

# EASEHALE RESPULES 0.025%

(IPRATROPIUM BROMIDE BP)

**Name of the medicine** Ipratropium Bromide.

Ipratropium Bromide (unit dose vial)

The chemical name for IPRATROPIUM BROMIDE (as monohydrate) is (1*R*,3*r*, 5*S*,8*r*)-3-[(*RS*)-(3-hydroxy-2-phenyl-propanoyl)-oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1] octane bromide monohydrate. The CAS number for IPRATROPIUM BROMIDE (as monohydrate) is 66985-17-9. The molecular formula is C<sub>20</sub>H<sub>30</sub>NO<sub>3</sub>Br.H<sub>2</sub>O and the molecular weight is 430.4.

Ipratropium Bromide (unit dose vial)

## DESCRIPTION

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. IPRATROPIUM BROMIDE is a white or off-white crystalline substance. It is freely soluble in methanol, soluble in water and sparingly soluble in ethanol 96% (v/v). IPRATROPIUM BROMIDE Unit Dose Vials (UDVs) contain sodium chloride, hydrochloric acid and water-purified.

## PHARMACOLOGY

**Pharmacotherapeutic Group:** Anticholinergics
**ATC Code:** R03BB01

IPRATROPIUM BROMIDE is an anticholinergic bronchodilator. It appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagal nerve. Anticholinergics prevent the increase in intracellular calcium concentration caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Bronchodilation following inhalation of IPRATROPIUM BROMIDE is primarily a local, site specific effect at the bronchial smooth muscle. IPRATROPIUM BROMIDE has no deleterious effect on airway mucous secretion or mucociliary clearance. The time course of action of IPRATROPIUM BROMIDE also differs from the β2 agonists in that although the onset of bronchodilator response is seen within 3-5 minutes of administration, peak response is not reached until 1.5-2 hours after inhalation. The duration of significant bronchodilator action is up to 6 hours. IPRATROPIUM BROMIDE may be used in combination with β2 agonists. There is evidence that in patients who respond to IPRATROPIUM BROMIDE, the concurrent administration of IPRATROPIUM BROMIDE and β2 agonists produces a greater relief of bronchospasm than either drug given alone. IPRATROPIUM BROMIDE inhibits acetylcholine-induced bronchospasm and provides partial protection against histamine and allergen-induced bronchospasm.

## PHARMACOKINETICS

### Absorption

Following inhalation, 10 to 30% of the dose (depending on the formulation and inhalation technique) is generally deposited in the lungs. The major part of the dose is swallowed and passes into the gastrointestinal tract. Due to the low gastrointestinal absorption of ipratropium bromide, the bioavailability of the portion of the dose swallowed, accounts for approximately 2% of the dose. This fraction of the dose does not make a relevant contribution to the plasma concentrations of the active ingredient. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes) and has nearly complete systemic availability. From renal excretion data (0-24 hours), the total systemic bioavailability (pulmonary and gastrointestinal portions) of inhaled doses of IPRATROPIUM BROMIDE was estimated to be in the range 7 to 28%. This is also a valid range for inhalation from IPRATROPIUM BROMIDECFC-free because the kinetic results (renal excretion, AUC and C<sub>max</sub>) from the CFC-free and the CFC-containing formulations are approximately comparable.

### Distribution

Kinetic parameters describing the disposition of IPRATROPIUM BROMIDE were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed. The volume of distribution (Vz) is 338 L (approximately 4.6 L/kg). The half-life of the terminal elimination phase is about 1.6 hours. The drug is less than 20% bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the ammonium structure of the molecule.

### Metabolism

The mean total clearance of the drug is 2.3 L/min. The major portion, approximately 60% of the systemically available dose, is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have no activity.

### Elimination

Approximately 40% of the systemically available dose is cleared via urinary excretion, corresponding to an experimental renal clearance of 0.9 L/min. After oral dosing less than 1% of the dose is renally excreted, indicating an insignificant absorption of IPRATROPIUM BROMIDE from the gastrointestinal tract. In excretion balance studies, after intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all 3 metabolites), are excreted via the biliary-faecal route. The dominant excretion of drug related radioactivity occurs via the kidneys.

## INDICATIONS

Moderate asthmatic attacks; chronic forms of asthma; asthma in patients with diminished cardiac reserve; chronic obstructive bronchitis with bronchospasm; bronchospasm during or after surgery, use during assisted ventilation with a respirator. Administration of IPRATROPIUM BROMIDE via a nebuliser is intended for those patients who cannot use a metered dose aerosol.

## CONTRAINDICATIONS

Known hypersensitivity to atropine or its derivatives (such as the active substance ipratropium bromide), or to any of the other ingredients of IPRATROPIUM BROMIDE (excipients are listed under DESCRIPTION).

## PRECAUTIONS

### Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of IPRATROPIUM BROMIDE, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngealoedema and anaphylaxis.

