PRODUCT MONOGRAPH

[Pr] phl-IPRATROPIUM

(Ipratropium Bromide Inhalation Solution)

125 µg/mL & 250 µg/mL

Bronchodilator

PHARMEL INC.
8699 8th Avenue
Montréal, Canada
H1Z 2X4

Date of Preparation:
December 14, 2004
Date of Revision:

Control #: 095748

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(Ipratropium Bromide Inhalation Solution)
125 µg/mL & 250 µg/mL

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTION AND CLINICAL PHARMACOLOGY

Ipratropium bromide, a quaternary ammonium derivative of atropine, is an anticholinergic drug which has bronchodilator properties. On inhalation, the onset of action is noted within 5 to 15 minutes, with a peak response between 1 and 2 hours, lasting about 2 additional hours, with subsequent decline from the peak. Bronchodilation is still evident 8 hours after inhalation.

In acute and maintenance therapy of chronic reversible airways obstruction, ipratropium has been shown to provide additive bronchodilating effects to theophylline and beta-adrenoceptor agonists (sympathomimetic amines). Repeated inhalation of ipratropium has not been linked to tolerance towards bronchodilating effects.

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 and $FEF_{25-75\%}$ in increases of 15% or more) occurred within 15 minutes, reached a peak in 1 to 2 hours, and persisted for periods of 4 to 5 hours in the majority of patients, with 25 to 38% of the patients demonstrating increases of at least 15% at 7 to 8 hours. Continued effectiveness of ipratropium solution was demonstrated throughout the 12-week period. In addition, significant changes in forced vital capacity (FVC) have been demonstrated.

Additional controlled 12-week studies were conducted to evaluate the safety and efficacy of ipratropium solution administered concomitantly with bronchodilator solutions of orciprenaline or salbutamol, compared with the administration of each of the beta agonists alone.

Combined therapy produced significant additional responses in FEV_1, FVC and $FEF_{25-75\%}$. On combined therapy, the median duration of 15% improvement in FEV_1 was 5 to 7 hours, compared with 3 to 4 hours in patients receiving a beta agonist alone.

Significant alterations in mucociliary clearance of tracheobronchial secretions (sputum) were not observed in short term clinical trials. Systemic absorption of ipratropium bromide is poor and the blood levels reached are very low. Metabolic studies in healthy volunteers show an average elimination half-life of 3.5 hours (range 1.5 to 4 hours). The drug is transformed to some 8 metabolites with little or no anticholinergic activity.

INDICATIONS AND CLINICAL USE

phl-IPRATROPIUM (ipratropium bromide) solution administered either alone or with a β_2-adrenergic stimulant solution is indicated as a bronchodilator for the maintenance treatment of bronchospasm associated with, or for the therapy of, acute exacerbations of chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. phl-IPRATROPIUM solution, when used in conjunction with a β_2-adrenergic stimulant solution such as fenoterol or salbutamol, is indicated for acute asthmatic attacks. Ipratropium bromide solution is to be administered by compressed air or oxygen driven nebulizers.

CONTRAINDICATIONS

Known hypersensitivity to phl-IPRATROPIUM (ipratropium bromide), to any of the product ingredients, or to atropinics.

WARNINGS

Ipratropium bromide solution in the 20-mL multidose bottle contains preservatives (benzalkonium chloride and disodium ethylene diamine tetraacetic acid – EDTA-disodium). It has been reported that these preservatives may cause bronchoconstriction in some patients with hyperreactive airways.

The unit dose vials do not contain preservatives.

Patients with Cystic Fibrosis may be more prone to gastrointestinal motility disturbances.

Ipratropium bromide should not be used alone for the abatement of an acute asthmatic attack since the drug has a slower onset of effect than that of an adrenergic β_2 agonist.

Glaucoma, Angle-Closure: Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulized solution does not escape into the eyes. In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of a combined ipratropium/β_2-agonist solution should be avoided unless measures (e.g. use of swimming goggles or use of a nebulizer with a mouth piece) are taken to ensure that nebulized solution does not reach the eye. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, angle closure glaucoma) when nebulized ipratropium either alone or in combination with an adrenergic β_2 agonist solution has escaped into the eyes. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition.

Pregnancy: The safety of ipratropium in pregnancy has not been established. The benefits of using ipratropium bromide when pregnancy is confirmed or suspected must be weighed against possible hazards to the fetus. Studies in rats, mice and rabbits showed neither embryotoxic nor teratogenic effects.

Lactation: No specific studies have been conducted on excretion of this drug in breast milk. Benefits of ipratropium bromide use during lactation should therefore be weighed against the possible effects on the infant.

Children: The efficacy and safety of ipratropium bromide in children younger than 5 years has not
been established.

PRECAUTIONS

- Ipratropium bromide solution (Bottles and UDVs) is intended for inhalation with suitable nebulizing devices and should not be taken orally or administered parenterally.
- Patients should be instructed in the proper use of the nebulizer.
- Caution is advised against accidental release of the solution into the eyes.
- In patients with glaucoma, prostatic hypertrophy or urinary retention, ipratropium bromide should be used with caution.
- If a reduced response to ipratropium bromide becomes apparent, the patient should seek medical advice.
- Ipratropium bromide solution, when administered to patients with acute severe asthma, should be used with concomitant β_2-adrenergic stimulant therapy.
- Immediate hypersensitivity reactions may occur after administration of ipratropium bromide solution, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal edema.

Use with other Drugs: In patients receiving other anticholinergic drugs, ipratropium bromide should be used with caution because of possible additive effects.

