The active ingredient in ATROVENT® Nasal Spray is ipratropium bromide monohydrate. It is an anticholinergic agent chemically described as bromine, (endo,syn)-endo,syn-8-azoniazidodecan-3-ol monohydrate (C_{16}H_{29}BrN_{2}O_{3}·H_{2}O). It is a synthetic quaternary ammonium compound, chemically related to atropine. Its structural formula is:

\[\text{C}_{16}\text{H}_{29}\text{BrN}_{2}\text{O}_{3} \cdot \text{H}_{2}\text{O}\]

Ipratropium bromide is a white odorless, crystalline substance. It is easily soluble in lower alkyl alcohols, slightly soluble in methanol, and insoluble in non-polar media.

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is a metered-dose, manual pump spray unit which delivers 84 micrograms of ipratropium bromide (as an aerosol base) per spray (76 mcg in an isotonic, aqueous solution with pH adjusted to 7.7). It also contains benzalkonium chloride, ethyl alcohol, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 sprays.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**
Ipratropium bromide is an anticholinergic agent that inhibits the parasympathetic action of acetylcholine at the cholinergic receptor in humans. Ipratropium bromide has an anti-secretory action when applied locally, inhibiting secretions from the airways and glands lining the nasal mucosa. Ipratropium bromide is a non-sedating anticholinergic, with only minimal central nervous system and gastrointestinal side effects (i.e., mydriasis, ptyalism, cardiac and gastrointestinal effects) that are seen with tertiary anticholinergic agents.

**Pharmacokinetics**
Absorption: Ipratropium bromide is poorly absorbed into the systemic circulation following oral administration (12%) and produces less than 2% of the in vivo potency. Ipratropium bromide administered as a 0.06% dose was absorbed from the nasal mucosa of normal volunteers, induced-cold adult volunteers, naturally acquired common cold pediatric patients, and premenopausal women.

Distribution: Ipratropium bromide is minimally bound (2% to 5%) to plasma albumin and β-globulin. Its plasma protein concentration ratio was estimated to be about 0.95. Studies in rats have shown that ATROVENT® Nasal Spray 0.06% does not penetrate the blood-brain barrier.

Metabolism: Ipratropium bromide is partially metabolized by the liver. As a tertiary anticholinergic, ipratropium bromide is not excreted in the urine or bile. It is not excreted effectively based on in vivo receptor affinity studies using rat brain homogenates.

Elimination: After intranasal administration of 2 mg of ipratropium bromide to 10 healthy volunteers, the mean terminal half-life of ipratropium bromide was approximately 1.6 hours. The total body clearance and renal clearance were estimated to be 2.3 mL/min and 1.019 mL/min, respectively. The amount of the total dose excreted as unchanged drug or metabolites within 24 hours was approximately one-half of the administered dose.

Pediatrics: Following administration of 8 mg of ipratropium bromide per nostril three times a day in patients 5-16 years old (n=42) with a naturally acquired common cold, the mean amount of the total dose excreted unchanged in the urine was 7.8% when compared to 8 mg/kg per four times a day in adult soybean oil control patients. The total body clearance and renal clearance were estimated to be 2.506 mL/min and 1.019 mL/min, respectively. The amount of the total dose excreted as unchanged drug or metabolites within 24 hours was approximately one-half of the administered dose.

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

**Drug-Drug Interactions:** No specific pharmacokinetic studies were conducted to evaluate potential drug-dosing interactions.

**Pharmacodynamics:**
In two single dose trials (n=17), doses up to 425 mcg of ipratropium bromide did not significantly affect autonomic parameters (heart rate, or systolic/diastolic blood pressure). Similarly, ATROVENT® Nasal Spray 0.06% did not alter heart rate or systolic/diastolic blood pressure in premenopausal women. ATROVENT® Nasal Spray 0.06% did not alter heart rate or systolic/diastolic blood pressure in patients 5-18 years old (n=42) with a naturally acquired common cold pediatric patients, or in patients age 15 years and older. ATROVENT® Nasal Spray 0.06% did not reduce nasal congestion or sneezing associated with the common cold or seasonal allergic rhinitis.

**Pharmacology:**
Ipratropium bromide is a non-sedating anticholinergic, with only minimal central nervous system and gastrointestinal side effects (i.e., mydriasis, ptyalism, cardiac and gastrointestinal effects) that are seen with tertiary anticholinergic agents.

**INDICATIONS AND USAGE**
ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is indicated for the symptomatic relief of rhinorrhea associated with the common cold or seasonal allergic rhinitis for adults and children age 5 years and older. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is not indicated for the treatment of sneezing or itching eyes.

