For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

NAME OF PRODUCT

Ipracip Respules 500mcg / 2mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml contains,

Ipratropium Bromide (monohydrate) BP ……522 mcg
Equivalent to Ipratropium Bromide (Anhydrous) ……500 mcg
In an isotonic solution ……q.s

PHARMACEUTICAL FORM

Solution for nebulization

PRODUCT -DESCRIPTION

A clear, colourless solution filled in 2 ml FFS vial. On visual inspection there is no sign of physical damage or leakage.

PHARMACODYNAMIC/ -PHARMACOKINETIC~~:~~

Pharmacodynamic properties:

Ipratropium is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties.~~ In preclinical studies~~, I~~i~~t 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 Nebulizer Solution 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 (FEV1 increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted for approximately 4 hours.~~

~~Preclinical and clinical evidence suggest no deleterious effect of Ipratropium Nebulizer Solution on airway mucous secretion, mucociliary clearance or gas exchange.~~

~~The bronchodilator effect of Ipratropium Nebulizer Solution in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children over 6 years of age. In most of these studies Ipratropium was administered in combination with an inhaled beta2-agonist.~~

Pharmacokinetic properties:

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-intestinal tract.

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

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

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, which are formed by hydrolysis, dehydration or elimination of the hydroxy-methyl group in the tropic acid moiety, show very little or no affinity for the muscarinic receptor and have to be regarded as ineffective.

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.

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~~Elimination~~

~~After inhalation of ipratropium bromide either with HFA 134a or CFC propellant, cumulative renal excretion over 24 hours was approximately 12% and 10%, respectively.~~

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~~I~~INDICATIONS

Ipratropium Nebulizer Solution is indicated for treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD).

Ipratropium Nebulizer Solution is indicated, when used concomitantly with inhaled beta2-agonists, for treatment of reversible airways obstruction as in acute and chronic asthma.

RECOMMENDED DOSE

The dosage should be adapted to the individual requirements and the patients should be kept under medical supervision during treatment. It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment.

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.

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

The following dosages are recommended:
Ipracip Respules 500 mcg / 2 mL
Maintenance treatment:
Adults (including elderly) and adolescents > 12 years of age:

1 unit dose vial (UDV) 3 to 4 times daily

Acute attacks:
Adults (including elderly) and adolescents > 12 years of age:
1 unit dose vial (UDV); repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.
Ipracip Respules can be administered combined with an inhaled beta-agonist.

Daily doses exceeding 2 mg ipratropium bromide anhydrous in adults and adolescents > 12 years of age should be given under medical supervision.

Instruction For Use
~~The dosage should be adapted to the individual needs of the patient. In children aged 12 years and under, only Ipratropium Nebulizer Solution, 1 ml should be used. The following doses are recommended:~~

~~Adults (including the elderly) and children over 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 children over 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).~~

~~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).~~

~~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.~~

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

Ipratropium Nebulizer Solution 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 Nebulizer Solution 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 Nebulizer Solution 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 should not be taken orally or administered parenterally.

MODE OF ADMINISTARTION

Oral inhalation

CONTRAINDICATIONS

Known hypersensitivity to atropine or its derivatives, or to any other component of the product.

WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of ipratropium, as demonstrated by rare cases of rash, urticaria, angioedema, oropharyngeal oedema bronchospasm and anaphylaxis.

Paradoxical bronchospasm

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

Ocular complications

Ipratropium should be used with caution in patients predisposed to narrow-angle glaucoma. 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 in contact with the eyes.

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.Care must be taken not to allow the solution or mist to enter into the eyes. It is recommended that the nebulised solution is administered via a mouth piece. 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 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 gastro-intestinal motility disturbances.

~~Use of the nebuliser solution should be subject to close medical supervision during initial dosing.~~

~~Immediate hypersensitivity reactions following the use of Ipratropium Nebulizer Solution have been demonstrated by cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.~~

~~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 gastro-intestinal motility disturbances, Ipratropium Nebulizer Solution, as with other anticholinergics, should be used with caution in these patients.~~

~~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.~~

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~~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 Nebulizer Solution should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.~~

INTERACTION WITH OTHER MEDICAMENTS

There is evidence that the administration of Ipratropium Nebulizer Solution 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 (see *Warnings and Precautions for Use*) may be increased when nebulised ipratropium bromide

and beta2-agonists are administered simultaneously.

PREGNANCY AND LACTATION

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

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 Nebulizer Solution is administered to nursing mothers.

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

SIDE EFFECTS

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Ipratropium Nebulizer Solution. As with all inhalation therapy Ipratropium Nebulizer Solution 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, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

~~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~~

Immune system disorder	
Hypersensitivity	Uncommon
Anaphyactic 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
Conjuctival hyperaemia	Uncommon
Corneal oedema	Uncommon
Accomodation 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
Gastro-intestinal Disorders	
Dry mouth	Common
Nausea	Common
Gastro-intestinal motility disorder	Common
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 beta2-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 Nebulizer Solution 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 reaction after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product.

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

SYMPTOMS AND TREATMENT OF OVERDOSE

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of Ipratropium Nebulizer Solution, 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.

PRESENTATION

——Carton containing 4 triple laminated pouches containing 5 FFS respules of 2mL each.

STORAGE CONDITION

Store below 30°C

SHELF LIFE

24 Months

PRODUCT REGISTRATION HOLDER

CIPLA MALAYSIA SDN BHD
Suite 1101, Amcorp Tower, Amcorp Trade Centre,
18 Persiaran Barat, 46 050 Petaling Jaya, Selangor, Malaysia

MANUFACTURED BY

CIPLA LTD.
Plot no – 9 & 10, Pharma Zone,
Phase II, Indore SEZ. Pithampur (MP)
India- 454775

DATE OF REVISION

January 2021

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