801-30
Ipratropium Bromide
Inhalation Solution
0.02% (0.5 mg / vial)
Manufactured By:
nephron pharmaceuticals corporation
Orlando, FL 32811
rev. 05-08-01
NDC 0487-9801-30
Ipratropium Bromide
Inhalation Solution
0.02% (0.5 mg / vial)
FOR ORAL INHALATION ONLY
Each low density polyethylene vial contains:
2.5 mL ipratropium bromide inhalation solution, 0.02% preservative-free isotonic sterile aqueous solution containing sodium chloride. Adjusted to pH 3.4 (3 to 4) with hydrochloric acid.
Store between 15°C and 30°C (59°F and 86°F).
Protect from light.
Store unused vials in the foil pouch.
Rx Only
1 foil pouch with 30 Sterile 2.5mL Unit-Dose Vials per pouch.
ON (IPRATROPIUM 30 X 2.5mL) Black Reflex Blue 3405 Green csk

3 04879 80100 4

0.02%
(0.5 mg / vial)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 1

2. **ANDA #** 75-562

3. **NAME AND ADDRESS OF APPLICANT:**

Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811-6458

Attention: Steven F. Simmons

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Ipratropium Bromide Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Nephron:

01/06/99	Submission of ANDA (received on 01/07/99)
01/29/99	Certification for Patent and MKT exclusivity

FDA:

02/05/98	Acknowledgment letter (accept for filling)
02/05/99	EERs were issued.
02/19/99	Labeling review was completed w/Deficiencies.
03/05/99	Bio review was completed on 3/5/99, with no further questions at this time.

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Atrovent® (Boehringer Ingeleim, NDA 20-228)---Innovator;

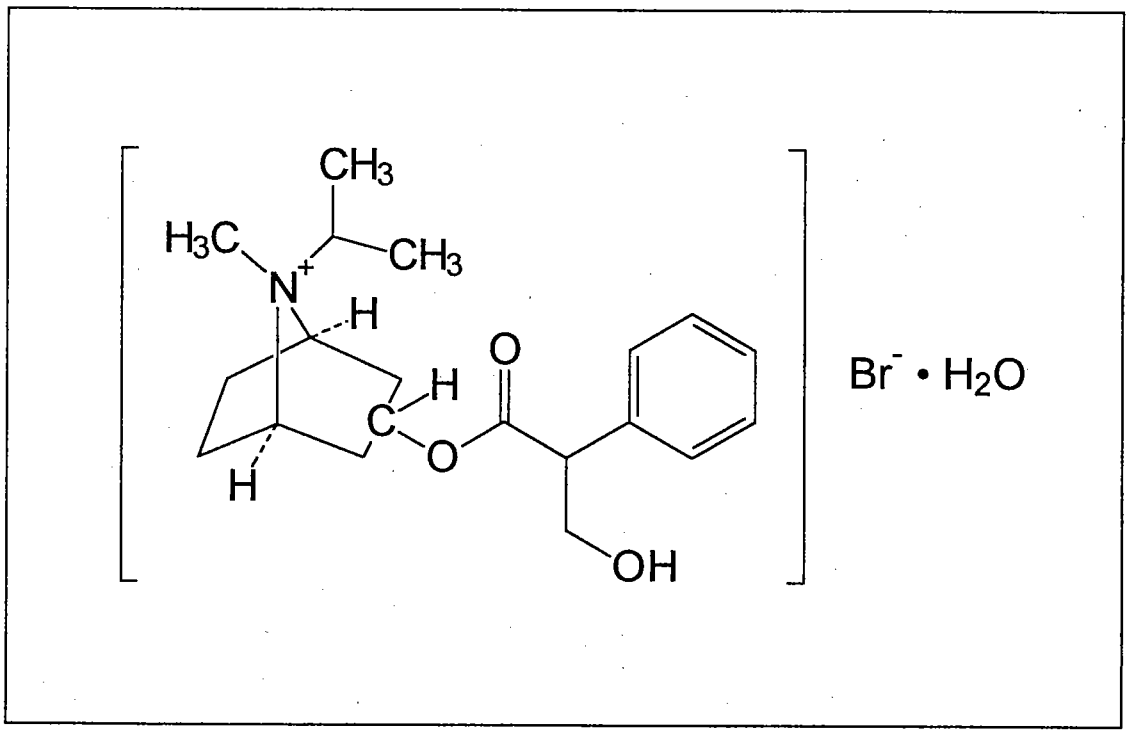
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**: Inhalation Solution (sterile)

14. **POTENCY**: 0.02%

15. **CHEMICAL NAME AND STRUCTURE**:
Ipratropium Bromide. 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate(*endo*,*syn*)-, (±)-.

