

ATROVENT® NASAL and ATROVENT® NASAL FORTE

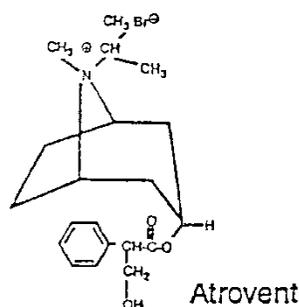
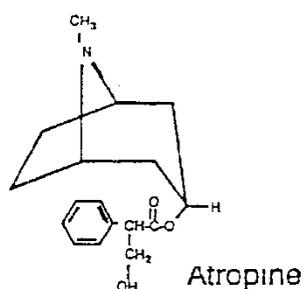
PRODUCT INFORMATION

DESCRIPTION

Approved Name Ipratropium bromide

Chemical Name (1R, 3r, 5S, 8r)-8-Isopropyl-3-(± tropoyloxytropanium bromide. C₂₀H₃₀NO₃Br. Molecular weight 412.37.

Ipratropium bromide is a synthetic quaternary ammonium compound, chemically related to atropine.



The addition of an N-isopropyl group distinguishes the molecule from atropine and is responsible for a lower lipid solubility. The compound is freely soluble in lower alcohols and water, existing in an ionised state in aqueous solutions.

Atrovent Nasal spray is available in two strengths in a pH-adjusted (pH 4.0-5.0), isotonic aqueous solution:

Atrovent Nasal – 0.03% ipratropium bromide (22 µg per metered dose) and

Atrovent Nasal Forte – 0.06% ipratropium bromide (44 µg per metered dose).

Both products also contain benzalkonium chloride, disodium edetate, sodium chloride, sodium hydroxide, hydrochloric acid and purified water.

PHARMACOLOGY

Ipratropium bromide is an anticholinergic agent which inhibits vagally-mediated reflexes by antagonising the action of acetylcholine. In humans, ipratropium bromide has anti-secretory properties and, when applied locally, inhibits secretions from the serous and seromucous glands lining the nasal mucosa, at dosages below those at which neurologic, ophthalmic, cardiovascular and gastrointestinal effects are usually seen.

Intranasal ipratropium bromide is effective in controlling the severity and duration of rhinorrhoea in patients with allergic and non-allergic perennial rhinitis and the common cold.

Nasal provocation trials in perennial rhinitis patients using Atrovent Nasal showed a dose-dependent increase in inhibition of methacholine-induced nasal secretion with an onset of action within minutes.

Ipratropium bromide does not alter physiologic nasal functions (eg. sense of smell, ciliary beat frequency, mucociliary clearance or the air conditioning capacity of the nose), as shown in controlled clinical trials with intranasal fluorocarbon-propelled Atrovent metered aerosol.

Pharmacokinetics

Ipratropium bromide is a quaternary amine that is poorly absorbed into the systemic circulation from the nasal mucosa. The active ingredient is absorbed very quickly and peak plasma concentrations are reached only minutes after inhalation.

Renal excretion of the active ingredient is given as 46% of the dose after intravenous administration, 3% of the dose after oral inhalation, and 3-5% of the dose after single intranasal administration.

The systemic absorption of ipratropium bromide across inflamed nasal mucosa due to the common cold was not altered. Following chronic dosing in rhinitis patients the amount of unchanged ipratropium bromide excreted in the urine over a 24-hour period at steady state was 3-6% of the dose.

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

The systemic bioavailability after intranasal administration as estimated from renal excretion is less than 13% of the dose.

The basic pharmacokinetic parameters were calculated from the plasma level data after intravenous administration. A rapid biphasic decline in plasma is noted for ipratropium. The half-life of the terminal elimination phase was about 1.6 hours. The half-life for elimination of the active ingredient and the metabolites was 3.6 hours, as determined by radio-labelling. The main metabolites found in the urine bind poorly to the muscarinic receptor. The total clearance of the active ingredient is 2.3 L/min. Approximately 40% of clearance is renal (0.9L/min) and 60% non-renal i.e. mainly hepato-metabolic. The volume of distribution (V_z) is 338 L (approximately 4.6 L/kg).

Clinical Trials

Studies on the relief of rhinorrhoea associated with the common cold.

There were two pivotal double-blind, randomised clinical trials (00729A & 00730A), which assessed the safety and efficacy of Atrovent Nasal sprays on the symptomatic relief of rhinorrhoea associated with the common cold. A total of 1276 patients were involved in these studies.

The primary endpoints in the two studies were the objective measure of rhinorrhoea using nasal discharge weights and the subjective measurement of the severity of rhinorrhoea by the patient's assessments of rhinorrhoea, sneezing and nasal congestion using a visual analog scale.