Ipratropium bromide solution with preservatives (i.e., from the 20 mL multidose bottle) should not be mixed with sodium cromoglycate, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with ipratropium bromide solution without preservatives (i.e., from the unit dose vial).

ADVERSE REACTIONS

Because of the low systemic absorption of ipratropium bromide, anticholinergic side effects, such as tachycardia and palpitations, ocular accomodation disturbances, gastrointestinal motility disturbances and urinary retention; are rare and reversible, although the risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Acute Administration: The frequency of adverse reactions recorded in 214 patients receiving ipratropium bromide solution was as follows:

ADVERSE EFFECT	***% OF PATIENTS***
Dry mouth or throat	9.3
Bad taste	5.1
Tremor	4.2
Exacerbation of symptoms	4.2
Burning eyes	0.9
Nausea	0.9
Sweating	0.9
Cough	0.9
Headache	0.5
Palpitations	0.5

The adverse effect judged to be most severe was exacerbation of bronchospasm. This occurred in 8 patients treated with ipratropium bromide solution alone, 6 of whom withdrew from the clinical studies.

Bronchospasm occurred in 3 patients with acute severe asthma who received ipratropium bromide solution alone. In two patients, this was reversed after therapy with a β_2 sympathomimetic solution. The third patient received no other therapy.

The following table compares the incidence of adverse effects of the combination of ipratropium bromide and a β_2 agonist (either fenoterol or salbutamol) solution with that of the β_2 agonist alone.

Adverse Effect	***Ipratropium+β_2 Agonist*** **(*% of 94 patients*)**	***β_2 agonist*** **(*% of 96 patients*)**
Tremor	31.9	26.0
Dry Mouth	16.0	28.1
Bad Taste	16.0	13.5
Vomiting	2.1	2.1
Palpitations	2.1	1.0
Headache	1.1	2.1
Cough	1.1	0.0
Flushing	1.1	0.0
Dizziness	0.0	1.0
Numbness in Leg	0.0	1.0

Chronic Administration: The frequency of adverse reactions reported as possibly related to ipratropium bromide treatment in 219 COPD patients participating in long-term (12-week) controlled clinical trials was as follows:

ADVERSE EFFECT	***% OF PATIENTS***
Dry Mouth	2.7
Coughing	1.8
Dyspnea	1.8
Headache	1.8
Urinary Retention	1.4
Tremor	0.9
Nausea	0.9
Palpitation	0.9
Sputum Increased	0.9
Rhinitis	0.9
Eye Pain	0.9

The following other adverse events were reported as possibly related to drug treatment in one patient each: bronchitis, bronchospasm, chest pain, depression, fatigue, flu-symptoms, hypoaesthesia, increased saliva, insomnia, nervousness, pain, paraesthesia, pharyngitis, somnolence, tachycardia and urticaria.

The frequency of adverse reactions reported as possibly related to drug treatment in >1% of COPD patients participating in long-term (12-week) controlled clinical trials that compared the efficacy and safety of ipratropium+β_2 agonists (metaproterenol or salbutamol) *vs* the β_2 agonist

alone, was as follows:

Adverse Effect	***Ipratropium + β_2 Agonist*** (***% of patients***) ***(n=208)***	***β_2 agonist*** (***% of patients***) ***(n=417)***
Headache	4.3	1.7
Tremor	3.8	3.4
Nervousness	3.8	1.9
Dyspnea	2.4	3.4
Dry mouth	2.4	1.0
Bronchitis	2.9	2.9
Dizziness	1.4	1.9
Coughing	1.4	1.0
Taste perversion	1.9	1.2
Insomnia	1.9	0.2
Dysuria	1.0	0.2
Nausea	1.0	1.7
Abnormal vision	0.5	1.2
Chest pain	1.4	0.7
Constipation	1.4	0.0
Dysphonia	1.0	0.2
Dyspepsia	1.0	0.0
Bronchospasm aggravated	1.0	0.7
Micturition frequency	1.0	0.2

There have been isolated reports of ocular effects such as mydriasis, increased intraocular pressure, and acute glaucoma associated with the escape of nebulized ipratropium bromide (alone or in combination with a β_2 agonist solution) into the eyes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Doses of ipratropium bromide up to 1.2 mg (approximately 30 times the therapeutic dose) have been administered by inhaler without the appearance of serious systemic anticholinergic effects.

Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

DOSAGE AND ADMINISTRATION

Counselling by physicians on smoking cessation should be the first step in treating patients with chronic obstructive pulmonary disease (COPD) who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

In adults, the average single dose of phl-IPRATROPIUM (ipratropium bromide) solution is 250–500 µg of ipratropium bromide. In children, aged 5–12 years, the recommended dose is 125–250 µg of ipratropium bromide. In most cases, dilution of the dose with sterile preservative-free saline is not necessary. However, volumes of ipratropium bromide solution less than 2 mLs are not appropriate for nebulization and must be diluted with saline or another suitable nebulizer solution to make up a total fill volume of 2-5 mL (see PHARMACEUTICAL INFORMATION).

Nebulization should take place using a gas flow (oxygen or compressed air) of 6–10 L/min and the solution nebulized to dryness over a 10–15 minute period. The Hudson Updraft™, Bennett Twin Jet®, Debilbiss, Pari Compressors and Inspiron Mini-Neb® nebulizers, with facemask or mouthpiece have been used. The manufacturers' instructions concerning cleaning and maintenance of the nebulizer should be strictly followed.