$C_{20}H_3BrNO_{30}\cdot H_2O$. 430.28



16. **RECORDS AND REPORTS**: N/A

17. COMMENTS:

18. CONCLUSIONS AND RECOMMENDATIONS:
Not approvable (Major Amendment).

19. REVIEWER:	DATE COMPLETED:	DATE REVISED:
Bing Cai, Ph.D.	06/30/99	07/02/99

Redacted 24

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

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 2

2. **ANDA #** 75-562

3. **NAME AND ADDRESS OF APPLICANT:**

Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811-6458

Attention: Steven F. Simmons

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Ipratropium Bromide Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Nephron:

01/06/99	Submission of ANDA (received on 01/07/99).
01/29/99	Certification for Patent and MKT exclusivity.
11/18/99	Request of application to be remained open.
05/23/00	Major Amendment (CMC)
07/05/00	Amendment(re Micro def. lett. dated 06/12/00)

FDA:

02/05/98	Acknowledgment letter (accept for filling).
02/05/99	EERs were issued.
02/19/99	Labeling review was completed w/Deficiencies.
03/05/99	Bio review was completed w/o further question
07/12/99	CMC review was completed, NA/Major.
07/06/99	PA/cGMP Inspection of Nephron: Acceptable.
12/20/99	TelCon,re

05/09/00 "10-days response" notice.
06/07/00 Micro review (1st round) completed w/def.
06/23/00 Labeling review completed, pending FPLs.

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Atrovent® (Boehringer Ingeleim, NDA 20-228)---Innovator;

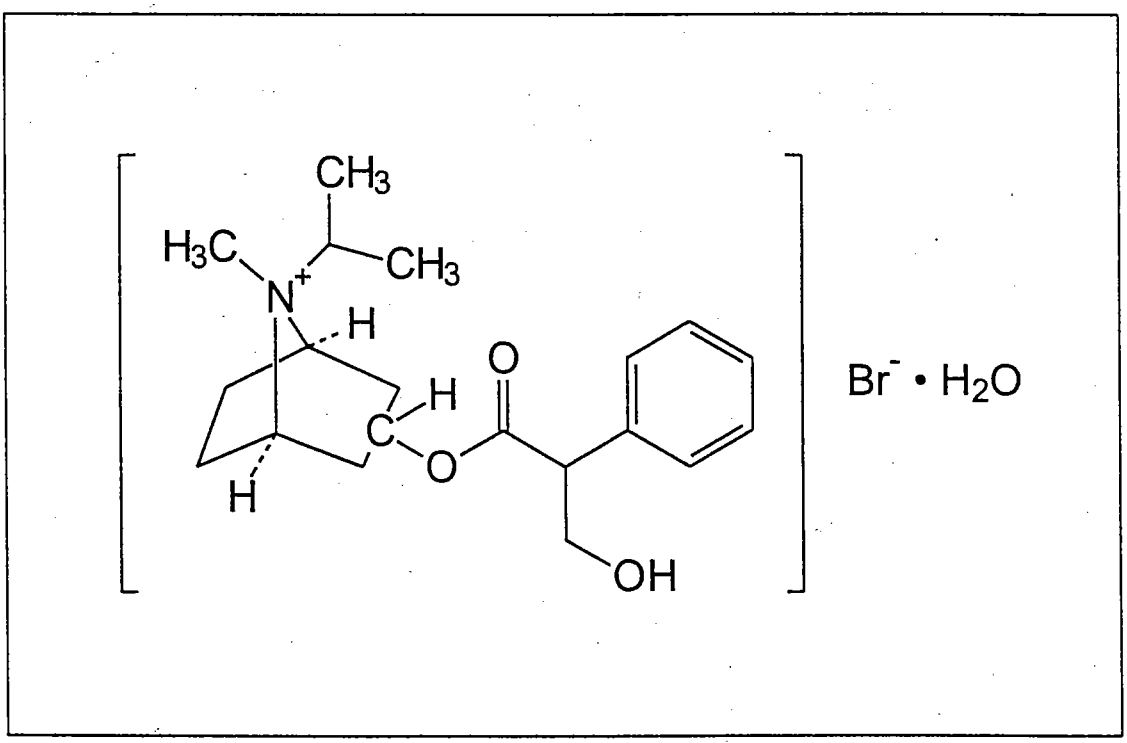
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**: Inhalation Solution (sterile)

14. **POTENCY**: 0.02%

15. **CHEMICAL NAME AND STRUCTURE**:
Ipratropium Bromide. 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate(*endo*,*syn*)-, (±)-.

$C_{20}H_3BrNO_{30}\cdot H_2O$. 430.28



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

[ ]

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (NA/FAX).

19. **REVIEWER**:	**DATE COMPLETED**:	**DATE REVISED**:
Bing Cai, Ph.D.	10/31/00	11/02/00

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

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 3

2. **ANDA #** 75-562

3. **NAME AND ADDRESS OF APPLICANT:**

Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811-6458

Attention: Steven F. Simmons

4. **LEGAL BASIS FOR ANDA SUBMISSION:**
505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Ipratropium Bromide Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Nephron:

01/06/99	Submission of ANDA (received on 01/07/99).
01/29/99	Certification for Patent and MKT exclusivity.
11/18/99	Request of application to be remained open.
05/23/00	Major Amendment (CMC)
07/05/00	Amendment(re Micro def. lett. dated 06/12/00)
03/07/01*	**Amendment/NC(re # of vial per carton)**
04/09/01*	**Amendment (re NA letter dated 11/13/00)**

*Subject for this review.

FDA:

02/05/98	Acknowledgment letter (accept for filling).
02/05/99	EERs were issued.
02/19/99	Labeling review was completed w/Deficiencies.
03/05/99	Bio review was completed w/o further question
07/12/99	CMC review was completed, NA/Major.
07/06/99	PA/cGMP Inspection of Nephron: Acceptable.