### Paradoxical Bronchospasm

As with other inhaled medicines IPRATROPIUM BROMIDE may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs IPRATROPIUM BROMIDE should be discontinued immediately and substituted with an alternative therapy.

### Anticholinergic Effects

Like other drugs with anticholinergic activity, IPRATROPIUM BROMIDE should be avoided or used with caution in patients where atropine-like effects may precipitate or exacerbate a pre-existing clinical condition. Patients at particular risk are those with eyes with narrow iridocorneal angles as acute angle-closure glaucoma may be precipitated, or patients with a tendency towards urinary retention or constipation.

### Ocular Complications

IPRATROPIUM BROMIDE should be used with caution in patients predisposed to narrow-angleglaucoma. There have been isolated reports of ocular complications (mydriasis, increased intraocular pressure, acute angle glaucoma, eye pain) as a result of direct eye contact of aerolised IPRATROPIUM BROMIDE either alone or in combination with an adrenergicβ2 agonist. Thus, patients must be instructed in the correct administration of IPRATROPIUM BROMIDE and warned not to allow the solution or mist to enter the eyes. A nebuliser mask must be fitted properly during inhalation. Patients who may be predisposed to glaucoma should be specifically warned to protect their eyes. Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal oedema, may be 4 signs of acute angle-closure glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

### Renal and Urinary Effects

IPRATROPIUM BROMIDE should be used with caution in patients with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

### Gastro-intestinal Motility Disturbances

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

### Local Effects

IPRATROPIUM BROMIDE Inhalation Solution in the multidose bottle contains benzal konium chloride and disodium edetate. When inhaled these agents may cause bronchospasm in sensitive patients with hyper reactive airways. If the multidose nebulising solution is prescribed, it is suggested that patients be monitored for their FEV1, and if the FEV1 falls, therapy with the preservative free Unit Dose Vials or Metered Dose Aerosol should be used.

### Effects on Fertility

Clinical data on fertility are not available for IPRATROPIUM BROMIDE.

## Use in Pregnancy

### Category b1

Care is recommended during pregnancy, particularly in the first trimester. The safety of IPRATROPIUM BROMIDE during 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 foetus. Studies in rats, mice and rabbits showed no embryo-toxic nor teratogenic effects.

### Use in Lactation

No specific studies are available to determine the excretion of IPRATROPIUM BROMIDE in human breast 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 administered by inhalation. However, as many drugs are excreted into breast milk, caution should be exercised when IPRATROPIUM BROMIDE is administered to breastfeeding mothers.

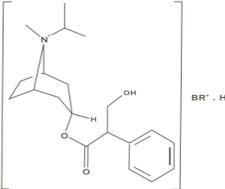
## Carcinogenicity

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

## Effects on ability to drive or operate machinery

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 IPRATROPIUM BROMIDE. 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.

## Structural formula



## INTERACTIONS WITH OTHER MEDICINES

The chronic co-administration of IPRATROPIUM BROMIDE inhalation with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of IPRATROPIUM BROMIDE with other anticholinergic drugs is not recommended. Beta-adrenergics and xanthine preparations may intensify the bronchodilatory effect. The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see PRECAUTIONS) may be increased when nebulised IPRATROPIUM BROMIDE and betamimetics are administered simultaneously.

### Physical Compatibility

IPRATROPIUM BROMIDE inhalation solutions and disodium cromoglycate inhalation solutions that contains the preservative benzal konium chloride should not be administered simultaneously in the same nebuliser as precipitation may occur. IPRATROPIUM BROMIDE UDVs and disodium cromoglycate inhalation solutions should not be administered simultaneously in the same nebuliser.

### ADVERSE EFFECTS

Many of the listed undesirable effects can be assigned to the anticholinergic properties of IPRATROPIUM BROMIDE. As with all inhalation therapy IPRATROPIUM BROMIDE 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 headache, dizziness, throat irritation, cough, gastrointestinal disorders (including constipation, diarrhea, gastrointestinal motility disorder, dry mouth, nausea, stomatitis, oedema mouth, and vomiting). If the substance enters the eyes by inappropriate handling, mild and reversible disturbance of accommodation may occur. Other ocular complications have also been reported (see PRECAUTIONS). However, acute angle-closure glaucoma has been reported following direct eye contact. Allergic-type reactions such as angio-oedema of the tongue, lips and face, may occur.