Treatment with phl-IPRATROPIUM solution may be repeated every 4–6 hours as necessary.

Daily doses exceeding 2 mg in adults should be given under medical supervision.

For the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, the recommended dose is 500 µg of phl-IPRATROPIUM solution given 3-4 times per day.

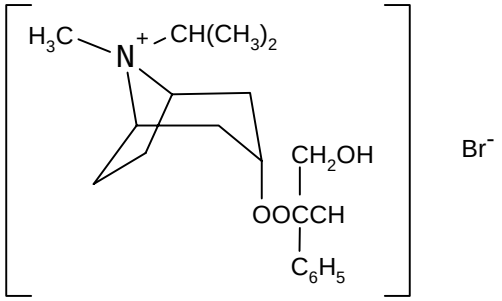
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Ipratropium Bromide (BAN, USAN, rINN)

Chemical Name: (8r)-3α hydroxy-8-Isopropyl-1αH, 5αH-tropanium bromide

Structural Formula:



Molecular Formula: $C_{20}H_{30}NO_3Br$

Molecular Weight: 412.37

Description: White crystalline substance with a bitter taste. Freely soluble in water and in alcohol; insoluble in chloroform and in ether. In neutral and acid solutions the substance is rather stable; in alkaline solutions the ester bond is rapidly hydrolyzed. Melting point: 230˚C, with decomposition.

Composition

1-mL Unit Dose Vial (single use): Ipratropium bromide 250 µg/mL (0.025%) in normal saline (9 mg/mL [0.9%] sodium chloride solution).

2-mL Unit Dose Vial (single use): Ipratropium bromide 125 µg/mL (0.0125%) in normal saline (9 mg/mL [0.9%] sodium chloride solution).

2-mL Unit Dose Vial (single use): Ipratropium bromide 250 µg/mL (0.025%) in normal saline (9 mg/mL [0.9%] sodium chloride solution).

20-mL Bottle (multidose): Ipratropium bromide 250 µg/mL (0.025%) in normal saline (9 mg/mL [0.9%] sodium chloride solution) with benzalkonium chloride and EDTA-disodium as preservatives.

Stability and Storage Recommendations

1 mL or 2 mL Unit Dose Vials: Unopened unit dose vials of phl-IPRATROPIUM solution should be stored at controlled room temperature (between 15˚ and 25˚C) and protected from heat and light. If required, the solution should be diluted with a preservative-free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

The solution is physically compatible with Alupent® (orciprenaline sulfate), Berotec® (fenoterol hydrobromide) or salbutamol sulfate (6 mg/mL) solutions. If such mixtures are prepared, they should be diluted with preservative-free sterile sodium chloride solution 0.9% and used immediately. Any unused portion of such combined solutions must be discarded.

20-mL Bottles: Unopened bottles of phl-IPRATROPIUM solution should be stored at controlled room temperature (between 15˚ and 25˚C). Solutions diluted with preservative-free sterile Sodium Chloride Inhalation Solution, USP 0.9% should be used within 24 hours from time of dilution when stored at room temperature and within 48 hours when stored in the refrigerator.

A controlled Preservative Challenge test, done in accordance with the current USP guideline for Preservative Efficacy Testing, indicated that bottles of Ipratropium Inhalation Solution, opened and closed several times, simulating patient use, were stable for up to 28 days when stored at room temperature (15˚-25˚C).

Controlled laboratory experiments using mixtures of the ipratropium bromide solution with Alupent® (orciprenaline sulfate), Berotec® (fenoterol hydrobromide) or salbutamol sulfate (6 mg/mL preserved with benzalkonium chloride) solutions and diluted with a sterile bacteriostatic sodium chloride solution 0.9% (i.e. normal saline), preserved with benzalkonium chloride, indicated that such mixtures were stable for 7 days at room temperature. For the preparation of such mixtures, it is recommended that only sterile solutions of bacteriostatic sodium chloride 0.9% preserved with 0.01% benzalkonium chloride be used to maintain the level of preservative in the mixture.
The safety of preservatives other than benzalkonium chloride has not been established.

Incompatibilities: phl-IPRATROPIUM solution with preservatives (i.e. from the 20 mL multidose bottle) should not be mixed with sodium cromoglycate solution, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with phl-IPRATROPIUM solution without preservatives (i.e. from the unit dose vial).

AVAILABILITY OF DOSAGE FORMS

1 mL Unit Dose Vial: phl-IPRATROPIUM (ipratropium bromide) solution provided as 1 mL of clear, colourless solution containing 250 µg/mL (0.025%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 250 µg of ipratropium bromide. Available is cartons of 10 and 20 vials.

2 mL Unit Dose Vial (125 µg/mL): phl-IPRATROPIUM solution provided as 2 mL of clear, colourless solution containing 125 µg/mL (0.0125%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 250 µg of ipratropium bromide. Available is cartons of 10 and 20 vials.

2 mL Unit Dose Vial (250 µg/mL): phl-IPRATROPIUM solution provided as 2 mL of clear, colourless solution containing 250 µg/mL (0.025%) ipratropium bromide in isotonic solution, presented in a plastic single use sterule (vial). Each vial contains a total of 500 µg of ipratropium bromide. Available in cartons of 10 and 20 vials.

20 mL Bottle: phl-IPRATROPIUM solution provided as 20 mL of clear, colourless or almost colourless solution containing 250 µg/mL (0.025%) ipratropium bromide in isotonic solution. This solution is preserved with benzalkonium chloride 250 µg/mL and EDTA-disodium 500 µg/mL at a pH of 3.4, and is presented in an amber glass bottle with screwcap.