12/20/99	TelCon,re [redacted]
05/09/00	"10-days response" notice.
06/07/00	Micro review (1st round) completed w/def.
06/23/00	Labeling review completed, pending FPLs.
11/13/00	CMC review and NA (MINOR)
03/06/01	TelCon (packaging issues)

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Atrovent® (Boehringer Ingeleim, NDA 20-228)---Innovator;

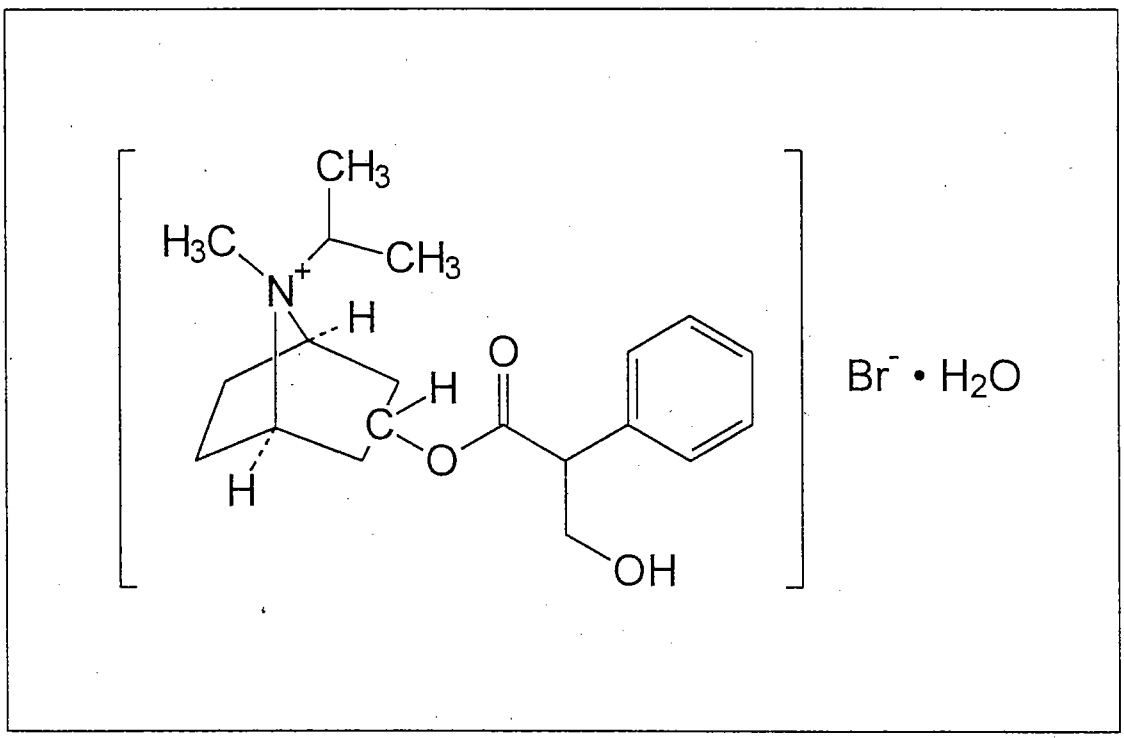
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**: Inhalation Solution (sterile)

14. **POTENCY**: 0.02%

15. **CHEMICAL NAME AND STRUCTURE**:
Ipratropium Bromide. 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate(*endo,syn*)-, (±)-.

$C_{20}H_3BrNO_{30}\cdot H_2O$. 430.28



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

[

]

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not approvable (NA/Minor).

19. **REVIEWER**:	**DATE COMPLETED**:	**DATE REVISED**:
Bing Cai, Ph.D.	05/09/01	05/11/01

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

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. The reference listed drug for this product is Atrovent® Inhalation Solution, 0.02% (NDA#20-228/S-001, Approved February 5, 1996.

2. The applicant certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 28-B.

3. The product is manufactured by Nephron Pharmaceuticals Corporation 4121 SW 34th Street Orlando, FL 32811. See Vol. 1.1, page 177.

4. [redacted] See Vol. 1.1, page 189.

5. Container/Closure

   Ampule: [redacted]
   Foil Pouch: [redacted]

   See Vol. 1.2, pages 431-436.

6. Finished product

   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. See Vol. 1.1, page 38.

7. Product line:

   Supplied as a 0.02% clear, colorless, solution containing 2.5 mL with 30 vials per foil pouch. See Vol. 1.1, page 48.

8. Components/Composition

Innovator:
Active: Ipratropium Bromide 0.02%
Inactive: preservative free, isotonic saline
pH adjusted to 3.4 (3 to 4)with hydrochloric acid

Applicant:
Active: Ipratropium Bromide 0.02%
Inactive: Sodium Chloride
Hydrochloric acid
Water for injection.

See Vol. 1.1, page 91.

9. Storage/Dispensing

NDA: Store between 59°F (15°C) and 86°F (30°C). Protect from light. Store unused vials in the foil pouch.

ANDA: Store between 59°F (15°C) and 86°F (30°C). Protect from light. Store unused vials in the foil pouch.

See Vol. 1.1, page 54.

