**IPRAVENT Inhaler (Ipratropium bromide)**

### Composition

**IPRAVENT-20 Inhaler**
Each actuation delivers:
Ipratropium Bromide ..... 20 mcg
Suspended in CFC-free propellant............HFA

**IPRAVENT-40 Inhaler**
Each actuation delivers:
Ipratropium Bromide ..... 40 mcg
Suspended in CFC-free propellant............HFA

### Dosage Form

Pressurised inhalation aerosol.

### Pharmacology

#### Pharmacodynamics

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In pre-clinical studies, it appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca^{++} caused by the interaction of acetylcholine with the muscarinic receptors on bronchial smooth muscle.

The bronchodilation following inhalation of ipratropium bromide is induced by local drug concentrations, sufficient for anticholinergic efficacy at the bronchial smooth muscle, and not by systemic drug concentrations.

In clinical trials using metered-dose inhalers in patients with reversible bronchospasm associated with asthma or COPD, significant improvements in pulmonary function (FEV\textsubscript{1} increases of 15% or more) occurred within 15 minutes, reached a peak in 1–2 hours, and persisted for approximately 4 hours.

Pre-clinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance, or gas exchange.

#### Pharmacokinetics

Absorption:

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

Following inhalation, 10 to 30% of a dose is generally deposited in the lungs, depending on the formulation, device and inhalation technique. The major part of the dose is swallowed and passes through the gastro-
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 approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose. Based on these data the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively.

Taking this into account, swallowed dose portions of ipratropium bromide do not contribute significantly to systemic exposure.

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

Biotransformation:
Ipratropium has a mean total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of the dose is metabolised, mainly by conjugation (40%), whereas after inhalation about 77% of the systemically available dose is metabolised by ester hydrolysis (41%) and conjugation (36%).

Elimination:
After inhalation of ipratropium bromide either with HFA or CFC propellant, cumulative renal excretion over 24 hours was approximately 12% and 10%, respectively.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.2 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

### Indications

IPRAVENT inhaler is indicated for the regular treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD) and chronic asthma.

### Dosage And Administration

**Adults (Including the Elderly)**

Usually 1 or 2 puffs, three or four times daily, although some patients may need up to 4 puffs at a time to obtain maximum benefit during early treatment.

**Children (6-12 years)**

1 or 2 puffs (20 or 40 micrograms) two times daily.

**Children below 6 years**

1 puff (20 micrograms) three times daily.

The recommended dose should not be exceeded.

IPRAVENT inhaler may be used with a Zerostat/Zerostat VT Spacer device in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.
Contraindications

IPRAVENT Inhaler should not be taken by patients with known hypersensitivity to atropine or its derivatives, or to ipratropium bromide or to any other component of the product.

Warnings And Precautions

IPRAVENT inhaler contains ipratropium, a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and asthma and, is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Caution is advocated in the use of anticholinergic agents in patients predisposed to or with narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-outflow obstruction). As patients with cystic fibrosis may be prone to gastrointestinal motility disturbances, ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

Ipratropium can produce paradoxical bronchospasm that can be life threatening. If this occurs, treatment with IPRAVENT inhaler should be stopped and other treatments considered.

Hypersensitivity reactions following the use of ipratropium bromide have been seen and have presented as urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis. In clinical trials and post marketing experience with ipratropium containing products, hypersensitivity reactions such as skin rash, pruritus, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported. If such a reaction occurs, therapy with IPRAVENT inhaler should be stopped at once and alternative treatment should be considered.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic beta₂-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of IPRAVENT inhaler and warned against the accidental release of the contents into the eye. Anti-glaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals and patients who may be susceptible to glaucoma should be warned specifically on the need for ocular protection.

Drug Interactions

There is evidence that the administration of ipratropium bromide with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect.

Pregnancy

Pregnancy Category B.

No adequate or well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, ipratropium bromide should be used
during pregnancy only if clearly needed.

**Lactation**

It is not known whether ipratropium bromide is excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that the active component, ipratropium bromide, would reach the infant to an important extent, especially when taken in aerosol form. However, because many drugs are excreted in human milk, caution should be exercised when ipratropium bromide is administered to a nursing mother.

**Undesirable Effects**

The following side effects have been reported. The frequencies given below are based on clinical trials involving patients who have been treated with ipratropium bromide.

<table>
<thead>
<tr>
<th>Frequencies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥1/100 &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1,000 &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000 &lt; 1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000</td>
</tr>
</tbody>
</table>

**Immune system disorders**

- Hypersensitivity: Uncommon
- Anaphylactic reaction: Uncommon
- Angio-oedema of tongue, lips, face: Uncommon

**Nervous system disorders**

- Headache: Common
- Dizziness: Common

**Eye disorders**

- Blurred vision: Uncommon
- Glaucoma (1): Uncommon
- Intraocular pressure increased (1): Uncommon
- Eye pain (1): Uncommon
- Mydriasis (1): Uncommon
- Halo vision: Uncommon
- Conjunctival hyperaemia: Uncommon
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Accommodation disorder</td>
<td>Rare</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
</tr>
<tr>
<td>Increased heart rate</td>
<td>Rare</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Rare</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
</tr>
<tr>
<td>Pharyngeal oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dry throat</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>Common</td>
</tr>
<tr>
<td>Paradoxical bronchospasm</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastro-intestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Dryness of mouth</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastro-intestinal motility disorder e.g.</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>Constipation</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and Subcutaneous Disorders</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

(1) Ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta<sub>2</sub>-agonist, has come into contact with the eyes during nebuliser therapy.
As with other inhalation therapy, inhalation induced bronchoconstriction may occur with an immediate increase in wheezing after dosing. This should be treated straight away with a fast acting inhaled bronchodilator. IPRAVENT inhaler should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.

The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

Other side-effects that have been reported include urticaria including giant urticaria, hypotension, back pain, influenza-like symptoms, dyspepsia, bronchitis, COPD exacerbations, dyspnea, sinusitis and urinary tract infection.

In a 5-year placebo-controlled trial, hospitalizations for supraventricular tachycardia and/or atrial fibrillation occurred with an incidence rate of 0.5% in COPD patients receiving ipratropium CFC.

In addition to the adverse reactions reported in the controlled clinical trials, adverse reactions have been identified during post approval use of ipratropium. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic-type reactions such as skin rash, angioedema including that of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases.

Additionally, urinary retention, mydriasis, gastrointestinal distress (diarrhoea, nausea, vomiting), cough and bronchospasm, including paradoxical bronchospasm, hypersensitivity reactions, intraocular pressure increased, accommodation disorder, heart rate increased, pharyngeal edema, and gastrointestinal motility disorders have been reported during the post-marketing period with use of ipratropium.

### Overdosage

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of ipratropium bromide, no serious anticholinergic symptoms are to be expected. As with other anticholinergics, dry mouth, visual accommodation disturbances and tachycardia would be the expected symptoms and signs of overdose.

### Packaging Information

IPRAVENT-20 Inhaler... canister containing 200 metered doses.
IPRAVENT-40 Inhaler... canister containing 200 metered doses.

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IPRAVENT Inhaler

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