INFORMATION FOR THE PATIENT

phl-IPRATROPIUM (Ipratropium Bromide) Solution (20 mL Bottle)

PLEASE READ THIS INFORMATION CAREFULLY AND COMPLETELY BEFORE YOU USE

phl-IPRATROPIUM

What is phl-IPRATROPIUM Solution (20 mL Bottle)

phl-IPRATROPIUM solution is a bronchodilator which relieves the wheezing and shortness of breath caused by chronic bronchitis or by asthma. For the treatment of asthma, phl-IPRATROPIUM must be used in conjunction with some other bronchodilating medication. phl-IPRATROPIUM contains 250 μg/mL (0.025%) ipratropium bromide and the preservatives benzalkonium chloride and disodium ethylene diamine tetraacetic acid (EDTA-disodium). It is available only on prescription.

Before starting treatment with phl-IPRATROPIUM, be certain that you are completely familiar with the use and proper care of your nebulizer.

What is COPD?

COPD (Chronic Obstructive Pulmonary Disease) is a type of lung disease in which there is permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. Smoking cessation produces symptomatic benefits and will slow the progression of chronic bronchitis (which is a form of COPD). COPD can be helped by medication as well.

What is Asthma?

Asthma is a disease in which the airways can become temporarily narrowed, leading to breathing difficulties. This narrowing of the airways is due to inflammation, which causes swelling and irritation of the airways and tightening of the muscles around the airways. The narrowed airway can be relieved with the help of medication.

It is important to know that the treatment of COPD and Asthma may be different for each patient. Your doctor will most likely discuss with you the best plan for the treatment of ***your*** *particular condition. This plan may include taking other medication(s) in addition to phl-IPRATROPIUM. It is necessary that you follow your doctor's directions for the treatment of your condition. If you have any questions about how you should treat your condition at home, you should consult your doctor.*

What you should tell your doctor before you use phl-IPRATROPIUM solution?

It is very important to tell your doctor the following:

- If you may be pregnant or wish to become pregnant;
- If you are breast feeding;
- If you are taking any medications, including those you can buy without a prescription and including eye drops;
- If you have any other medical problems such as difficult urination or enlarged prostate;
- If you have eye problems, such as glaucoma or eye pain;
- If you have any special allergies to foods or drugs.

Usage Instructions (20 mL Bottle)

Your doctor or pharmacist will tell you how to prepare your phl-IPRATROPIUM solution for inhalation. If you are told to dilute phl-IPRATROPIUM solution, you must do so immediately before you plan to use the solution.

In most cases, dilution of the dose with sterile preservative-free saline is not necessary. However, volumes of ipratropium bromide solution less than 2 mLs are not appropriate for nebulization and must be diluted with saline or another suitable nebulizer solution to make up
a total fill volume of 2-5 mL.

1) Immediately before you plan to use the nebulizer, using a syringe, withdraw the prescribed dose (usually ½ to 2 mL [cc]) of phl-IPRATROPIUM solution from the bottle and add to the nebulizer chamber. Do not store the prescribed dose in the syringe for later use.

2) If your doctor has instructed you to use another inhalation solution in combination with phl-IPRATROPIUM solution, you should add the appropriate amount of that solution to the nebulizer chamber as well.

3) Add sodium chloride solution to the chamber, if you have been directed to do so by your physician or pharmacist.

4) Gently shake the nebulizer chamber and connect it to the mouthpiece or face mask. Then connect the nebulizer tube to the air or oxygen pump and begin therapy.

5) Breathe calmly and deeply through the mask or mouthpiece until no more mist is formed in the nebulizer chamber. This usually takes 10-15 minutes. **It is very important to adjust the face mask, if required, to prevent the mist from getting in your eyes.**

6) Store your re-capped bottle of phl-IPRATROPIUM solution and sodium chloride solution in the refrigerator until the next treatment.

7) Follow the instructions provided by the nebulizer and air pump manufacturers for the proper care and maintenance of the equipment. Keep the nebulizer, nebulizer tube and face mask clean to minimize microbial contamination.

Please Remember

- **Do not exceed the prescribed dose or frequency of treatments.**
- **Do not mix this medication with any other medications in the nebulizer unless instructed to do so by your doctor or pharmacist.**
- **This medication has been prescribed for you and should not be given to other people.**
- **Keep out of the reach of children.**
- **The solution is intended for inhalation only. Do not inject or drink it.**
- **Do not let the nebulized mist get into your eyes. Patients with glaucoma should use swimming goggles or a nebulizer with a mouthpiece to prevent nebulized solution from getting to the eyes.**

As well as its desired effects, phl-IPRATROPIUM solution, like any medication, may cause some unwanted effects.

If you experience a dry mouth or bad taste, sucking on a sour candy or rinsing your mouth may help.

Check with your doctor if the dry mouth or bad taste persists or if you experience

constipation.

Consult your doctor immediately if you experience any of the following:

- **Increased wheezing or tightness in the chest;**
- **Swelling of the tongue or lips;**
- **Difficulty in swallowing;**
- **Fast or irregular heart beat;**
- **Blurred vision or pain in the eyes;**
- **Difficult or painful urination;**
- **Skin rash.**

If you do not get the expected relief from your treatment, you should contact your doctor.

Remember to tell any other doctor, dentist or pharmacist you consult that you are taking this medication.

If you have any questions about phl-IPRATROPIUM solution or your nebulizer, contact your doctor or pharmacist.