In Trial 00729A, patients received either 2 sprays of Atrovent Nasal Forte (88 µg/nostril) or placebo, four times daily for four days. In Trial 00730A, patients received no treatment or two sprays of Atrovent Nasal (44 µg/nostril), Atrovent Nasal Forte (88 µg/nostril), or 0.12% (176 µg/nostril), or saline vehicle 3 times daily for four consecutive days.

In Trial 00729A, it was demonstrated that treatment with Atrovent Nasal Forte resulted in less nasal discharge, with a difference between the groups of 14% on Day 1, 23% on Day 2 and 18% for the average of the two test days. This difference achieved statistical significance on day 2 ($p=0.01$) as well as for the average of the two days ($p=0.02$). Excluding patients with relatively minor rhinorrhoea, among patients with at least 1.0 g of nasal discharge at baseline, the average difference between the two groups on the two days was even greater, 23% ($p=0.003$).

The patient's daily assessment of symptoms of rhinorrhoea, nasal congestion and sneezing for the four days of treatment indicated that treatment with Atrovent Nasal Forte resulted in an improvement in rhinorrhoea which was significantly better than that with placebo over the first two days ($p=0.02$) and approached significance over the last two days ($p=0.06$). There was no difference between the two treatment groups with respect to sneezing and nasal congestion.

In Trial 00730A, it was demonstrated that all groups showed a substantial reduction in nasal discharge weight from baseline which persisted through the six hour observation period post-dose in Day 1 and the three hour period post-dose on Day 2. The reduction was significantly greater for those groups receiving blinded treatment, including vehicle, compared to the no-treatment group. Treatment with Atrovent Nasal 88 µg/nostril and 176 µg/nostril resulted in significantly less nasal discharge than vehicle ($p<0.02$), with a difference in mean hourly discharge weight ranging from 21% to 35% for the 88 µg/nostril group and 26% to 33% for the 176 µg/nostril group.

The patient's daily assessment of severity of rhinorrhoea indicated that treatment with Atrovent Nasal sprays produced a dose-related improvement in rhinorrhoea over the vehicle for the average of Days 1 and 2, and for the average of Days 3 and 4. This difference between Atrovent Nasal sprays and vehicle achieved statistical significance for all three Atrovent groups on Days 1 and 2, and for the higher dose groups, on Days 3 and 4. The results of the analysis of sneezing and nasal congestion in all groups showed a slight improvement over the treatment period, however there were no statistically significant differences noted among the treatment groups.

Studies on the relief of rhinorrhoea associated with allergic and non-allergic perennial rhinitis.

Trials 00612A and 00847A were double-blind parallel-group studies in patients with allergic perennial rhinitis. In Trial 00612A, patients received Atrovent Nasal Forte (88 µg/nostril, three times daily), and Atrovent Nasal (44 µg/nostril, three times daily) or

placebo. In Trial 00847A, patients received Atrovent Nasal Forte (88 µg/nostril, twice daily), Atrovent Nasal 0.12% (176 µg/nostril, twice daily), or placebo.

The studies indicated that doses of 44, 88 and 176 µg/nostril were significantly better in reducing both the severity and duration of rhinorrhoea ($p < 0.01$) than placebo, averaged over an 8 week treatment period. No significant difference was found between the different strengths of Atrovent solutions. The reduction in the severity and duration was maintained in all treatment groups with significant differences between Atrovent and placebo occurring either in the first 2-3 weeks or throughout the eight weeks. There is no evidence of an increased advantage of using a 176 µg dose in more severe rhinorrhoea. Furthermore, Atrovent Nasal sprays were well tolerated in patients who received treatment for up to 12 months.

Trial 00848A was a double-blind, parallel-group study in patients with non-allergic perennial rhinitis. In this trial, patients received Atrovent Nasal Forte (88 µg/nostril, twice daily), Atrovent Nasal 0.12% (176 µg/nostril twice daily), or placebo, for an 8 week treatment period. Doses of 176 µg and 88 µg per nostril were effective when administered twice daily. Although the majority of patients (> 80%) tolerated the 176 µg/nostril dose well, 10% to 17% of patients experienced excessive nasal dryness (greater than placebo) when maintained on a fixed dosing regimen of Atrovent nasal spray 88 µg or 176 µg/nostril twice daily.

The safety and efficacy of Atrovent Nasal and Atrovent Nasal Forte beyond 12 months in patients with perennial rhinitis has not been established.

INDICATIONS

Atrovent Nasal and Atrovent Nasal Forte are indicated for the symptomatic relief of rhinorrhoea associated with allergic and non-allergic perennial rhinitis, and the common cold.

