

## NEW ZEALAND DATA SHEET

### Ipratropium Steri-Neb 250 mcg/1ml Ipratropium Steri-Neb 500 mcg/2ml

#### Presentation

IPRATROPIUM STERI-NEBS are presented as unit dose, low-density polyethylene, hermetically sealed ampoule containing Ipratropium bromide 250mcg/ml (0.025%w/v).

IPRATROPIUM STERI-NEB 250 mcg/1ml: 250mcg Ipratropium bromide (equivalent to 261 mcg as the monohydrate) in 1ml

IPRATROPIUM STERI-NEB 500 mcg/2ml: 500mcg Ipratropium bromide equivalent to 522 mcg as the monohydrate) in 2ml

#### Uses

##### **Actions**

IPRATROPIUM STERI-NEBS contain ipratropium bromide which is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical 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 cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor 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 controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV<sub>1</sub> and FEF<sub>25-75%</sub> increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted in the majority of patients for up to 6 hours. In controlled 90 day studies in patients with bronchospasm associated with asthma, significant improvements in pulmonary function (FEV<sub>1</sub> increases of 15% or more) occurred in 40% of the patients.

Preclinical 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 children over 6 years of age. In most of these studies ipratropium bromide was administered in combination with an inhaled beta-agonist.

Although the data are limited, ipratropium bromide has been shown to have a therapeutic effect in the treatment of bronchospasm associated with viral bronchiolitis and bronchopulmonary dysplasia in infants and very small children.

##### **Pharmacokinetics**

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

Following inhalation dose portions from 10 to 30%, depending on the formulation and inhalation technique, are generally deposited in the lungs. The major part of the dose is swallowed and passes the gastro-intestinal tract. Due to the negligible gastro-intestinal absorption of ipratropium bromide the bioavailability of the swallowed dose portion accounts for only ~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 a nearly complete systemic availability. From data of renal excretion (0-24 hrs) the total systemic bioavailability (pulmonary and gastro-intestinal portions) of inhaled doses of ipratropium bromide was estimated to be in the range 7 to 28%. It is assumed that this is also a valid range for the inhalation from the solution for inhalation preparation. Kinetic parameters describing the

disposition of ipratropium bromide were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The volume of distribution ( $V_z$ ) is 338 L ( $\approx 4.6$  L/kg). The drug is minimally (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. The half-life of the terminal elimination phase is about 1.6 hours. The mean total clearance of the drug is determined to be 2.3 L/min. The major portion of approximately 60% of the systemic available dose is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective. A portion of approximately 40% of the systemic 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 gastro-intestinal 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 metabolites) are excreted via the biliary-faecal route. The dominant excretion of drug-related radioactivity occurs via the kidneys.

### **Indications**

IPRATROPIUM STERI-NEBS are indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema and when used concomitantly with inhaled beta-agonists, for asthma.

### **Dosage and Administration**

The following dosages should be regarded as a guide and adjusted to suit the requirements of the individual patient to provide optimal routine maintenance. 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.

One IPRATROPIUM STERI-NEB ampoule to be nebulised and inhaled until finished. Normally one ampoule will be sufficient to provide optimal bronchodilation, however, in more severe cases it may be necessary to administer an additional ampoule. This dosage regimen should be administered 3 to 4 times daily.

#### **Adults (including elderly) and adolescents over 12 years of age:**

The usual dose for adults is 0.4-2.0ml Ipratropium bromide solution (100-500 micrograms Ipratropium bromide) up to four times daily.

Steri-Neb 500 mcg/2ml:

Maintenance Treatment: One Steri-Neb 3 to 4 times daily

Acute Attacks: One Steri-Neb; repeated doses can be administered until the patient is stable. The time interval between doses may be determined by the doctor.

#### **Children:**

The usual dose for children is 0.4-2.0ml Ipratropium bromide solution (100-500 micrograms Ipratropium bromide) up to three times daily.