INFORMATION FOR THE PATIENT

phl-IPRATROPIUM INHALATION SOLUTION (Unit Dose Vial)

Ipratropium Bromide Solution STERILE

Directions for use of phl-IPRATROPIUM INHALATION SOLUTION at home.

Please read this insert carefully before you start your medicine. For further information or advice, ask your doctor or pharmacist. You may want to read this insert again. PLEASE DO NOT THROW IT AWAY UNTIL YOU HAVE FINISHED YOUR MEDICINE.

What is phl-IPRATROPIUM Solution?

phl-IPRATROPIUM solution is a bronchodilator which relieves the wheezing and shortness of breath caused by chronic bronchitis or by asthma. For the treatment of asthma, phl-IPRATROPIUM must be used in conjunction with some other bronchodilating medication. phl-IPRATROPIUM solution is available only on prescription.

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COPD (Chronic Obstructive Pulmonary Disease) is a type of lung disease in which there is permanent narrowing of the airways, leading to breathing difficulties. In many patients, this narrowing of the airways is a result of many years of cigarette smoking. Smoking cessation produces symptomatic benefits and will slow or stop the progression of chronic bronchitis (which is a form of COPD). COPD can be helped by medication as well.

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- If you are taking any medications, including those you can buy without a prescription and including eye drops;
- If you have any other medical problems such as difficult urination or enlarged prostate;
- If you have eye problems, such as glaucoma or eye pain;
- If you have any special allergies to foods or drugs.

Polynebs®

1 mL polyneb®

250 µg/mL

Each plastic polyneb® contains 1 mL phl-IPRATROPIUM solution. Each millilitre (mL) of solution contains 250 µg (0.025%) ipratropium bromide in an isotonic solution.

2 mL polyneb®

125 µg/mL

Each plastic polyneb® contains 2 mL phl-IPRATROPIUM solution. Each millilitre (mL) of solution contains 125 µg (0.0125%) ipratropium bromide in an isotonic solution.

250 µg/mL

Each plastic polyneb® contains 2 mL phl-IPRATROPIUM solution. Each millilitre (mL) of solution contains 250 µg (0.025%) ipratropium bromide in an isotonic solution.

Before starting treatment with phl-IPRATROPIUM solution, be certain that you are completely familiar with the use and proper care of your nebulizer.

Usage Instructions:

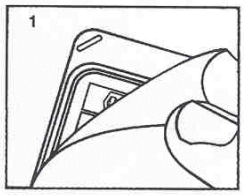
Your doctor or pharmacist will tell you how to prepare your phl-IPRATROPIUM solution for inhalation. If you are told to dilute phl-IPRATROPIUM solution, you must do so immediately before you plan to use the solution.

Your doctor of pharmacist might instruct you to use preservative-free, sterile sodium chloride solution 0.9% to dilute the phl-IPRATROPIUM solution if necessary.

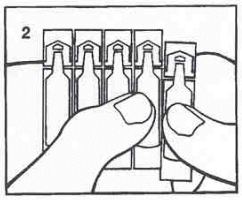
1) The contents of phl-IPRATROPIUM polynebs® are to be inhaled from a nebulizer. Do not open the foil pack until the polynebs® are required.

2) To open the foil pack, lift the foil at the black arrow and peel (**Diagram 1**). Do not peel the lid off completely. Remove the polynebs®.

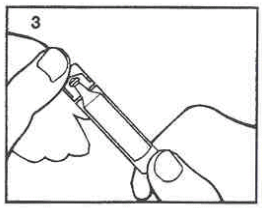
3) To detach a phl-IPRATROPIUM polyneb® push one polyneb® downwards and away while holding the remaining polynebs® securely (**Diagram 2**). Return the remaining polynebs® to the foil tray, cover the tray with the foil lid and place the tray back in the carton.

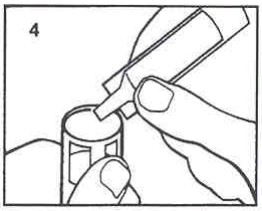


4) Holding the top of the polyneb® securely, twist the body to open (**Diagram 3**). It is important that you use the contents of the polyneb® **as soon as possible** after opening it.



5) Place the open end of the polyneb® well into the nebulizer cup and squeeze slowly (**Diagram 4**). Squeeze the contents of the polyneb® into your nebulizer chamber. If your doctor has instructed you to use less than one complete polyneb®, use a syringe to withdraw the prescribed dose. Any solution left in the polyneb® must be thrown away.





6) If your doctor has instructed you to use another inhalation solution in combination with phl-IPRATROPIUM solution, you should add the appropriate amount of that solution to the nebulizer chamber as well.

7) Using a syringe, add sodium chloride solution to the chamber if you have been directed to do so by your pharmacist or physician.

8) Gently shake the nebulizer chamber and connect it to the mouthpiece or face mask. Then connect the nebulizer tube to the air or oxygen pump and begin therapy.

9) Breathe calmly and deeply through the mask or mouthpiece until no more mist is formed in the nebulizer chamber. This usually takes 10 to 15 minutes. **It is very important** to adjust the face mask, if required, to prevent the mist from getting in your eyes.

10) Follow the instructions provided by the nebulizer and air pump manufacturers for the proper care and maintenance of the equipment. Keep the nebulizer, nebulizer tube and face mask clean to minimize microbial contamination.

11) The polynebs® should be stored at room temperature (between 15˚ and 25˚C). The polynebs® should be protected from heat and light. Discard any unused polynebs® in opened foil packs after 3 months.