Date of Review: February 9, 1999
Date of Submission: January 6, 1999

Reviewer: /S/ **Date:** 2/18/99

Team Leader: /S/ **Date:** 2/19/99

cc:
ANDA: 75-562
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
V:\FIRMSNZ\NEPHRON\LTRS&REV\75562na1.1
Review

Chemistry Closed

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **CHEMIST'S REVIEW NO.:** No. 4

2. **ANDA #** 75-562

3. **NAME AND ADDRESS OF APPLICANT:**

Nephron Pharmaceuticals Corporation
4121 34th Street
Orlando, FL 32811-6458
Attention: Steven F. Simmons

4. **LEGAL BASIS FOR ANDA SUBMISSION:** 505 j

5. **Supplement(s):** N/A

6. **PROPRIETARY NAME:** None

7. **NONPROPRIETARY NAME:** Ipratropium Bromide Inhalation Solution

8. **SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**

Nephron:

01/06/99	Submission of ANDA (received on 01/07/99).
05/23/00	Major Amendment (CMC)
07/05/00	Amendment(re Micro def. lett. dated 06/12/00)
03/07/01	Amendment/NC(re # of vial per carton)
04/09/01	Amendment (re NA letter dated 11/13/00)
08/13/01*	Amendment (re NA letter dated 05/18/01)

*Subject for this review.

FDA:

02/05/98	Acknowledgment letter (accept for filling).
02/19/99	Labeling review was completed w/Deficiencies.
03/05/99	Bio review was completed w/o further question
07/12/99	CMC review was completed, NA/Major.
07/06/99	PA/cGMP Inspection of Nephron: Acceptable.
06/07/00	Micro review (1st round) completed w/def.
06/23/00	Labeling review completed, pending FPLs.
11/13/00	CMC review and NA (MINOR)
05/18/01	CMC review and NA (MINOR)

10. **PHARMACOLOGICAL CATEGORY**: Bronchodilator

11. **Rx or OTC**: Rx

12. **RELATED IND/NDA/DMF(s)**:
Atrovent® (Boehringer Ingeleim, NDA 20-228)---Innovator;

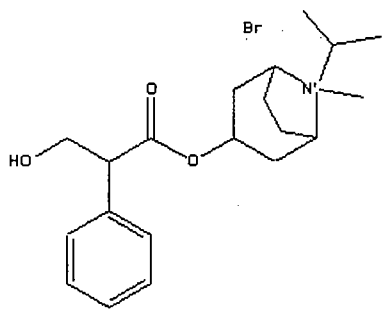
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**: Inhalation Solution (sterile)

14. **POTENCY**: 0.02%

15. **CHEMICAL NAME AND STRUCTURE**:
Ipratropium Bromide. 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide, monohydrate(*endo,syn*)-, (±)-.

$C_{20}H_3BrNO_{30} \bullet H_2O$. 430.28



16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

- EERs Found AC per 08/03/99 **(NEED TO BE RE-ISSUED)**
- Labeling Review: Pending
- Bio-review was completed & it is acceptable (03/05/99).
- Micro-review: Acceptable (08/22/01)
- MVP: Pending
- Chemistry: Acceptable at this time.

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Chemistry Closed. Pending Labeling Review/EER FUR.

19.

REVIEWER:	**DATE COMPLETED:**	**DATE REVISED:**
Bing Cai, Ph.D.	08/24/01	08/29/01

Labeling amendment of 9/5/01 found acceptable on 9/12/01 by A. Payne

dated 9/19/01. to EER

is pending.

MVP pending in SERL.

/S/

9/21/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

MICROBIOLOGY REVIEW

Microbiology Comments to be Provided to the Applicant

ANDA: 75-562 APPLICANT: Nephron Pharmaceuticals Corporation

DRUG PRODUCT: Ipratropium Bromide, 0.02%, Inhalation

A. Microbiology Deficiencies:

1. Regarding environmental monitoring:
   a. You stated that WFI testing is performed weekly. WFI should be tested daily or at a minimum on each day of production. Please also describe at what temperature WFI is maintained during the storage.

   b. [redacted]

   Please consider routine monitoring of the operator hands for bioburden as they are in a controlled environment.

   c. The diagram showing sampling sites for the environmental monitoring (volume 1.2, page 297) [redacted]

   d. [redacted]

   e. Do you routinely perform identification of the environmental isolates? Please describe your policy in this regard.

2. Regarding sterilization, you stated that a report of

Micro comments (A)

Redacted 1

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

Please provide data to show the [redacted] method used.

c. [redacted]

d. [redacted]

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

The [redacted] validation should be included in the ANDA for all [redacted] produced drugs. An application without it may not be reviewed.

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. The above deficiencies represent major amendment.

Sincerely yours,

/S/

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

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #1
May 25, 2000

A. 1. **ANDA** 75-562

APPLICANT Nephron Pharmaceuticals Corp.

2. PRODUCT NAME: Ipratropium Bromide, 0.02%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2.5-mL/3mL LDPE vial, Single dose, Oral Inhalation

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: January 6, 1999
Subject of this Review (Received January 7, 1999)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: May 22, 2000

C. REMARKS: The subject drug product was manufactured by Nephron Pharmaceuticals of Orlando, FL in 3mL, single use, [redacted] vials made by [redacted]

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

/S/

Nrapendra Nath, Ph. D.

/S/ 6/7/00

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75-562.doc
Initialed by A. High

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

OFFICE OF GENERIC DRUGS, HFD-620
Microbiology Review #2
April 16, 2001

A. 1. **ANDA** 75-562

APPLICANT: Nephron Pharmaceuticals Corp.