**CONTRAINDICATIONS**
ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is contraindicated in patients with a history of allergy to any of the other ingredients.

**WARNINGS**
Ipratropium bromide may cause decreased accommodation and may induce mydriasis. Patients who experience eye pain, blurred vision, or difficulty with accommodation should be instructed to discontinue use.

**PRECAUTIONS**
Ipratropium bromide is a non-sedating anticholinergic, with only minimal central nervous system and gastrointestinal side effects (i.e., mydriasis, ptyalism, cardiac and gastrointestinal effects) that are seen with tertiary anticholinergic agents.

**Pregnancy**
Ipratropium bromide has not been studied in pregnant women. Ipratropium bromide, like other quaternary ammonium compounds, may cause a decrease in the conception rate.

**Breastfeeding**
Ipratropium bromide is not known to be excreted in human milk. Because animal reproduction studies have not always predicted human response, ipratropium bromide should be used during pregnancy only when clearly needed.

**ADVERSE REACTIONS**
The adverse reactions associated with the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% are generally mild and nonspecific. 

**Application-Specific Adverse Reactions**
Patients who experience eye pain, blurred vision, or difficulty with accommodation should discontinue use.

**Ocular Side Effects**
Cases of precipitating or worsening of narrow-angle glaucoma and acute eye pain have been reported with direct eye contact of ipratropium bromide administered by oral inhalation.

**Other Adverse Reactions**
Systemic side effects associated with ipratropium bromide therapy have included chest tightness, hypokalemia, dizziness, and gastrointestinal effects that are usually mild and transient.

**Drug Interactions**
No controlled clinical trials were conducted to investigate potential drug-drug interactions. ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is contraindicated in patients with a history of allergy to any of the other ingredients.

**Other Medications**
Ipratropium bromide is a non-sedating anticholinergic, with only minimal central nervous system and gastrointestinal side effects (i.e., mydriasis, ptyalism, cardiac and gastrointestinal effects) that are seen with tertiary anticholinergic agents.

**PATIENT’S INSTRUCTIONS FOR USE**
ATROVENT® (ipratropium bromide) Nasal Spray 0.06% should not be used for the treatment of sneezing or itching eyes.

To use:

1. Remove the clear plastic dust cap and the green safety clip from the nasal spray pump. Direct the nozzle slightly upward to prevent the accidental discharge of the spray in your pocket or purse.

2. Direct the nasal spray pump by spraying, then priming, the nasal spray pump. Each spray pump must be primed prior to each use. After the spray pump is primed, the nasal spray pump may be used for up to 7 days, repriming the pump will require 2 to 3 seconds. Your pump should not be used for more than 7 days or for more than 24 hours; repriming the pump will only revive the pump and not the nasal spray pump for more than seven days. After 7 days, the nasal pump will require seven sprays.

3. Before using ATROVENT® (ipratropium bromide) Nasal Spray 0.06%, blow your nose to clear your nostrils if necessary.

4. Gently pluck your finger as you raise your index and middle fingers on the base of your nose. Pinch your thumb against the side of your nose, tilt your head back, and hold the bottle steady, insert the nasal tip into the other nostril (Figure 2). Point the tip toward the back and side wall of the nose.

5. Press firmly and quickly upward (about 10 times per second) to deliver the dose. Hold the bottle steady and breathe out through your mouth.

6. After spraying the nostril and rinsing the nasal pump, repeat the process for the opposite nostril. After spraying each nostril, rinse your index and middle fingers on the base of your nose. Keep the spray pump out of reach of children.

7. Repeat steps 4 through 6 in the same nostril.

8. Repeat steps 4 through 7 in the other nostril (i.e., two sprays per nostril).
is not intended to relieve your rhinitis

If the nasal tip becomes clogged, remove the plastic dust cap.

For most patients, the recommended daily intranasal dose in adults and children, respectively, on an mg basis, 5.7 mg/kg to 15.5 mg/kg. While the safety and effectiveness of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in pediatric patients under 5 years of age have not been established.

ADVERSE REACTIONS

Adverse reaction information on ATROVENT®

If you are pregnant or breast feeding your baby be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

Storage:

This study is a double-blind, placebo-controlled clinical trial involving 1,276 pediatric common cold patients. The safety and efficacy of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in adults and adolescents 12 years of age have not been established.

Additional anticholinergic effects noted with other anticholinergic agents include: dry mouth and throat; constipation; urination difficulty; blurred vision; and drowsiness.