Please Remember

- **Do not exceed the prescribed dose or frequency of treatments.**
- **Do not mix this medication with any other medications in the nebulizer unless instructed to do so by your doctor or pharmacist.**
- **This medication has been prescribed for you and should not be given to other people.**
- **Keep out of the reach of children.**
- **The solution is intended for inhalation only. Do not inject or drink it.**
- **Do not let the nebulized mist get into your eyes. Patients with glaucoma should use swimming goggles or a nebulizer with a mouthpiece to prevent nebulized solution from getting into the eyes.**

As well as its desired effects, phl-IPRATROPIUM solution, like any medication, may cause some unwanted effects.

If you experience a dry mouth or bad taste, sucking on a sour candy or rinsing your mouth may help.

Check with your doctor if the dry mouth or bad taste persists or if you experience constipation.

Consult your doctor immediately if you experience any of the following:

- **Increased wheezing or tightness in the chest;**
- **Swelling of the tongue or lips;**
- **Difficulty in swallowing;**
- **Fast or irregular heart beat;**
- **Blurred vision or pain in the eyes;**
- **Difficult or painful urination;**
- **Skin rash.**

If you do not get the expected relief from your treatment, you should contact your doctor.

Remember to tell any other doctor, dentist or pharmacist you consult that you are taking this medication.

If you have any questions about phl-IPRATROPIUM solution or your nebulizer, contact your doctor or pharmacist.

PHARMEL INC.
Montréal, CANADA, H1Z 2X4

PHARMACOLOGY

Ipratropium bromide is an anticholinergic agent which, when delivered by aerosol, exerts its effects primarily in the bronchial tree. It abolishes acetylcholine-induced bronchospasm in the guinea pig and dog after intravenous administration at an ED_{50} of 0.15–0.40 μg/kg with a transient effect on blood pressure. By inhalation, approximately 25 μg of ipratropium bromide produces a 50% inhibition of acetylcholine-induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to i.v. administration. Histological evaluation of human bronchial mucosae following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 μg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from an s.c. dose of about 0.011 mg/kg, equipotent to atropine, but the equi-effective oral dose of ipratropium was 58 times greater. When given by inhalation, no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. In another experiment, blood pressure and heart rate in the dog could be modulated after i.v. administration of low doses of ipratropium bromide, but metered aerosol administration of 100 puffs (40 μg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff) produced a 50% inhibition of salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after s.c. doses but were 10-20 times less after oral administration. Tests of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system.

Ipratropium bromide, subcutaneously, inhibited the secretory effects of the cholinergic agonist, oxtremorine, in mice. It also exhibited spasmolytic effects equivalent to or greater than atropine in isolated guinea pig gut. *In vitro* tests with the isolated rectum of the guinea pig demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride induced spasm. Ipratropium bromide exerted anticholinergic effects on the *in situ* bladder and intestine preparations of the dog. Intravenous doses were 500 times more potent than oral or intraduodenal administration. Ipratropium bromide was administered by inhalation in combination with a β_2 sympathomimetic agent (fenoterol hydrobromide). In both the dog and guinea pig, these agents were additive in antagonizing acetylcholine induced bronchospasm with ED_{50} being 19.8 μg (ipratropium), 49.25 μg (fenoterol) and 11.05 μg + 27.63 μg (ipratropium + fenoterol). In the dog, 50 μg of fenoterol by inhalation produced an 8% increase in heart rate and a 16% increase in left ventricular dp/dt. When 20 μg ipratropium was added to the above, the corresponding increases were 8% and 9%.

Clinical Pharmacology

Pharmacokinetics

In man, inhalation of 555 μg by inhaler of radiolabelled ipratropium bromide, about 14 times the recommended therapeutic dose, produced peak plasma levels (ipratropium and its metabolites) of 0.06 ng/mL after 3 hours. The time to reach peak plasma concentration was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited on the pharyngeal mucosae and swallowed. Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues (half-life of an alpha phase approximately 5 minutes), and a terminal half-life (beta phase) of 3-4 hours. Plasma concentrations after inhaled ipratropium bromide were about 1000 times lower than equipotent oral or intravenous doses (15 & 0.15 mg respectively). Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog. However, the main metabolites bind poorly to the muscarinic receptor.

In man, about 70% of the ^{14}C labelled drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination of ipratropium and its metabolites occurs primarily via the kidney with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the radiolabelled dose is detectable in the feces, suggesting relatively low lung deposition and poor absorption of the swallowed portion.

Direct (non-radioactive) determination of ipratropium bromide revealed that this active ingredient is absorbed very quickly after oral administration. The peak plasma concentrations are reached only minutes after inhalation. The systemic bioavailability after inhalation of 2 mg ipratropium bromide, via an ultrasonic Mizer inhaler, over 20 minutes is estimated to be 7% of the dose. The bioavailability of the swallowed portion of the dose is approximately 2%.

Parameters describing the disposition of ipratropium bromide were calculated from the plasma concentrations after i.v. administration. A rapid biphasic decline in plasma is noted for ipratropium. The half-life of the terminal elimination phase is about 1.6 hours. The total clearance of the active ingredient is 2.3 L/min. Approximately 40% of the clearance is renal (0.9 L/min) and 60% non-renal i.e. mainly hepato-metabolic. The volume of distribution is 338 L (corresponding to approximately 4.6 L/kg).