2. PRODUCT NAME: Ipratropium Bromide, 0.02%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2.5-mL/3mL LDPE vial, Single dose, Oral Inhalation

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: January 6, 1999

2. DATE OF AMENDMENT: July 5, 2000
Subject of this Review (Received July 7, 2000)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: April 6, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated June 12, 2000.

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

/S/ 4/25/01
Nrapendra Nath, Ph. D.

/S/ 4/30/01

CC: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75-562a2.doc
Initialed by A. High

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Microbiology Comments to be Provided to the Applicant

ANDA: 75-562 APPLICANT: Nephron Pharmaceuticals Corporation

DRUG PRODUCT: Ipratropium Bromide, 0.02%, Inhalation

A. Microbiology Deficiencies:

1. In response to the Deficiency #1a you stated that WFI

[redacted]

data on bioburden in support of your claim as personnel monitoring is considered part of the "environment".

3. Please provide a copy of your SOP or a summary of the procedure used to monitor personnel in the production area for bioburden.

4. [redacted]

5. [redacted]

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,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS, HFD-620

Microbiology Review #3
August 20, 2001

A. 1. **ANDA** 75-562

APPLICANT: Nephron Pharmaceuticals Corp.

2. PRODUCT NAME: Ipratropium Bromide, 0.02%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2.5-mL/3mL LDPE vial, Single dose, Oral Inhalation

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Bronchodilator

B. 1. DATE OF INITIAL SUBMISSION: January 6, 1999

2. DATE OF AMENDMENT: August 13, 2001
Subject of this Review (Received August 14, 2001)

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: August 20, 2001

C. REMARKS: The subject amendment provides for the response to microbiology deficiencies in the correspondence dated May 18, 2001.

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

/S/ 8/22/01
Nrapendra Nath, Ph. D.

/S/ 8/22/01

CC: Original **ANDA**
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Field Copy
Drafted by N. Nath, HFD 600; V:\microrev\75-562a3.doc
Initialed by A. High

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

BIOEQUIVALENCE REVIEW

Ipratropium Bromide Inhalation Solution
0.02% (500 mcg/25 ml) Unit-Dose Vial
ANDA #75-562
Reviewer: Jahnavi S. Kharidia
V:\FIRMSNZ\NEPHRON\LTRS&REV\75562w.199

Nephron Pharm. Corp.
Orlando, FL
Submission Date:
January 6, 1999

Review of a Waiver Request

Background:

The firm has requested a waiver of an in vivo bioequivalence study requirement for its test product, Ipratropium Bromide Inhalation Solution, 0.02%. The reference listed product is Atrovent® (Ipratropium Bromide) Inhalation Solution, 0.02%. The test and the reference listed product are both administered by oral nebulization.

Comparative Formulation:

The test and reference formulations are compared as shown below:

Ingredient	Test product	Atrovent®
Ipratropium Bromide (0.5 mg/2.5 mL)	0.02%	0.02%
Sodium Chloride, USP	[redacted]	[redacted]
[redacted] Hydrochloric Acid, NF	[redacted]	[redacted]
Water for Injection, USP	[redacted]	[redacted]

Comments:

1. The test product, Ipratropium Bromide Inhalation Solution, 0.02%, contains the same active and inactive ingredient at the same concentrations as the reference product, Atrovent® (Ipratropium Bromide) Inhalation solution, 0.02%.

2. A waiver is granted under 21 CFR 320.22 (b)(3).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Nephron Pharm. Corp. on its drug product, Ipratropium Bromide Inhalation Solution, 0.02%, falls under 21 CFR section 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Ipratropium Bromide Inhalation Solution, 0.02%, bioequivalent to the reference product,

Atrovent (Ipratropium Bromide) Inhalation Solution, 0.02%, manufactured by Boehringer Ingelheim Pharmaceuticals, Inc.

/S/

Jahnavi S. Kharidia, Ph.D.
Division of Bioequivalence
Review Branch III

3/1/99

RD INITIALLED BY BDAVIT /S/ /S/
FT INITIALLED BY BDAVIT Date: 3/1/99

Concu: /S/ Date: 3/5/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-562 APPLICANT: Nephron Pharm. Corp.

DRUG PRODUCT: Ipratropium Bromide Inhalation Solution, 0.02%

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

(2)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #75-562 SPONSOR: Nephron Pharm. Corp.
DRUG & DOSAGE FORM: Ipratropium Bromide Inhalation Solution
STRENGTH (s): 0.02%
TYPE OF STUDY: SD SDF MULT OTHER X
(Waiver)

Formulation: Acceptable

Waiver is granted.

PRIMARY REVIEWER: Jahnavi S. Kharidia, Ph.D. BRANCH: 3
INITIAL: /S/ DATE: 3/1/99

TEAM LEADER: Barbara M. Davit, Ph.D. BRANCH: 3
INITIAL: /S/ DATE: 3/1/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: /S/ DATE: 3/5/99

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: _____ DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

ADMINISTRATIVE DOCUMENTS

2.1

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

ANDA Number: 75-562 **Date of Submission: May 23, 2000**
Applicant's Name: Nephron Pharmaceuticals
Established Name: Ipratropium Bromide Inhalation Solution, 0.02%
Labeling Deficiencies:

1. CONTAINER (2.5 mL vials): Satisfactory in draft.
2. FOIL POUCH (30 x 2.5 mL): Satisfactory in draft.
3. CARTON (30 x 2.5 mL): Satisfactory in draft.
4. PHYSICIAN'S INSERT: Satisfactory in final.
5. PATIENT INSTUCTIONS FOR USE: Satisfactory in final.