There were no reports of allergic-type reactions in the controlled trials. Atropinic-type reactions such as skin rash, angioedema of the throat, tongue, lips, face, generalized urticaria, laryngospasm, and anaphylactic reactions have been reported with ATROVENT® Nasal Spray 0.06% and other ipratropium bromide products.

OVERDOSAGE

Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically. Animal data indicate that the oral dose equivalent to ingesting more than two bottles of ATROVENT® Nasal Spray (6 mg) does not induce vomiting, nausea or vomiting, or diarrhea in mice and rats. Absorption of ipratropium bromide from the nasal cavity is about 20% to 30% of the dose and is essentially complete in 15 minutes to the same 10 male volunteers, plasma ipratropium concentrations were observed (<100 times the concentrations observed following intranasal administration). Following intranasal infusion these 10 volunteers had a mean increase of heart rate of 10 beats per minute and a 10 to 20 mm systolic or diastolic blood pressure at the time of peak plasma ipratropium levels.

Oral median lethal doses of ipratropium bromide were greater than 1,000 mg/kg in mice (approximately 6,400 and 3,600 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg basis), 1,700 mg/kg in rats (approximately 21,000 and 13,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg basis) and 160 mg/kg in dogs (approximately 10,000 times the maximum recommended daily intranasal dose in adults and children, respectively, on a mg basis). No anticholinergic drug should be administered to a nursing woman.

DOSE AND ADMINISTRATION

For Symptomatic Relief of Rhinitis Associated with the Common Cold

The recommended dose of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is two sprays (48 mcg per nostril) three or four times daily total dose 5% to 10% (22-45 mcg/mL) in adults and children ages 12 years and older. Optimum dosage varies with response of the individual patient. The recommended dose of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is two sprays (48 mcg per nostril) three or four times daily total dose 10% mg/kg). In adults and children age 5 years and older.

The safety and effectiveness of the use of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond four days in patients with the common cold have not been established.

Initial pump priming requires seven sprays of the pump. If used regularly an accommodation is further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than 24 hours, the pump will require seven sprays to reprimed.

HOW SUPPLIED

ATROVENT® (ipratropium bromide) Nasal Spray 0.06% is supplied in a high density polyethylene (HDPE) bottle fitted with a fine orifice spray pump, a green safety clip to prevent accidental discharge of the spray, and a clear, protective cap. Each HDPE bottle contains 100 mcg of ipratropium bromide, 10 sprays, each delivering 10 mg/kg of ipratropium bromide per spray. Each HDPE bottle contains an instructional insert containing the recommended dose (two sprays per nostril four times daily).

Store tightly closed between 59° F (15°C) and 100° F (38°C). Avoid freezing. Keep out of reach of children.

For Symptomatic Relief of Rhinitis Associated with Seasonal Allergic Rhinitis

The safety and effectiveness of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% beyond three weeks in patients with seasonal allergic rhinitis have not been established.

Initial pump priming requires seven sprays of the pump. If used regularly an accommodation is further priming is required. If not used for more than 24 hours, the pump will require two sprays, or if not used for more than 24 hours, the pump will require seven sprays to reprimed.

Table 1 % of Patients with Common Cold Reporting Events

If you have glaucoma or dysfunction due to an enlargement of the prostate, be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

Do not spray ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in your eye. Should this occur; immediately flush your eye with cool tap water for several minutes. If you accidentally spray ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in your eye, you may experience a temporary blurring of vision, increased sensitivity to light, and a widening of the pupil, which may last a few hours. Should any part of blurred vision occur, contact your doctor.

Should you experience excessive nasal dryness or episodes of nasal bleeding contact your doctor.

If you have glaucoma or dysfunction due to an enlargement of the prostate, be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

Storage:

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ADVERSE REACTIONS

Adverse reaction information on ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in patients with the common cold was derived from two multicentre, vehicle-controlled clinical trials involving 1,276 patients (635 patients on ATROVENT® Nasal Spray 0.06%, 352 patients on ATROVENT® Nasal Spray 0.03%, 187 patients on ATROVENT® Nasal Spray 0.12%, 21 patients on vehicle and 199 patients receiving no treatment).

Table 1 % of Patients with Common Cold Reporting Events

Table 2 % of Patients with SAR Reporting Events

If you are pregnant or breast feeding your baby be sure to tell your physician prior to using ATROVENT® Nasal Spray 0.06%.

Storage:

Caution:

This study is a double-blind, placebo-controlled clinical trial involving 1,276 pediatric common cold patients. The safety and efficacy of ATROVENT® (ipratropium bromide) Nasal Spray 0.06% in adults and adolescents 12 years of age have not been established.

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