Renal excretion of the active ingredient is 46% of the dose after intravenous administration and ≤3% of the dose after oral inhalation. Depending on the formulation and inhalation technique, renal excretion may increase up to 13% of the dose (40 or 80 μg dose), reflecting a higher deposition in

the airways and a higher bioavailability.

Radio-labelled technetium was administered with ipratropium solution in an adult dose finding study. The following table outlines the doses reaching the patient. The figures for ipratropium inhaler are published estimates.

Dose Available (µg)	**Amount Reaching Patient (µg)**	**Lung Dose (µg)**
500	53	17.0
250	27	8.5
125	13	4.3
40 (ipratropium inhaler)	40	4.4

The drug is minimally (less than 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the quartenary amine structure of the molecule.

Pharmacodynamics

Large, single inhaled doses of ipratropium bromide have been given to man without any signs of toxicity. After the administration of 400 μg by inhaler (10 times the recommended single dose) to 10 normal subjects, no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accomodation or electrocardiograms. Likewise, in another study, no changes in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhaler to 12 normal volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients again have not revealed any systemic anticholinergic effects. In one study, 14 patients were treated for 45 days with either ipratropium bromide inhaler 40 μg q.i.d. or ipratropium bromide inhaler 40 μg q.i.d. + oral Berotec 5 mg q.i.d. No changes in visual acuity, intraocular pressure, pupil size or accomodation of vision occurred. Micturition function studies in 20 male patients showed no differences in urinary flow, total flow time, and time until maximum flow between placebo and ipratropium bromide inhaler 40 μg t.i.d. administered for 3 days.

Deterioration in pulmonary function in patients treated in all clinical trials with therapeutic doses of ipratropium solution was examined. The following table shows the number of patients who showed a 15% or greater fall in FEV_1 at any time within 2 hours following the administration of the drug. Also shown are the figures for comparative agents used.

Treatment	**Incidence**	
Normal saline	15/90	(16.7%)
Ipratropium Solution	14/214	(6.5%)
Ipratropium Inhaler	4/78	(5.1%)
Berotec Solution	4/83	(4.8%)
Ipratropium Soln+Berotec Soln	1/81	(1.2%)

Dose titration studies in stable asthmatic patients with ipratropium bromide solution have indicated that maximal improvement in pulmonary function occurs at approximately 250 μg for adults and 125 μg for children over 5 years.

A clinical pharmacology study comparing single doses of ipratropium inhaler (80 μg) and ipratropium solution (250 μg) in 16 stable adult asthmatics was performed. No difference between the regimens was found, based on an improvement in pulmonary function over a 2 hour period.

A wide variety of challenge studies have been conducted utilizing ipratropium bromide as a protective agent. In pharmacologically induced bronchospasm, ipratropium bromide, in clinical doses, was very effective against methacholine and acetylcholine, moderately effective against propranolol but had little or no effect against histamine or serotonin. Studies in exercise-induced bronchospasm have yielded variable results. Some investigations have indicated that ipratropium bromide has little or no effect but other studies have shown that some patients are protected against bronchospasm induced by exercise. Likewise, the protective effects of ipratropium bromide against cold air induced bronchospasm have been variable.

Antigen challenge studies have demonstrated that ipratropium bromide offers some protection against the "early" allergic asthma response, but has no effect on the "late" response.

TOXICOLOGY

Acute

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322
Mouse		s.c.	300
Mouse		oral	2010
Mouse		oral	1038
Rat		i.v.	15.8
Rat		s.c.	1500
Rat		oral	4000
Rat		oral	1722

The signs of toxicity were apathy, reduced mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after i.v. administration and for 8 days after oral administration.

Ipratropium Bromide + Fenoterol Hydrobromide (Ratio 1:2.5)

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	M	i.v.	23.6
Mouse	F	i.v.	26.2
Mouse	M	oral	630
Mouse	F	oral	650
Rat	M	i.v.	32.5
Rat	F	i.v.	32.5
Rat	M	oral	3200
Rat	F	oral	2450

The signs of toxicity were spasmodic breathing, tonic, clonic and saltatory convulsions, sedation, ataxia, spasms, exophthalmus, chromolacryorrhoea, reduced motility, tremor and positive sliding test. Late mortality occurred only after oral administration.

Acute dose tolerance studies were performed in dogs. No deaths occurred up to doses of 400 mg/kg oral or 50 mg/kg s.c. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature, and death from respiratory failure.

An acute inhalation toxicity study of ipratropium bromide administered as 4% and 8% solution to guinea pigs was performed. No toxic signs were observed with the 4% solution and death occurred after 5 hours of administration with the 8% solution (approximately 200 mg/kg).

An acute inhalation tolerance study was performed in rats with benzalkonium chloride (0.025%) or benzalkonium chloride (0.025%) + ipratropium bromide (0.025%) administered over 8 hours. No clinical signs of intolerance were observed. Necropsy and histological findings (16 hours and 14 days after administration) were also negative.

Anesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given i.v. infusions (10 mg/kg/min) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

An acute inhalation dose tolerance study in rats using doses of up to 160 puffs (3.2 mg) from an ipratropium bromide inhaler was performed. No deaths occurred. A combination of ipratropium bromide (up to 3.2 mg/kg) with fenoterol hydrobromide (up to 8 mg/kg) was administered by inhaler (up to 320 puffs) to rats. There were no deaths or clinical signs observed.

Subacute

Oral: A subacute toxicity study of 9 weeks duration in rats utilizing doses of 10, 100 and 500 mg/kg revealed no pathological findings apart from a dose related decrease in food consumption and growth rate.