Please submit 12 copies of final printed container labels, along with 12 copies of final printed foil pouch and carton 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
Unit Dose Container Labels: (2.5 mL vial)
Foil Pouch: (30 x 2.5 mL)
Unit Dose Carton Label: (30 x 2.5 mL)
Professional Package Insert Labeling:
Patient Package Insert Labeling:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: ATROVENT®
NDA Number: 20-228/S-001
NDA Drug Name: Ipratropium Bromide Inhalation Solution 0.02%
NDA Firm: Boehringer Ingelheim
Date of Approval of NDA Insert and supplement #: February 5, 1996/S-001
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.
Basis of Approval for the Carton Labeling: Side-by-side comparison with innovator labeling in jacket.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

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

FOR THE RECORD:

1. The reference listed drug for this product is Atrovent® Inhalation Solution, 0.02% (NDA#20-228/S 001, Approved February 5, 1996.
2. The applicant certifies there are no patents/exclusivities in effect for this drug product. See Vol. 1.1, page 28-B.
3. The product is manufactured by Nephron Pharmaceuticals Corporation 4121 SW 34th Street Orlando, FL 32811. See Vol. 1.1, page 177.
4. Outside firms are utilized for testing only. See Vol. 1.1, page 189.
5. Container/Closure
   Ampul:
   Foil Pouch: See Vol. 1.2, pages 431-436.
6. Finished product: 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. See Vol. 1.1, page 38.
7. Product line: Supplied as a 0.02% clear, colorless, solution containing 2.5 mL with 30 vials per foil pouch. See Vol. 1.1, page 48.
8. Components/Composition
   Innovator:
   Active: Ipratropium Bromide 0.02%
   Inactive: preservative free, isotonic saline, pH adjusted to 3.4 (3 to 4)with hydrochloric acid
   Applicant:
   Active: Ipratropium Bromide 0.02%
   Inactive: Sodium Chloride, Hydrochloric acid, Water for injection. See Vol. 1.1, page 91.
9. Storage/Dispensing
   NDA: Store between 59°F (15°C) and 86°F (30°C). Protect from light. Store unused vials in the foil pouch.
   ANDA: Store between 59°F (15°C) and 86°F (30°C). Protect from light. Store unused vials in the foil pouch. See Vol. 1.1, page 54.

Date of Review: May 30, 2000 /S/ **Date of Submission:** May 23, 2000
Reviewer: /S/ **Date:** 6/12/00
Team Leader: **Date:** 6/23/2000

cc: ANDA 75-562
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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Review

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

ANDA Number: 75-562 **Date of Submission: January 6, 1999**

Applicant's Name: Nephron Pharmaceuticals

Established Name: **Ipratropium Bromide Inhalation Solution, 0.02%**

Labeling Deficiencies:

1. GENERAL COMMENTS:

2. CONTAINER (2.5 mL vials)

   a. Revise "[redacted]" to read "FOR ORAL INHALATION ONLY".

3. FOIL POUCH (30 x 2.5 mL)

   a. Revise your storage recommendation to read as follows:

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

   b. Revise "[redacted]" to read "FOR ORAL INHALATION ONLY".

4. CARTON (30 x 2.5 mL)

   a. Revise your storage recommendation to read as follows:

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

   c. Revise "[redacted]" to read "FOR ORAL INHALATION ONLY".

   d. Revise your statement of quantity to read "2.5 mL" rather than "[redacted]".

5. PHYSICIAN'S INSERT

a. HOW SUPPLIED

i. Revise your storage recommendation to read as follows:

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

ii. Relocate "Rx only" to the TITLE section of the insert.

b. TABLE

i. Replace '[redacted]' with "Ipratropium Bromide".

ii. Replace "[redacted]" with "Metaproterenol".

6. PATIENT INSTUCTIONS FOR USE

Revise your storage recommendation to read as follows:

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

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

/S/

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

APPEARS THIS WAY
ON ORIGINAL

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:

Unit Dose Container Labels: (2.5 mL vial)

Foil Pouch: (30 x 2.5 mL)

Unit Dose Carton Label: (30 x 2.5 mL)

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ATROVENT®

NDA Number: 20-228/S-001
NDA Drug Name: Ipratropium Bromide Inhalation Solution 0.02%
NDA Firm: Boehringer Ingelheim

Date of Approval of NDA Insert and supplement #: February 5, 1996/S-001
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
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Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
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Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
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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	

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-562

FIRM: Nephron Pharmaceuticals

DOSAGE FORM: Inhalation Solution

STRENGTH: 0.02%

DRUG: Ipratropium Bromide Inhalation Solution

cGMP STATEMENT/EIR UPDATED STATUS: EER FUR is pending

BIOEQUIVALENCE: Acceptable 03/05/99

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Pending in SERL (see e-mail sent to S. Roberts dated 08/25/01)

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Yes. Stability data to support the new proposed 2nd packaging system provided. Expiration dating period is 24 months for the drug product.