CONTRAINDICATIONS

Known hypersensitivity to atropine or its derivatives, or to any of the ingredients of Atrovent Nasal and Atrovent Nasal Forte.

WARNINGS AND PRECAUTIONS

General

Atrovent Nasal sprays should be used with caution in patients predisposed to narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder neck obstruction). Patients with cystic fibrosis using anticholinergics may be more prone to gastro-intestinal motility disturbances.

Atrovent Nasal sprays contains the (antimicrobial) preservative benzalkonium chloride which may cause irritation of the nasal mucosa.

There have been isolated reports of ocular complications (mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) as a result of direct eye contact with ipratropium bromide aerosol formulations. Thus, patients must be instructed in the correct administration of Atrovent Nasal sprays and should be reminded to read and follow the Directions for Use in the Consumer Medicine Information leaflet carefully.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema, may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Immediate hypersensitivity reactions may occur after administration of Atrovent Nasal sprays, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Use in Children

The safety and effectiveness of Atrovent Nasal and Atrovent Nasal Forte in patients below the age of 12 years has not been established.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with Atrovent Nasal sprays. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Effects on Fertility

Clinical data on fertility are not available for ipratropium bromide.

Use in Pregnancy Category B1

The safety of Atrovent Nasal and Atrovent Nasal Forte administered during pregnancy has not yet been established. The benefits of using Atrovent Nasal sprays when pregnancy is present or suspected must be weighed against possible hazards to the fetus.

Studies of rats, mice and rabbits showed no embryotoxic or teratogenic effects following inhalation at doses considerably higher than those recommended to man. Animal reproduction studies have shown no evidence of embryotoxic or teratogenic effects as a result of ipratropium bromide at oral doses up to 10mg/kg/day (mice and rabbits) and 90mg/kg/day (rats), or at inhalation doses up to 1.5mg/kg/day (rats) and 1.8mg/kg/day (rabbits). In male and female rats, a slight increase in resorption rate was observed with oral doses of 90mg/kg/day.

Use in Lactation

It is not known whether ipratropium bromide is excreted in human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken intranasally. However, since many drugs are excreted in human breast milk, caution should be exercised when Atrovent Nasal and Atrovent Nasal Forte are administered to a nursing mother.

Interactions with Other Drugs

There is no evidence that the concomitant use of Atrovent Nasal sprays with other drugs commonly prescribed for perennial rhinitis (antihistamines, decongestants and nasal steroids) and the common cold (decongestants), increases the incidence of side effects.

Atrovent Nasal sprays are minimally absorbed into the systemic circulation; nonetheless, there is some potential for an additive interaction with other concomitantly administered anticholinergic medications, including ipratropium bromide containing aerosols for oral inhalation.

ADVERSE REACTIONS

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Atrovent Nasal sprays. As with all topical therapy Atrovent Nasal spray may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

The most frequent side effects reported in clinical trials were epistaxis, nasal dryness, headache, nasal discomfort and throat irritation..

Adverse events are usually mild to moderate and transient. In the majority of cases, nasal dryness and epistaxis resolved with continued treatment or a dose reduction. There was no evidence of nasal rebound (a clinically significant increase in rhinorrhoea, posterior nasal drip, sneezing or nasal congestion severity compared to baseline) upon discontinuation of double-blind therapy in the clinical trials. There were no drug related serious or anticholinergic adverse reactions with the exception of dry mouth.

Immune system disorders

anaphylactic reaction
hypersensitivity

Nervous system disorders

headache
dizziness

Eye disorder

accomodation disorder
mydriasis
intraocular pressure increased
glaucoma
eye pain
vision blurred
halo vision
conjunctival hyperamia
corneal oedema

Cardiac disorders

supraventricular tachycardia
atrial fibrillation
heart rate increased
palpitations

Respiratory, thoracic and mediastinal disorders

epistaxis
nasal dryness
throat irritation
nasal discomfort
dry throat
bronchospasm
laryngospasm
pharyngeal oedema

Gastrointestinal disorders

dry mouth
nausea
gastrointestinal motility disorder (including reports of change in bowel motions and habits, dyspepsia, gastrointestinal reflux and flatulence)¹
oedema mouth
stomatitis

Skin and subcutaneous tissue disorders

rash
angioedema
pruritus
urticaria

Renal and urinary disorders

urinary retention

¹ ¹ The definition is based on a post-hoc review of all ADR terms reported in the defined study dataset. Terms that report a clinically related term with greater medical specificity were excluded and added to the more specific term (e.g. "nausea", "vomiting").