A 4-week study in dogs, using doses of 3, 30 and 150 (for 3 weeks) increased to 300 mg/kg showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of 6 dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study in dogs of 13 weeks duration, using doses of 1.5, 3.0 and 15 mg/kg revealed no pathological changes apart from a dose-related inhibition of lacrimal secretions and associated keratoconjunctivitis and dryness of the mouth.

Intravenous: A 32-day study in rats was conducted with the combination of ipratropium bromide and fenoterol hydrobromide at doses of 1.32+3.32 μg/kg (Group 1), 8+20 μg/kg (Group 2), and 24+60 μg/kg (Group 3) respectively. Fenoterol 60 μg/kg (Group 4) and ipratropium 24 μg/kg (Group 5) were also administered. Increases in heart rate (dose related in all treated animals) and dry mouth and nose (Groups 3 and 5) were seen. Increases in LDH (Groups 3 and 4), creatine kinase (all treated Groups), potassium (Groups 2, 3 and 4) and cholesterol (Groups 3 and 4) were observed. Myocardial scars were seen in one animal in Group 3 and fatty changes in the liver were noted in one animal in Group 4.

Subcutaneous: Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg dose group from paralytic ileus. Inflammatory changes were noted at the injection site.

A 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last 5 days) was conducted. Dryness of the oral and nasal mucous membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and body weight also occurred. One dog died in the high dose group. Signs of liver damage were noted in 2 high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation: Twelve rats were exposed to aerosolized ipratropium bromide in a concentration of 11.5 μg/L for 1 hour, 4 times per day for 7 days. No drug toxicity was found.

In another study, administration of ipratropium bromide in doses of 128, 256 and 384 μg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2/9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 μg of ipratropium bromide twice a day (total dose 1 mg/day) for 7 days without the appearance of any drug induced toxicity.

In another study rhesus monkeys were given ipratropium bromide in doses of 200, 400 and 800

µg/day by inhalation for 6 weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

Rats were exposed to a combination of fenoterol and ipratropium twice, 4 times and 8 times per day. Metered dose inhalers containing 50 µg fenoterol and 20 µg ipratropium per actuation were discharged into the exposure chamber at a rate of 6 doses per minute for 25 minutes over a 7 day period. No changes apart from a reduction in food consumption in the first 2 days in the high dose group were noted.

A 28 day study in dogs was conducted using fenoterol and ipratropium in the following doses respectively: 350+140 µg (Group 3); 1050+420 µg (Group 4); 3150+1260 µg (Group 5). Vasodilation occurred in Groups 4 and 5 and heart rate was increased in the treated animals. Potassium levels were raised in Group 5. Liver glycogen content was raised in 4 (of 6) animals in Group 5 and 2 in Group 4.

A further 13 week combination study was done in dogs using doses 23+9 µg (Group 1), 160+64 µg (Group 2) and 1100+440 µg (Group 3) fenoterol+ipratropium respectively. Peripheral hyperemia and dry mucous membranes were observed in all treated animals. Increases in heart rate were seen in Groups 1 to 3, and 5 of 6 dogs in Group 3 had disturbances of impulse formation and conduction. Slight increases in GPT in Groups 2 and 3, as well as increases in AP in individual animals of Groups 1 to 3 were noted. Histological findings consisted of a scar in the papillary muscle of the left ventricle of one dog in Group 3 as well as centrolobular fatty infiltration of hepatocytes in dogs of Groups 2 and 3.

Chronic

Oral: A 6 month and a 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after 14 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostasis and dilatation of the intestines was observed in the highest dose groups. A toxic hepatosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs in doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions -- the latter

leading to keratoconjunctivitis – was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in 2 dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver, which varied from animal to animal, was also seen.

Inhalation: A 6 month study in rats was performed using doses of 128, 256 and 384 μg per rat per day. Measurements included ciliary beat frequency, lung mechanics and blood gas. The only finding was a dose related decrease in growth rate of the male animals.

A 6 month inhalation toxicity study was performed in rhesus monkeys utilizing daily doses of 20, 800 and 1600 μg. All findings were negative including measurements of lung mechanics, ciliary beat frequency and blood gases.

Mutagenicity

Three Ames tests, a micronucleus test in mice, a cytogenetic study in Chinese hamsters, and a dominant lethal test in mice were performed to assess the mutagenic potential of ipratropium bromide. Two positive tests (one Ames and the micronucleus study) were apparently spurious as they could not be reproduced with subsequent exhaustive experimentation. In the cytogenetic study, a dose related increase in the number of chromatid gaps, but not of other aberrations, was seen. The significance of this finding is not known. All other test results were negative.

Carcinogenicity

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorigenic or carcinogenic effect.

Reproductive Studies

Three teratological studies, one in mice using oral doses of 2 and 10 mg/kg, and two in rats, were performed. The first study used the same doses and the second employed 10 and 20 mg/kg and revealed no drug induced fetal abnormalities.

A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again showed no teratogenic or

embryotoxic effects of ipratropium bromide.

An inhalation teratology study in rabbits using doses of 0.3, 0.9 and 1.8 mg/kg demonstrated no effect on litter parameters, and no embryotoxic or teratogenic effects.

Two inhalation teratology studies with the combination of fenoterol and ipratropium in rats (doses up to 8 x 25 minute exposures of 7.5 mg fenoterol+3.0 mg ipratropium per day) and rabbits (doses up to 3.0 mg fenoterol+1.2 mg ipratropium) revealed no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg being given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at 500 mg/kg and spurious pregnancy in 5 of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

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