

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipratropium Steri-Neb 250 micrograms/ml Nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Steri-Neb containing 1ml of solution contains 250 micrograms of Ipratropium Bromide (250 micrograms/1ml).
Each Steri-Neb containing 2ml of solution contains 500 micrograms of Ipratropium Bromide (250 micrograms/1ml).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution

Clear colourless to almost colourless sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease and, when used concomitantly with inhaled beta₂-agonists, for treatment of acute and chronic asthma and acute bronchospasm associated with chronic obstructive pulmonary disease.

4.2 Posology and method of administration

The dosage should be adapted to the individual needs of the patient. Unless otherwise prescribed the following doses are recommended:

Adults (including the elderly) and children over 12 years of age:

500 micrograms 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.

Paediatric population

Children 6-12 years of age:

250 micrograms, up to a total daily dose of 1 mg. The time interval between doses should be determined by a physician.

Children 0-5 years of age (for treatment of acute asthma only):

Since there is limited information for the use of this product in children, the following dosage should be given under medical supervision: 125 - 250 micrograms: (i.e. half to one ampoule of 250 micrograms in 1 ml) up to a total daily dose of 1 mg (4 ampoules).

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.

It is advisable not to exceed the recommended daily dose. Daily doses exceeding 1 mg in this age group should be given under medical supervision.

Ipratropium Steri-Neb can be administered combined with an inhaled beta₂-agonist.

The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used; if dilution is necessary use only sterile sodium chloride 0.9% solution e.g. Steri-Neb sodium chloride 0.9 % w/v.

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

Ipratropium Steri-Neb can be administered using a range of commercially available nebulising devices.

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

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

4.3 Contraindications

Known hypersensitivity to atropine or its derivatives, or to any of the components of Ipratropium Steri-Neb.

4.4 Special warnings and precautions for use

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

Caution is advocated in the use of anticholinergic agents in patients predisposed to narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-outflow obstruction), or intestinal obstruction.

As patients with cystic fibrosis may be prone to gastro-intestinal motility disturbances, Ipratropium, 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.

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 Steri-Neb. 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.

Caution should be used in patients with cardiac disease.

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm), the patient's treatment plan should be reassessed.

Paediatric population

Ipratropium should not be used for the initial treatment of acute episodes of bronchospasm when a rapid response is required.

4.5 Interaction with other medicinal products and other forms of interaction

There is evidence that the administration of Ipratropium with beta-adrenergic drugs and xanthine preparations may intensify the bronchodilator effect of Ipratropium.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see Special Warnings and Special Precautions for Use) may be increased when nebulised ipratropium bromide and beta₂-agonists are administered simultaneously.

The side effects of other anticholinergic compounds may be potentiated.

Ipratropium bromide and other nebuliser solutions should not be used together in the same nebuliser.

4.6 Fertility, pregnancy and lactation

The safety of Ipratropium during human pregnancy has not been established. The benefits of using Ipratropium 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 is excreted into breast milk. It is unlikely that Ipratropium would reach the infant to an important extent, however caution should be exercised when Ipratropium 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.

4.7 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. 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.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Ipratropium. As with all inhalation therapy Ipratropium Steri-Neb 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, gastrointestinal 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 disorders

| | |
|-----------------------|----------|
| Hypersensitivity | Uncommon |
| Anaphylactic reaction | Uncommon |

Nervous system disorders

| | |
|-----------|--------|
| Headache | Common |
| Dizziness | Common |

Eye disorders

| | |
|---|----------|
| Vision blurred | 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 |
| Bronchospasm paradoxical | Uncommon |
| Laryngospasm | Uncommon |
| Pharyngeal oedema | Uncommon |
| Dry throat | Uncommon |
| Bronchoconstriction | Very rare |

Gastro-intestinal Disorders

| | |
|------------------------------------|-----------|
| Dry mouth | Common |
| Nausea | Common |
| Gastrointestinal motility disorder | Common |
| Diarrhoea | Uncommon |
| Constipation | Uncommon |
| Vomiting | Uncommon |
| Stomatitis | Uncommon |
| Oedema mouth | Uncommon |
| Intestinal obstruction | Very rare |

Skin and subcutaneous tissue disorders

| | |
|------------|----------|
| Rash | Uncommon |
| Pruritus | Uncommon |
| Angioedema | Uncommon |
| Urticaria | Rare |

Renal and Urinary Disorders

| | |
|----------------------------------|----------|
| Urinary retention ⁽²⁾ | Uncommon |
|----------------------------------|----------|

- (1) ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic β_2 -agonist, has come into contact with the eyes during nebuliser therapy– see section 4.4.
- (2) 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 authorisation 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No specific symptoms have been observed after an overdose. In view of the broad therapeutic range and local administration, no serious anticholinergic symptoms are to be expected with possible administration of an overdose of ipratropium bromide. Slight systemic expressions of the anticholinergic effect can occur, for example a dry mouth, disorders of visual accommodation and tachycardia. A severe overdose is characterised by symptoms of intoxication which are similar to those of atropine, for example tachycardia, tachypnoea, a high fever and CNS effects such as restlessness, confusion and hallucinations. These symptoms should be treated on a symptomatic basis. If respiration is unsatisfactory, ventilation is necessary. The use of physostigmine is usually not advisable on account of the cardiotoxic effects and induction of convulsions. Administration is only possible subject to ECG monitoring and provided that there is the possibility of ventilation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ipratropium 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 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 is primarily local and site specific to the lung and not systemic in nature.

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

In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (e.g. chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV1 and FEF 25-75% increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted in the majority of patients up to 6 hours.

The bronchodilator effect of Ipratropium 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 β_2 -agonist.

Although the data are limited, Ipratropium 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.

5.2 Pharmacokinetic properties

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 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 relevantly contribute to systemic exposure.

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

Kinetic parameters describing the distribution of ipratropium bromide were calculated from plasma concentrations after i.v. administration.

A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (V_{dss}) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. The quarternary amine of the ipratropium ion does not cross the blood-brain barrier.

The half-life of the terminal elimination phase is approximately 1.6 hours.

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 a dose is metabolised probably the major portion in the liver by oxidation.

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 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid dilute (for pH adjustment)
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

Unopened: 2 years.

Once opened: use immediately. Discard any unused portion.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

Store in the original container to protect from light.

6.5 Nature and contents of container

Unit dose, blow moulded, hermetically sealed 3 mL Steri-Neb made from low density polyethylene. Contents: 1 ml or 2 ml solution.

Available in boxes containing 20 and 100 Steri-Nebs. (Steri-Nebs are packed into foil laminate pouches, containing strips of 5x Steri-Nebs per pouch).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

- Prepare the nebuliser for use.
- Remove a Steri-Neb from the strip by twisting and pulling.
- Hold the Steri-Neb upright and twist off the cap, transfer the contents to the reservoir of the nebuliser.
- Use the nebuliser according to the manufacturer's instructions.
- After use throw away any remaining solution and clean the nebuliser.
- If dilution is required sterile sodium chloride 0.9% w/v should be used (Steri-Neb Sodium Chloride 0.9% w/v)
- Do not take the medicine if the solution is cloudy.

7 MARKETING AUTHORISATION HOLDER

Norton Healthcare Ltd
T/A IVAX Pharmaceuticals UK
Ridings Point
Whistler Drive
Castleford
West Yorkshire WF10 5HX
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8 MARKETING AUTHORISATION NUMBER

PA 0282/085/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 November 2007

10 DATE OF REVISION OF THE TEXT

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