IPTROW

(Ipratropium bromide)

0.025% Nebulizer solution

COMPOSITION
Each ml Contains:
Ipratropium Bromide 0.025% (0.25mg/ml)
(Product complies to BP Specifications)

THERAPEUTIC INDICATIONS
IPRATROPIUM BROMIDE UDVs are indicated for treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

IPRATROPIUM BROMIDE UDVs are indicated, when used concomitantly with inhaled beta2-agonists, for the treatment of reversible airways obstruction as in acute and chronic asthma.

DOSAGE AND ADMINISTRATION
The dosage should be adapted to the individual needs of the patient. In children aged 12 years and under, only IPRATROPIUM BROMIDE 250 UDVs, 1 ml should be used. The following doses are recommended:

Adults (including the elderly) and adolescents > 12 years of age:

250 - 500 micrograms (i.e. one vial of 250 micrograms in 1 ml or 1 vial of 500 micrograms in 2 ml) 3 to 4 times daily.

For treatment of acute bronchospasm, 500 micrograms.
Repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician. It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment. Daily doses exceeding 2 mg in adults and adolescents > 12 years of age should only be given under medical supervision.

Children 6 - 12 years of age:
250 micrograms (i.e. one vial of 250 micrograms in 1ml) up to a total daily dose of 1mg (4 vials).
Take 1ml quantity from vial with the help of syringe.
The time interval between doses may be determined by the physician.

Children 0 – 5 years of age (for treatment of acute asthma only):
125 – 250 micrograms (i.e. half to one vial of 250 micrograms in 1 ml) up to a total daily dose of 1 mg (4 vials).
Take 1ml quantity from vial with the help of syringe.
Ipratropium bromide should be administered no more frequently than 6 hourly in children under 5 years of age.
For acute bronchospasm, repeated doses may be administered until the patient is stable.

The patient should be instructed that in the case of acute or rapidly worsening dyspnoea a physician should be consulted immediately.

Private purchase of nebuliser devices for use at home to deliver rescue therapy for the acute treatment of asthma in children and adolescents is not recommended.

Only specialists in respiratory medicine should initiate and clinically manage use of nebulisers and associated nebulised medicines at home for acute treatment of asthma in children and adolescents.

Children should be trained in the correct use of their device to deliver rescue therapy and use should be supervised by a responsible adult.

Urgent medical assistance should be sought if worsening asthma symptoms are not relieved by rescue medicines, even if there is short-term recovery following use of prescribed nebulised medication.

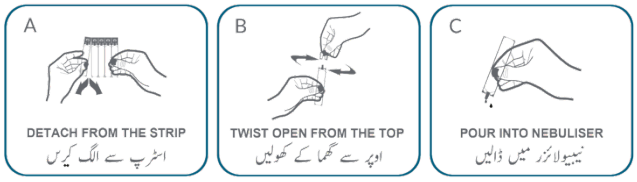
IPRATROPIUM BROMIDE UDVs may be combined with a short-acting beta2-agonist in the same nebuliser chamber, for simultaneous administration where co-administration is required. The solution should be used as soon as possible after mixing and any unused solution should be discarded.

IPRATROPIUM BROMIDE UDVs can be administered using a range of commercially available nebulising devices. The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used (usually 2 – 4 mL); if dilution is necessary use only sterile sodium chloride 0.9% solution.

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

The unit dose vials are intended only for inhalation with suitable nebulising devices and must not be taken orally or administered parenterally.

Instructions for Use/ Handling
Operate as follows, to use the unit dose vials:
1) Detach from the strip (see figure A)
2) Twist open from the top (see figure B)
3) Pour into the Nebuliser (see figure C)
4) For half dose (1ml) , use syringe to measure the quantity.



Please refer to the patient information leaflet for instructions on use with a nebuliser.

CONTRAINDICATIONS
IPRATROPIUM BROMIDE UDVs are contraindicated in patients with known hypersensitivity to atropine or its derivatives (such as the active substance ipratropium bromide) or to any other component of the product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Use of the nebuliser solution should be subject to close medical supervision during initial dosing.
Hypersensitivity
Immediate hypersensitivity reactions following the use of IPRATROPIUM BROMIDE have been demonstrated by cases of

urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Paradoxical bronchospasm

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. IPRATROPIUM BROMIDE UDVs should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.

Ocular complications

Caution is advocated in the use of anticholinergic agents in patients predisposed to or with narrow-angle glaucoma.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular 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 during nebuliser therapy.

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?

Patients must be instructed in the correct administration of IPRATROPIUM BROMIDE UDVs. Care must be taken not to allow the solution or mist to enter the eyes. It is recommended that the nebulised solution is administered via a mouthpiece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Renal and urinary effects

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

Gastro-intestinal motility disturbances

As patients with cystic fibrosis may be prone to gastro-intestinal motility disturbances, IPRATROPIUM BROMIDE, as with other anticholinergics, should be used with caution in these patients.

Interaction with other medicinal products and other forms of interaction

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. There is evidence that the administration of IPRATROPIUM BROMIDE with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect. The risk of acute glaucoma in patients with a history of narrow-angle glaucoma may be increased when nebulised ipratropium bromide and beta2-agonists are administered simultaneously.

DRUG INTERACTIONS

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FERTILITY, PREGNANCY AND LACTATION

Pregnancy

The safety of IPRATROPIUM BROMIDE during human pregnancy has not been established. The benefits of using IPRATROPIUM BROMIDE during a confirmed or suspected pregnancy must be weighed against the possible hazards to the unborn child. Nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

Lactation

It is not known whether ipratropium bromide is excreted into breast milk. It is unlikely that ipratropium bromide would reach the infant to an important extent, however caution should be exercised when IPRATROPIUM BROMIDE is administered to nursing mothers.