The following adverse reactions were reported in the clinical studies at the following frequency: very common (≥ 1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

### Immune System Disorders

Uncommon: hypersensitivity, anaphylactic reaction

### Nervous System Disorders

Common: headache, dizziness

### Eye Disorders

Uncommon: vision blurred, mydriasis, intraocular pressure increased, glaucoma, eye Pain, halo vision, conjunctival hyperaemia, corneal oedema
Rare: accommodation disorder

### Cardiac Disorders

Uncommon: palpitations, supraventricular tachycardia

Rare: atrial fibrillation, heart rate increased

### Respiratory, Thoracic and Mediastinal Disorders

Common: throat irritation, cough

Uncommon: bronchospasm, bronchospasm paradoxical, laryngospasm, pharyngeal Oedema, dry throat

### Gastrointestinal Disorders

Common: dry mouth, nausea, gastrointestinal motility disorder (including reports of Change in bowel motions and habits, dyspepsia, gastrointestinal reflux andflatulence)
uncommon: diarrhea, constipation, vomiting, stomatitis, oedema mouth

### Skin and Subcutaneous Tissue Disorders

Uncommon: rash, pruritus, angioedema

Rare: urticaria

## Renal and Urinary Disorders

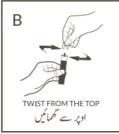
Uncommon: urinary retention

## DIRECTIONS FOR USE

### How to use your nebuliser?

Get your nebuliser ready by following the manufacturer’s instructions. Ask your doctor if you are not sure how to use it.

Read below from A to C first, before starting to use your nebuliser.

		
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Open the pouch and remove the strip of unit dose vials. Carefully separate a new dose unit from the strip. Do not use it if it is already open.

Twist off the top. Always hold it upright while you do this.

Squeeze all the contents of the dose unit into the nebuliser chamber.

## Warnings

- Your doctor will tell you if you need to use a different amount
- If you have also been prescribed a medicine called a 'short-acting beta2-agonist nebuliser solution' such as salbutamol the liquids can be mixed in the same nebulizer chamber
- If your doctor has told you that your medicine needs to be diluted, you will be given 'sterile sodium chloride 0.9%' solution. Your doctor will tell you how to do this
- Use your nebuliser as directed by your doctor
- After you have finished, dispose of any leftover medicine carefully
- Follow the manufacturer’s instructions on how to clean your nebulizer
- It is important to keep your nebulizer clean

## Directions

## DOSAGE AND ADMINISTRATION

IPRATROPIUM BROMIDE solution can be administered via a range of commercially available nebulising devices. Where wall oxygen is available, solutions are best administered at a flow rate of 6-8 litres per minute. Dosage is dependent on the mode of inhalation and the quality of nebulisation. The duration of inhalation can be controlled by the dilution volume. It is advisable not to greatly exceed the recommended daily dose as this suggests additional therapeutic modalities may be needed.

### Note

20 drops from the dropper insert in the multidose bottle equal approximately 261 µg of IPRATROPIUM BROMIDE (equivalent to 250 µg IPRATROPIUM BROMIDE (anhydrous)). The dosage should be adapted to the individual requirements of the patient; patients should also be kept under medical supervision during treatment. Unless otherwise prescribed, the following doses are recommended:

### Adults

The recommended dose is 261-522 µg [equivalent to 250-500 µg IPRATROPIUM BROMIDE Anhydrous], 4 times daily, diluted to 2-3 ml with normal saline, and nebulised until the Entire volume of solution is consumed. Daily dose exceeding 2.088 mg [equivalent to 2 mg IPRATROPIUM BROMIDE anhydrous] in adults should be given under medical supervision. In cases of moderate bronchospasm or with assisted ventilation, a dose in the lower Range of 261 µg [equivalent to 250 µg IPRATROPIUM BROMIDE anhydrous] is recommended. In more severely distressed patients, 522 µg IPRATROPIUM BROMIDE [equivalent to 500 µg IPRATROPIUM BROMIDE anhydrous] has been shown to produce optimal bronchodilatation. IPRATROPIUM BROMIDE can be administered combined with an inhaled β2-agonist.

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").

### Children

The recommended dose is 261 µg [equivalent to 250 µg IPRATROPIUM BROMIDE anhydrous], 4 times daily, diluted to 2-3 ml with normal saline and nebulised until the entire volume of Solution is consumed. Daily dose exceeding 1.044 mg [equivalent to 1 mg ipratropium Bromide anhydrous] in children ≤12 years of age should be given under medical Supervision.

IPRATROPIUM BROMIDE can be administered combined with an inhaled β2 agonist.

It is advisable not to greatly exceed the recommended daily dose.

If therapy does not produce a significant improvement or if the patient’s condition gets worse, medical advice must be sought in order to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

## OVERDOSAGE

No symptoms specific to over-dosage have been encountered. In view of the wide therapeutic range and topical administration of IPRATROPIUM BROMIDE inhalation solutions, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disturbances and tachycardia may occur.

## PRESENTATION AND STORAGE CONDITIONS

EASEHALE 0.025% 2ML Respule - preservative free, clear, colorless solution, each 2 mL respule contains 522 micrograms IPRATROPIUM BROMIDE [equivalent to 500 micrograms IPRATROPIUM BROMIDE(monohydrate)]. Respules of 2 mL, packs of 5s.

## IPRATROPIUM BROMIDE

Store the unopened respules at below 25°C. Protect from light. Diluted solutions should be freshly prepared before use and any solution remaining in the nebuliser, on completion of inhalation, should be discarded.

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Ipratropium Bromide (unit dose vial)

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