

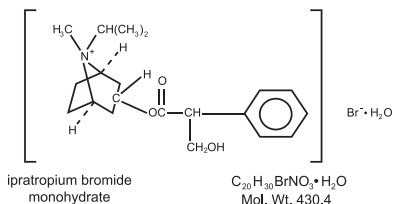
Ipratropium Bromide Inhalation Solution, USP 0.02%

For Oral Inhalation Only
Not for Injection
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 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 USP is administered by oral inhalation with the aid of a nebulizer. Each mL contains ipratropium bromide USP 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 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 α -acid glycoproteins. It is partially metabolized. Autoradiographic studies in rats have shown that ipratropium bromide 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 twelve-week studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV₁ 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 was demonstrated throughout the 12-week period. In addition, significant increases in forced vital capacity (FVC) have been

demonstrated. However, ipratropium bromide did not consistently produce significant improvement in subjective symptom scores nor in quality of life scores over the 12-week duration of study. Additional controlled 12-week studies were conducted to evaluate the safety and effectiveness of ipratropium bromide inhalation solution administered concomitantly with the beta adrenergic bronchodilator solutions metaproterenol and albuterol compared with the administration of each of the beta agonists alone. Combined therapy produced significant additional improvement in FEV₁ and FVC. On combined therapy, the median duration of 15% improvement in FEV₁ 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 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 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 mydriasis, 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 has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Ipratropium bromide has also been used with other pulmonary medications, including methylxanthines and corticosteroids, without adverse drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day was unaffected by ipratropium bromide 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

Patient's Instructions for Use

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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, pupil enlargement, 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 5-10 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.