LABELING:
Acceptable, 09/12/2001

STERILIZATION VALIDATION (IF APPLICABLE):
Acceptable, 08/22/2001

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

Batch # (bulk solution)		Batch Sizes	Pouch Used
Bio/Stability batch	Lot# P1497B	[redacted]	[redacted]
Additional batch for new secondary package system	**Lot# P0143A**	[redacted]	[redacted]

NDS Source	Ipratropium Bromide
DMF#	DMF [redacted]
Manufacturer	[redacted]
DMF status	Last Submission: amendment dated 05/15/01 Last Review: Acceptable per 06/22/01 No new submission since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Batch # (bulk solution)		Batch Sizes	Pouch Used
Bio/stability batch	Lot# P1497B	[redacted]	[redacted]
Additional batch for new package system	Lot# P0143A	[redacted]	[redacted]

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

Batch (bulk solution)	Batch Sizes	Pouch Used
Production Batch	[redacted]	[redacted]

Bing Cai
Review ... ist 9/21/01

Mike Smela
Team Leader 9/21/01

Division of Chemistry I
OGD/CDER
09/12/01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-562

CORRESPONDENCE

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

SEP 19 2001

REFERENCE: TELEPHONIC AMENDMENT to ANDA 75-562

ORIG AMENDMENT
N/AM

Gentlemen:

Nephron hereby withdraws [redacted], FDA Registration Number [redacted] as the [redacted] proposed drug product as specified in our Abbreviated New Drug Application 75-562 for the production of Ipratropium Bromide Inhalation Solution, 0.02%.

1. PURPOSE OF THE SUBMISSION:

   To withdraw a [redacted], previously submitted in ANDA 75-562. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a 3.8mL (2.5mL fill) [redacted] container, packaged 30 vials in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a TELEPHONIC AMENDMENT to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
   1 Review Copy, containing 1 volume
   1 Field Submission Copy, containing 1 volume, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 20 2001
DGD

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

AUG 1 3 2001

N|AM
ORIG AMENDMENT

REFERENCE: MINOR AMENDMENT to ANDA 75-562

Gentlemen:

Attached, please find our response to the deficiencies found during review of our Abbreviated New Drug Application 75-562 for the production of Ipratropium Bromide Inhalation Solution, 0.02%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To respond to the Chemistry and Microbiology deficiencies found during review of ANDA 75-562. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a 3.8mL (2.5mL fill) [redacted] container, packaged 30 vials in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a MINOR AMENDMENT to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
   1 Review Copy, containing 1 volume
   1 Field Submission Copy, containing 1 volume,
   (submitted to the Orlando District)

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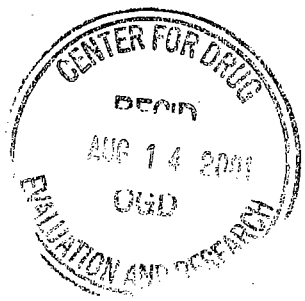

4121 34th Street Orlando, FL 32811 (407) 246-1389

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[redacted]

[redacted]

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Steven F. Simmons
President

nephron
pharmaceuticals
corporation
SINCE 1937

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/Am

REFERENCE: Minor Amendment to ANDA 75-562

Gentlemen:

Attached, please find our response to the Chemistry deficiencies found during review of our Abbreviated New Drug Application 75-562 for the production of Ipratropium Bromide Inhalation Solution, 0.02%, as outlined below.

1. PURPOSE OF THE SUBMISSION:

   To respond to the deficiencies found during review of ANDA 75-562. Also, to provide additional information for the microbiology reviewer addressing ~~~~ validation using the proposed drug product. Nephron's goal is to gain approval from the Food and Drug Administration for the production of the proposed drug product at Nephron's manufacturing facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a 3mL (2.5mL fill) ~~~~ container, packaged 30 vials in a foil pouch overwrap.

2. TYPE OF SUBMISSION: This submission is a Minor Amendment to an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
   1 Review Copy, containing 1 volume
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[redacted]

[redacted]

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Sincerely,

NEPHRON PHARMACEUTICALS CORP.

CENTER FOR DRUG EVALUATION AND RESEARCH
APR 10 2001
OGD

Steven F. Simmons
President

nephron
pharmaceuticals
corporation
SINCE 1937

ORIG AMENDMENT
N/As.

JUL 0 5 2000

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: Ammendment to ANDA 75-562
for Ipratropium Bromide Inhalation Solution, 0.02%

Gentlemen:

Attached, please find our Ammendment to Abbreviated New Drug Application 75-562 for the production of Ipratropium Bromide Inhalation Solution, 0.02%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To address microbiology review deficiencies noted by the agency in their review letter of ANDA 75-562, dated June 12, 2000. To gain approval from the Food and Drug Administration for the production of ipratropium bromide inhalation solution, 0.02% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a unit-dose 3 mL container, packaged 30 vials to a foil pouch.

2. TYPE OF SUBMISSION: This submission is an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 1 volume
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CENTER FOR DRUG
REC'D
JUL 0 7 2000
OGD
EVALUATION AND RESEARCH

4121 34th Street Orlando, FL 32811 (407) 246-1389

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We appreciate the agency's expedient review of our application, and look forward to an early reply.

