Aerovent
Ipratropium Bromide 0.25 mg/ml

Respirator solution

1. NAME OF THE MEDICINAL PRODUCT

AEROVENT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml (20 drops) contains:
Ipratropium bromide 0.25 mg

Excipient with known effect: 0.10 mg benzalkonium chloride/ml see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RESPIRATOR SOLUTION

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of symptoms of reversible bronchospasm associated with asthma, chronic bronchitis and emphysema.
Aerovent respirator solution is of particular benefit in relieving acute bronchospasm when used concomitantly with inhaled beta agonists.

4.2 Posology and method of administration

The dosage should be adapted to the individual requirements of the patient; patients should also be kept under medical supervision during treatment. It is advisable not to greatly exceed the recommended daily dose during both acute and maintenance treatment.

If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought in order to determine a new regimen of therapy. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Note: Aerovent and disodium cromoglycate inhalation solutions should not be simultaneously administered in the same nebulizer as precipitation may occur.
Aerovent Respirator Solution may be administered from an intermittent positive pressure ventilator or from suitable nebulizers.

The following dosages are recommended:

Adults

0.1 - 0.5 mg (0.4 - 2.0 ml = 8-40 drops) up to 4 times daily.

Children

6-12 Years: 0.25 mg (20 drops, i.e., 1 ml) 3 to 4 times daily.

Children < 6 years of age:
As only limited information is available for this age group, the following dose schedule should only be given under regular medical supervision:
The single inhaled dose is 0.1 - 0.25 mg ipratropium bromide, (8-20 drops, i.e.: 0.4-1.0 ml)

N.B. For ease of administration, the dose may need to be diluted in order to obtain a final volume suitable for the nebulizer being used. If dilution is necessary, only normal saline should be used.

4.3 Contraindications

Aerovent is contraindicated in patients with hypersensitivity to the active substance, to atropine or atropine derivatives (such as ipratropium bromide) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
Immediate hypersensitivity reactions may occur following the use of Aerovent, such as rare cases of rash, urticaria, angioedema, oropharyngeal oedema, bronchospasm and anaphylaxis.

Paradoxical bronchospasm
As with other inhaled medications, Aerovent may cause paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, Aerovent must be discontinued immediately and replaced with an alternative therapy.

Special populations:

Ocular complications
Care must be taken not to allow the solution or mist to enter into the eyes.
Aerovent should be used with caution in patients with a predisposition for narrow-angle glaucoma.
If the product accidentally comes into contact with the eyes during use, mild, reversible ocular complications may occur. There is a risk of an acute glaucoma attack, particularly in patients with narrow-angle glaucoma; the characteristic symptoms are eye pain, blurred vision, visual halos or coloured images, red eyes and corneal oedema.
If mydriasis and mild accommodation disorders occur, treatment with miotic drops may be given. In the event of severe ocular complications, an ophthalmologist should also be consulted.

In these patients, a mouthpiece rather than a face mask should ideally be used for inhalation in order to prevent the product from getting into the eyes.

Effect on the kidneys and urinary tract

In patients with micturition disorders (such as in prostatic hypertrophy or bladder neck obstruction), the benefit of treatment with ipratropium bromide must be carefully weighed against the potential risk of aggravating urinary retention.

Gastrointestinal motility disorders
Patients with cystic fibrosis are more likely to develop gastrointestinal motility disorders.

Local effects

This product contains the preservative benzalkonium chloride (100 µg/mL). Benzalkonium chloride can cause bronchospasms, especially in patients with asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Chronic use of inhaled Ipratropium bromide together with other anticholinergic drugs has not been studied and is therefore not recommended.

β-adrenergic agents and xanthine derivatives (such as theophylline) may enhance the therapeutic effect.

Other anticholinergic medications, such as those containing pirenzepine, may increase both the therapeutic and undesirable effects.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma may be increased when Aerovent and β-mimetics are administered simultaneously.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
There are no data from use in pregnant or breast-feeding women.
Although no teratogenic effects have been identified to date, Aerovent should not be used during pregnancy (especially the first trimester) or while breast-feeding unless considered necessary by the treating physician after careful benefit/risk assessment.
The risks of inadequate treatment should be given due weight in this assessment.

Fertility
Clinical data on fertility are not available for ipratropium bromide. Non-clinical studies performed with ipratropium bromide showed no adverse effect on fertility (see section 5.3).

4.7 Effects on ability 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 undesirable effects such as dizziness, accommodation disorders , mydriasis and blurred vision may occur during treatment with Aerovent. Caution is therefore required when driving or using machines.