Atrovent Nasal

Percentages of adverse events reported in controlled clinical trials for 705 patients with perennial rhinitis who received Atrovent Nasal (44 µg/nostril) or placebo two or three times daily, where the prevalence in the Atrovent group is 2.0% or greater and exceeds the prevalence in the placebo group, are listed below. Percentage prevalences in placebo patients are provided in parentheses.

Headache 9.8% (9.2%); Upper respiratory tract infection 9.8% (7.2%); Pharyngitis 8.1% (4.6%); Epistaxis 9.0% (4.6%); Nasal dryness 5.1% (0.9%); Nasal irritation 2.0% (1.7%); Other nasal symptoms 3.1% (1.7%); Nausea 2.2% (0.9%).

Atrovent Nasal Forte

Adverse reaction information on Atrovent Nasal Forte is derived from two controlled clinical trials involving 1276 patients with the common cold. Of these patients, 352 patients received Atrovent Nasal Forte at the recommended dose of 88 µg per nostril, and 351 patients received placebo administered three or four times daily. The list below indicates the frequency of adverse events reported by patients who received Atrovent Nasal Forte or placebo where the prevalence in the Atrovent group is 1% or greater and exceeds the prevalence in the placebo group (percentage prevalences in placebo patients are provided in parentheses):

Epistaxis 5.4% (1.4%); Blood tinged nasal mucus 2.8% (0.9%); Dry mouth/throat 1.4% (0.3%); Nasal congestion 1.1% (0.0%); Nasal dryness 4.8% (2.8%).

Atrovent Nasal Forte was well tolerated by most patients. The most frequently reported adverse reactions were transient episodes of nasal dryness or epistaxis. The majority of these adverse events (96%) were mild or moderate in nature, none requiring hospitalisation. No patient required treatment for nasal dryness, and three patients (<1%) required treatment for epistaxis, which consisted of local application of pressure or a moisturising agent. No patient discontinued from the trial due to either nasal dryness or bleeding.

The following list indicates the frequency of adverse events from pooled perennial rhinitis controlled studies reported by patients who received Atrovent Nasal Forte or placebo where the prevalence in the Atrovent group is 2% or greater (percentage prevalences in placebo patients are provided in parentheses):

Epistaxis 8.3% (5.1%); Blood tinged nasal mucus 4.9% (2.4%); Dry mouth/throat 3.1% (0.3%); Nasal congestion 2.8% (1.2%); Nasal dryness 9.2% (3.3%); Pharyngitis 5.5% (1.8%); Taste perversion 4.9% (1.2%); Coughing 2.8% (1.2%); Myalgia 2.2% (0.9%).

DOSAGE AND ADMINISTRATION

For symptomatic relief of rhinorrhoea associated with allergic or non-allergic perennial rhinitis:

Adults and children 12 years of age and over:

The recommended dose is 44 µg to 88 µg into each nostril 2 to 3 times a day. This is equivalent to 2 to 4 sprays of Atrovent Nasal or 1 to 2 sprays of Atrovent Nasal Forte into each nostril, 2 to 3 times a day.

The dose may be reduced when symptoms of rhinorrhoea improve.

For symptomatic relief of rhinorrhoea associated with the common cold:

Adults and children 12 years of age and over:

The recommended dose is 88 µg into each nostril 3 to 4 times a day. This is equivalent to 4 sprays of Atrovent Nasal or 2 sprays of Atrovent Nasal Forte into each nostril, 3 to 4 times a day. Treatment for the common cold should be limited to 4 days.

The dose may be reduced when symptoms of rhinorrhoea improve.

OVERDOSAGE

Acute overdosage by intranasal administration is unlikely since ipratropium bromide is not well absorbed systemically after intranasal or oral administration. No symptoms of specific overdosage have been encountered. In view of the wide therapeutic range and topical administration of Atrovent Nasal sprays, no serious anticholinergic symptoms are expected. Minor systemic signs of anticholinergic action including dry mouth, visual accommodation disorder and tachycardia may occur. Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

PRESENTATION

Atrovent Nasal is supplied in pump-activated, metered dose containers of 15 mL (180 metered doses), containing 314 µg/mL ipratropium bromide. Each valve actuation delivers 70 µL [22 µg of ipratropium bromide equivalent to ipratropium bromide (anhydrous) 21 µg] of the solution.

Atrovent Nasal Forte is supplied in pump-activated, metered dose containers of 10 mL (120 metered doses) and 15 mL (180 metered doses), containing 626.2 µg/mL ipratropium bromide. Each valve actuation delivers 70 µL [44 µg ipratropium bromide equivalent to ipratropium bromide (anhydrous) 42 µg] of the solution.

Atrovent Nasal sprays should be protected from heat and subzero temperatures. Store below 25°C.

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
78 Waterloo Road
NORTH RYDE NSW 2113

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