Fertility

Clinical data on fertility are not available for ipratropium bromide. Nonclinical studies performed with ipratropium bromide showed no adverse effect on fertility.

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 IPRATROPIUM BROMIDE. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery

ADVERSE DRUG REACTIONS

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.

Summary of the safety profile

The most frequent side effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during use of IPRATROPIUM BROMIDE in clinical trials and during the post-marketing experience.

Frequencies

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

MedDRA System Organ Class Adverse reaction	**Frequency**
Immune system disorders	
Hypersensitivity	Uncommon

Anaphylactic reaction	Uncommon
Angioedema of tongue, lips & face	Uncommon
Nervous system disorders	
Headache	Common
Dizziness	Common
Eye disorders	
Blurred vision	Uncommon
Mydriasis (1)	Uncommon
Intraocular pressure increased (1)	Uncommon
Glaucoma (1)	Uncommon
Eye pain (1)	Uncommon
Halo vision	Uncommon
Conjunctival hyperaemia	Uncommon
Corneal oedema	Uncommon
Accommodation disorder	Rare
Cardiac disorders	
Palpitations	Uncommon
Supraventricular tachycardia	Uncommon
Atrial fibrillation	Rare
Heart rate increased	Rare
Respiratory, thoracic and mediastinal disorders	
Throat irritation	Common
Cough	Common
Bronchospasm	Uncommon
Paradoxical bronchospasm(2)	Uncommon
Laryngospasm	Uncommon
Pharyngeal oedema	Uncommon
Dry throat	Uncommon
Gastrointestinal disorders	
Dry mouth	Common
Nausea	Common
Gastro-intestinal motility disorder	Common
e.g. Diarrhoea	Uncommon
Constipation	Uncommon
Vomiting	Uncommon
Stomatitis	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Pruritus	Uncommon
Urticaria	Rare
Renal and urinary disorders	
Urinary retention(3)	Uncommon

(1) ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta$_2$-agonist, has come into contact with the eyes

(2) 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. IPRATROPIUM BROMIDE UDVs should be discontinued immediately, the patient assessed and, if necessary, alterative treatment instituted.

(3) the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: pv@searlecompany.com

OVERDOSE

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties.

Pharmacotherapeutic group: Anticholinergics ATC Code: R03BB01

IPRATROPIUM BROMIDE is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In non-clinical studies, it appears to inhibit 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 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 chronic obstructive pulmonary disease significant improvements in pulmonary function (FEV_1 increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted for approximately 4 hours.

Non-clinical and clinical evidence suggest no deleterious effect of IPRATROPIUM BROMIDE on airway mucous secretion, mucociliary clearance or gas exchange.

The bronchodilator effect of IPRATROPIUM BROMIDE 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 IPRATROPIUM BROMIDE was administered in combination with an inhaled $beta_2$-agonist.

Pharmacokinetic properties

Absorption

The therapeutic effect of IPRATROPIUM BROMIDE 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-intestinal tract.

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

Cumulative renal excretion (0-24 hrs) of the 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. Non-clinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

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

Biotransformation

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%).

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

Elimination

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

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.

PRECLINICAL SAFETY DATA

The toxicity of ipratropium bromide has been investigated extensively in the following types of studies: acute, subchronic and chronic toxicity, carcinogenicity, reproductive toxicity and mutagenicity via oral, intravenous, subcutaneous, intranasal and/or inhalation routes. Based on these toxicity studies, the probability of systemic anticholinergic side effects decreases in the following order:
intravenous > subcutaneous > oral > inhalation > intranasal.

Pre-clinically, ipratropium bromide was found to be well-tolerated. Two-year carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to approximately 1,200 times the maximum recommended human daily dose for intranasal ipratropium. Results of various mutagenicity tests were negative.

Studies to investigate the possible influence of ipratropium bromide on fertility, embryo- fetotoxicity, and peri-/postnatal development have been performed on mice, rats and rabbits. High oral levels, i.e. 1000 mg/kg/day in the rat and 125 mg/kg/day in the rabbit were maternotoxic for both species and embryo-/fetotoxic in the rat, where the fetal weight was reduced. Treatment-related malformations were not observed. The highest, technically feasible doses for inhalation of the pressurised inhalation, solution, 1.5 mg/kg/day (human equivalent dose of 0.24 mg/kg/day) in rats and 1.8 mg/kg/day (human equivalent dose of 0.576 mg/kg/day) in rabbits, showed no adverse effects on reproduction.

These doses are 6- and 14-fold the maximum recommended human daily dose (MRHDD) of 2 mg or 0.04 mg/kg (based on a body weight of 50 kg).

PRESENTATION

Box of 5 unit dose vials of 2ml.

INSTRUCTIONS

To be sold on the prescription of a registered medical practitioner only.
Protect from sunlight, moisture and heat.
Store and transport below 30°C.
Keep all medicines out of sight & reach of children.
Store unused vial in the foil pouch.

- The expiry date printed on the package is intended for un-opened and correctly stored product.
- Do not use any residual liquid of vial and discard it.

REGISTRATION NUMBER

Iptrow Nebulization Solution 0.025% : 123346

Manufactured by:

Hudson Pharma Pvt. Ltd.
D-93, North Western Industrial Zone,
Port Qasim, Karachi.
DML No. 000842

Manufactured for:

The Searle Company Limited,
F-319, S.I.T.E., Karachi-Pakistan.
M.L. 000016

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