4.8 Undesirable effects

Like all medicines, Aerovent can cause side effects.

a) Summary of the safety profile
Many of the undesirable effects listed can be attributed to the anticholinergic properties of Aerovent.

b) Tabulated summary of undesirable effects

The undesirable effects listed were identified from clinical trial data and postmarketing surveillance. Their frequency is defined using the following convention:

Very common	(≥ 1/10)
Common	(≥ 1/100 - < 1/10)
Uncommon	(≥ 1/1000 - < 1/100)
Rare	(≥ 1/10,000 - < 1/1000)
Very rare	(< 1/10,000)
Not known	(Frequency cannot be estimated from the available data)

Immune system disorders
Uncommon: Anaphylactic reactions, hypersensitivity

Nervous system disorders
Common: Headache, dizziness

Eye disorders
Uncommon: Blurred vision, mydriasis, increased intraocular pressure (sometimes with eye pain), foggy vision, halo or rainbow vision, conjunctival hyperaemia and corneal oedema, glaucoma
Rare: Accommodation disorders

Cardiac disorders
Uncommon Palpitations, (supraventricular) tachycardia
Rare: Atrial fibrillation

Respiratory, thoracic and mediastinal disorders
Common: Cough, throat irritation
Uncommon: (Paradoxical) bronchospasm, laryngospasm, pharyngeal oedema, dry throat

Gastrointestinal disorders
Common: Dry mouth, taste disturbance, gastrointestinal motility disorders, nausea
Uncommon: Constipation, diarrhoea, abdominal pain, vomiting, stomatitis, oral oedema

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, angioedema
Rare: Urticaria

Renal and urinary disorders
Uncommon: Urinary retention

c) Common undesirable effects
As with any other inhaled medication, Aerovent may also be associated with local irritation in the throat. The most common undesirable effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhoea and vomiting), nausea and dizziness.

Reporting of suspected adverse reactions

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

4.9 Overdose

No specific signs of overdose have been encountered to date.

However, in view of the wide therapeutic window and the fact that the product is administered topically, no serious anticholinergic symptoms are to be expected. Mild systemic anticholinergic side effects such as dry mouth, accommodation disorders and increased heart rate may occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants / Anticholinergics
ATC code: R03BB01

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical studies, it inhibits vagally-mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca^{++} which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca^{++} release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilation following inhalation of Aerovent (ipratropium) is primarily local and specific to the lung and is not systemic in nature.

Non-clinical and clinical evidence suggests that Aerovent (ipratropium) has no adverse effect on airway mucus secretion, mucociliary clearance or gas exchange.

Clinical trials
In controlled 85-day to 90-day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema), significant improvements in lung function occurred within 15 min. These improvements reached a peak in 1-2 hours and persisted for 4-6 hours.
The bronchodilator effect of Aerovent in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children ≥ 6 years of age. In most of these studies Aerovent was administered in combination with an inhaled beta-agonist.

5.2 Pharmacokinetic properties

Absorption
The therapeutic effect of Aerovent is produced by a local action in the airways. Time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.

Following inhalation, 10 - 30% of a dose is generally deposited in the lungs, depending on the formulation and inhalation technique. The majority of the dose is swallowed and passes through the gastrointestinal tract.

The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).

Cumulative renal excretion (0 - 24 hours) of parent compound is below 1 % of an oral dose and approx. 3 - 13% of an inhaled dose. On the basis of these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 - 28% respectively.
Taking this into account, swallowed portions of ipratropium bromide doses do not contribute significantly to systemic exposure.

Distribution
Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations was observed. The apparent volume of distribution at steady state (Vd_{ss}) is approx. 176 l (equivalent to 2.4 l/kg). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical data indicate that the quaternary ammonium compound ipratropium does not cross the placenta or the blood-brain barrier.

The known metabolites show little or no affinity to the muscarinic receptor and must be regarded as ineffective.

Biotransformation
After intravenous administration, approx. 60% of the dose is metabolised, probably to a large extent by oxidation in the liver.

The known metabolites are formed by hydrolysis, dehydration or elimination of the hydroxymethyl group in the tropic acid moiety.

Elimination
The terminal elimination half-life is approx. 1.6 hours.

Ipratropium has a total clearance of 2.3 l/min and a renal clearance of 0.9 l/min.

After inhalation of ipratropium bromide with HFA 134a as the propellant, cumulative renal excretion over 24 hours was approx. 12%.
In an excretion balance study, cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) was 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was, 88.5% after oral administration and 69.4% after inhalation. Drug-related radioactivity after intravenous administration is excreted mainly via the kidneys. The elimination half-life of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

5.3 Preclinical safety data

Local and systemic tolerability of ipratropium bromide has been comprehensively investigated in several animal species using various administration routes.