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NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

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SINCE 1937

MAY 2 3 2000

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

N/AC

REFERENCE: Ammendment to ANDA 75-562
for Ipratropium Bromide Inhalation Solution, 0.02%

Gentlemen:

Attached, please find our Ammendment to Abbreviated New Drug Application 75-562 for the production of Ipratropium Bromide Inhalation Solution, 0.02%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To gain approval from the Food and Drug Administration for the production of ipratropium bromide inhalation solution, 0.02% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a unit-dose 3 mL container, packaged 30 vials to a foil pouch.

2. TYPE OF SUBMISSION: This submission is an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

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CENTER FOR DRUG EVALUATION AND RESEARCH
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Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

ANDA 75-562

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

Nephron Pharmaceuticals Corporation
Attention: Steven F. Simmons
4121 34th Street
Orlando, FL 32811

MAY 9 2000

Dear Sir:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated Janaury 6, 1999, 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 July 21, 1999, which detailed the deficiencies identified during our review of your ANDA. Although we acknowledge your communication dated November 18, 1999, 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

nephron
pharmaceuticals
corporation
•SINCE 1937

NEW CORRESP
NC
NA 1

November 18, 1999

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: Ammendment to ANDA 75-562 for Ipratropium Bromide Inhalation Solution, 0.02%

Gentlemen:

We are presently working to answer all deficiencies found in the above application, and anticipate filing of the amendment before December 31, 1999. We would appreciate the Agency's cooperation in holding our application open until receipt of the amendment.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

NOV 22 1999

4121 34th Street Orlando, FL 32811 (407) 246-1389

ANDA 75-562

Nephron Pharmaceuticals Corp.
Attention: Steven F. Simmons
4121 34th Street
Orlando, FL 32811-6458

FEB 5 1999

Dear Sir:

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

Reference is made to the telephone conversation dated January 29, 1999 and your correspondence dated January 29, 1999.

NAME OF DRUG: Ipratropium Bromide Inhalation Solution, 0.02%

DATE OF APPLICATION: January 6, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 7, 1999

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,

/S/

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

nephron
pharmaceuticals
corporation
SINCE 1937

January 29, 1999

VIA FACSIMILE
AND AIRBORNE EXPRESS

Mr. Greg Davis
Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

REFERENCE: ANDA 75-562 – New Correspondence

Gentlemen:

As instructed, please find our revised Patent Certification Statement for Ipratropium Bromide Inhalation Solution, 0.02%. This page will replace page 000028 of our original submission. This cover letter and attachment will be designated as pages 000028-A. and 000028-B, respectively.

A copy of this correspondence has been forwarded to the Orlando District Office for inclusion in the Field Submission Copy of the application.

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President

000028-A

4121 34th Street Orlando, FL 32811 (407) 246-1389

nephron
pharmaceuticals
corporation
SINCE 1937

505(j)(2)(A) OK
91 1/11/99
91 S
V J

January 6, 1999

Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

REFERENCE: ANDA for Ipratropium Bromide Inhalation Solution, 0.02%

Gentlemen:

Attached, please find our Abbreviated New Drug Application for the production of Ipratropium Bromide Inhalation Solution, 0.02%, as outlined below.

1. PURPOSE OF THE SUBMISSION: To gain approval from the Food and Drug Administration for the production of ipratropium bromide inhalation solution, 0.02% at Nephron's current facility in Orlando, Florida. The proposed drug product is an orally administered bronchodilator, in sterile form, in a unit-dose 3 ml container, packaged 30 vials to a foil pouch.

2. TYPE OF SUBMISSION: This submission is an Abbreviated New Drug Application.

3. PROPRIETARY NAME: None. The generic drug name will be used.

4. NUMBER OF VOLUMES SUBMITTED: 1 Archive Copy, containing 2 volumes
   1 Review Copy, containing 2 volumes
   1 Field Submission Copy, containing 2 volumes, (submitted to the Orlando District)

5. THIRD COPY CERTIFICATION STATEMENT: We certify that the third (field) copy of this Abbreviated New Drug Application contains a true copy of all sections, both administrative and technical and has been sent directly to the Orlando District Office.

6. Rx / OTC DRUG STATEMENT: This application is for the production of a prescription drug product (Rx).

RECEIVED
JAN 07 1999
GENERIC DRUGS

4121 34th Street Orlando, FL 32811 (407) 246-1389

7. FACILITY PERSONNEL: The following Nephron Pharmaceuticals Corporation personnel are available to answer questions concerning this submission:

Administration:	Steven F. Simmons, President
Quality Assurance:	J. Brian Lundberg, Director of Quality Assurance
Quality Control:	Angel Pérez, Manager - Quality Control, Chemistry
	Karen Pendleton, Manager - Quality Control, Microbiology
Production:	Raúl Lugo, Manager - Production

8. CONSULTANTS: The following consultants are authorized to act on behalf of Nephron Pharmaceuticals Corporation concerning this ANDA, in the following capacities:

Outside Counsel:

David L. Rosen, R.Ph., J.D.
Attorney at Law
McDermott, Will & Emery
600 13th St, N.W.
Washington, DC 20005-3096
(202) 756-8075

[redacted]

[redacted]

We appreciate the agency's expedient review of our application, and look forward to an early reply.

Sincerely,

NEPHRON PHARMACEUTICALS CORP.

Steven F. Simmons
President