Steri-Neb 250 mcg/1ml:

Children 6 to 12 years: One Steri-Neb; repeated doses can be administered until the patient is stable. The time interval may be determined by the doctor. Daily dosage exceeding 1mg in children under 12 years of age should be given under medical supervision.

Under 6 years of age: One Steri-Neb; should be given under medical supervision, repeated doses can be administered until the patient is stable. The time interval may be determined by the doctor.

IPRATROPIUM STERI-NEBS can be administered using a range of commercially available nebulising devices. Where wall oxygen is available it is best administered at a flow rate of 6 - 8 litres per minute. If dilution is required sterile Sodium chloride 0.9% solution should be used.

Ipratropium bromide may also be given in combination with a  $\beta_2$ -agonist agent to maximise bronchodilation.

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

### **Contraindications**

IPRATROPIUM STERI-NEBS should not be taken by patients with known hypersensitivity to atropine or its derivatives or to any other component of the product.

### **Warnings and Precautions**

Ipratropium bromide should be used with caution in patients predisposed to narrow-angle glaucoma, or with prostatic hyperplasia or bladder-neck obstruction.

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

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

#### **Ocular complications**

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 beta<sub>2</sub>-agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of ipratropium bromide when nebulised. Care must be taken not to allow the solution or mist 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.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion 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 should be sought immediately.

#### **Use in 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 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.

#### **Use in Lactation**

It is not known whether ipratropium bromide is excreted into 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, when administered by inhalation. However, because many drugs are excreted into breast milk, caution should be exercised when ipratropium bromide is administered to nursing mothers.

#### **Effect on driving or operating machinery**

Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

### **Adverse Effects**

The most frequent non-respiratory adverse events reported in clinical trials with ipratropium bromide were gastro-intestinal motility disorders (e.g. constipation, diarrhoea and vomiting) headache and dryness of the mouth.

The following side effects have been observed with ipratropium bromide: increased heart rate, palpitations, supraventricular tachycardia and atrial fibrillation in patients known to be susceptible, ocular accommodation disturbances, gastro-intestinal motility disturbances, nausea and urinary retention. These side effects have been rare and reversible. The risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Ocular side effects have been reported (see: Warnings and Precautions).

As with other inhaled therapy including bronchodilators cough, local irritation and, inhalation induced bronchoconstriction have been observed.

Allergic-type reactions such as skin rash, angio-oedema of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases. Many of the patients have had a history of allergy to other drugs and/or foods, including soybean (see: Contraindications).

### **Interactions**

Beta-adrenergics and xanthine preparations may intensify the bronchodilator effect.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see Warnings and Precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

### **Overdosage**

No symptoms specific to overdose have been encountered. In view of the wide therapeutic range and topical administration of ipratropium bromide, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disturbances and increase of heart rate may occur.

### **Pharmaceutical Precautions**

Shelf-life:

IPRATROPIUM STERI-NEB 250 mcg/1ml

IPRATROPIUM STERI-NEB 500mcg/2ml

24 months when stored in their original pack at less than 25°C.

Storage: Do not store above 25°C. Do not refrigerate or freeze. Protect from light.

### **Medicine Classification**

Prescription Medicine

### **Package Quantities**

IPRATROPIUM STERI-NEB 250mcg/1ml: Packs of 20 ampoules

IPRATROPIUM STERI-NEB 500mcg/2ml: Packs of 20 ampoules

### **Further Information**

Pre-clinical Information

For ipratropium bromide, *in vitro* bacterial mutagenicity assays (Ames test) did not indicate a mutagenic potential. The results of *in vivo* assays (micronucleus test, dominant lethal test in mice, cytogenic assay on bone marrow cells of Chinese hamsters), did not demonstrate an increase in the rate of chromosomal aberrations.

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

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. Even the highest oral dose levels employed (1000 mg/kg/day in the rat and 125 mg/kg/day in the rabbit, which proved to be maternotoxic and, to some extent, embryo-/fetotoxic at dosages, far in excess to the human therapeutic dose, did not induce malformations in the offspring.

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