Single-dose toxicity
Acute inhalational, oral and intravenous toxicity has been assessed in several rodent and non-rodent species.
When administered by inhalation, the minimum lethal dose in male guinea pigs was 199 mg/kg. In rats, no mortality was observed up to the highest technically feasible doses (0.05 mg/kg after 4 hours of administration or 160 puffs of ipratropium bromide at a dose of 0.02 mg/puff).
The oral LD_{50} values for mice, rats and rabbits were 1585, 1925 and 1920 mg/kg respectively. The intravenous LD_{50} values for mice, rats and dogs were 13.6, 15.8 and approx. 18.2 mg/kg respectively. Clinical symptoms included mydriasis, dry oral mucosa, dyspnoea, tremor, spasms and/or tachycardia.

Repeated-dose toxicity

Repeated-dose toxicity studies have been performed in rats, rabbits, dogs and rhesus monkeys.
In inhalation studies up to 6 months in rats, dogs and rhesus monkeys, the no observed adverse effect levels (NOAELs) were 0.38 mg/kg/day, 0.18 mg/kg/day and 0.8 mg/kg/day respectively. Dryness of the oral mucosa and tachycardia were noted in dogs. No histopathological lesions related to ipratropium bromide were observed in the bronchopulmonary system or in any other organs. In rats, the NOAEL after 18 months of oral administration was 0.5 mg/kg/day.
Repeated-dose inhalation toxicity studies in rats for up to 6 months and in dogs for up to 3 months - with other formulations (intranasal formulation, alternative propellant HFA 134a and lactose powder formulations) revealed no additional information on the general toxicity profile of ipratropium bromide.
Intranasal administration for up to 6 months revealed a no effect level (NOEL) of > 0.20 mg/kg/day in dogs and confirmed the results of earlier studies with intranasal administration for up to 13 weeks.
Repeated-dose toxicity studies of ipratropium bromide have shown the toxicological profiles of the HFA formulation and the conventional CFC formulation to be similar.

Local tolerability
An aqueous solution of ipratropium bromide (0.05 mg/kg) was locally well tolerated when administered to rats by inhalation (single administration over 4 hours). In the repeated-dose toxicity study, ipratropium bromide was locally well tolerated.

Immunogenicity
Neither active anaphylaxis nor passive cutaneous anaphylactic reactions occurred in guinea pigs.

Genotoxicity and carcinogenicity
There was no evidence of genotoxicity *in vitro* (Ames test) or *in vivo* (micronucleus test, dominant lethal test in mice, cytogenetic assay in Chinese hamster bone marrow cells).

No tumorigenic or carcinogenic effects were demonstrated in long-term studies in mice and rats.

Reproductive and developmental toxicity
Studies to investigate the possible influence of ipratropium bromide on fertility, embryo-/foetotoxicity and peri-/postnatal development have been performed in mice, rats and rabbits.
High oral doses (1000 mg/kg/day in rats and 125 mg/kg/day in rabbits) were maternotoxic for both species and embryo-/foetotoxic in rats and resulted in lower foetal weight. Malformations related to ipratropium bromide were not observed. The highest technically feasible doses for inhalation of the metered-dose aerosol (1.5 mg/kg/day in rats and 1.8 mg/kg/day in rabbits) had no adverse effects on reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water ,sodium chloride , 1 N hydrochloric acid , Disodium edetate dihydrate Benzalkonium chloride,

6.2 Incompatibilities

Aerovent and disodium cromoglicate inhalation solutions should not be administered simultaneously in the same nebuliser as precipitation may occur.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Aerovent should be used within 1 month from opening.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

Amber glass bottle of 20 ml with dropper with screw closure.

6.6 Special precautions for disposal and other handling

For inhalation using a nebuliser following dilution

For each use, Aerovent, respirator solution, should be freshly diluted with 3 - 4 ml of an isotonic solution (e.g. sodium chloride solution 0.9%) and the diluted solution should be inhaled until it is used up. Any diluted solution remaining after inhalation must be discarded.
The duration of inhalation can be controlled by the dilution volume.

Aerovent can be administered using a range of commercially available nebulisers. Where wall oxygen is available, it is best administered at a flow rate of 6 - 8 l/min.

Aerovent, respirator solution, is suitable for concurrent inhalation with mucolytic agents such as ambroxol hydrochloride and bromhexine hydrochloride or fenoterol hydrobromide . The solution must not be taken orally.

Care must be taken not to allow the solution or mist to enter the eyes. The nebulised solution should be administered via a mouthpiece. If a mouthpiece is not available and a nebuliser mask is used, care must be taken to ensure that it fits properly. Patients who are predisposed to glaucoma should take particular care to ensure their eyes are protected during inhalation.

The solution should ideally be administered with the patient in a sitting or standing position.

7. MANUFACTURER

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Localita Prulli Di Sotto, 103/C, 50066 Reggello, Italy

8. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Israel LTD
Medinat Ha-Yehudim 89 St., P.O. Box 4124, Herzliya Pituach 4676672, Israel

9. MARKETING AUTHORISATION NUMBER(S)

055-80-27113-01

This leaflet was revised in January 2022 acording to the MOH’s guidelines