

Arrow – Combipramol

Ipratropium bromide 500 micrograms/2.5ml, Salbutamol 2.5 mg/2.5ml
inhalation, solution

Presentation

Each 2.5mL ampoule contains:

2.5 mg salbutamol (equivalent to 3.01 mg salbutamol sulphate) *and*

500 micrograms ipratropium bromide anhydrous (equivalent to 520 micrograms ipratropium bromide monohydrate)

Uses

Actions

Arrow – Combipramol contains two active bronchodilating substances, salbutamol sulphate and ipratropium bromide.

Salbutamol sulphate is a beta₂-adrenergic agonist which acts on airway smooth muscle resulting in muscle relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and aids to prevent bronchoconstriction when challenged.

Ipratropium bromide 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 of intracellular concentration of Ca²⁺ which is caused by interaction of acetylcholine with muscarinic receptors on bronchial smooth muscle. Ca²⁺ release is mediated by the second messenger system consisting of IP₃ (inositol triphosphate) and DAG (diacylglycerol). The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Arrow – Combipramol provides the simultaneous release of ipratropium bromide and salbutamol allowing the synergistic efficacy on the muscarinic and beta₂-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent and with no potentiation of adverse events.

Pharmacokinetics

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as assessed by blood level and renal excretion studies. The elimination half-life of drug and metabolites is about 3 to 4 hours after inhalation or intravenous administration. Ipratropium bromide does not cross the blood-brain barrier.

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or the gastric route. Peak plasma salbutamol concentrations are seen within three hours of administration and the drug is excreted unchanged in the urine after 24 hours. The elimination half-life is 4 hours. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about five percent of the plasma concentrations.

It has been shown that co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and that therefore the additive activity of Arrow – Combipramol is due to the combined local effect on the lung following inhalation.

Indications

Arrow – Combipramol is indicated for the treatment of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

Dosage and Administration

Arrow – Combipramol inhalation solution in ampoules may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

Adults (including elderly):

1 ampoule as required for the relief of symptoms or as directed. Up to three to four ampoules daily.

Patients should be advised to consult a doctor or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea if additional inhalations do not produce adequate improvement.

Contraindications

Arrow – Combipramol is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any other component of the product and in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia.

Warnings and Precautions

In the case of acute, rapidly worsening dyspnoea a doctor should be consulted immediately.

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

There have been isolated reports of ocular complications (e.g. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist containing ipratropium bromide have escaped into 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 should be instructed in the correct administration of Arrow – Combipramol and care must be taken to prevent Arrow – Combipramol from entering the eye. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

In the following situations Arrow – Combipramol should only be used after careful risk / benefit assessment, especially when doses higher than recommended are used: Insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Cardiovascular effects may be seen with sympathomimetic drugs, including Arrow – Combipramol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol.

Patients with underlying severe heart disease (e.g. ischaemic heart disease, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Potentially serious hypokalaemia may result from prolonged and / or high dose beta2-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

If higher than recommended doses of Arrow – Combipramol are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

The use of Arrow – Combipramol may lead to positive results with regards to salbutamol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Use in Pregnancy

The safety of Arrow – Combipramol during human pregnancy is not established. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed. The inhibitory effect of Arrow – Combipramol on uterine contraction should be taken into account.

Arrow – Combipramol during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child.

For ipratropium bromide, preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulphate, non-inhalation preclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (please refer to section Toxicology).

No studies on the effect on human fertility have been conducted for Arrow – Combipramol. Preclinical studies performed with ipratropium bromide and salbutamol showed no adverse effect on fertility (please refer to section Toxicology).

Use in Lactation

It is not known whether salbutamol sulphate and ipratropium bromide are excreted in breast milk. Although lipid-insoluble quaternary cations pass into breast milk, it is considered unlikely that ipratropium bromide would reach the infant to an important extent when administered by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when Arrow – Combipramol is administered to nursing mothers.

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 Arrow – Combipramol. 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.

Adverse Effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta₂-sympathomimetic properties of Arrow – Combipramol. As with all inhalation therapy Arrow – Combipramol 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.

Immune system disorders:

- Anaphylactic reaction
- Hypersensitivity

Metabolism and nutrition disorders:

- Hypokalaemia

Psychiatric disorders:

- Mental disorder
- Nervousness

Nervous system disorders:

- Dizziness
- Headache
- Tremor

Eye disorders:

- Glaucoma
- Eye pain
- Intraocular pressure increased
- Mydriasis
- Vision blurred
- Accommodation disorder
- Corneal oedema
- Conjunctival hyperaemia
- Halo vision

Cardiac disorders:

- Arrhythmia
- Atrial fibrillation
- Myocardial ischaemia
- Palpitations

- Tachycardia
- Supraventricular tachycardia

Respiratory, thoracic and mediastinal disorders:

- Bronchospasm
- Bronchospasm paradoxical
- Laryngospasm
- Pharyngeal oedema
- Cough
- Dysphonia
- Dry throat

Gastrointestinal disorders:

- Oedema mouth
- Dry mouth
- Throat irritation
- Diarrhoea
- Gastrointestinal motility disorder
- Constipation
- Nausea
- Vomiting
- Stomatitis

Skin and subcutaneous tissue disorders:

- Skin reactions such as:
 - Rash
 - Pruritus
 - Urticaria
- Angioedema
- Hyperhidrosis

Musculoskeletal and connective tissue disorders:

- Muscle spasms
- Muscular weakness
- Myalgia

Renal and urinary disorders:

- Urinary retention

General disorders and administration site conditions:

- Asthenia

Investigations:

- Blood pressure diastolic decreased

- Blood pressure systolic increased
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Interactions

The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the side effects.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. It is recommended that serum potassium levels be monitored in such situations.

A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

Overdosage

Symptoms

The effects of overdosage are expected to be primarily related to salbutamol. The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disorders) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Treatment

Administration of sedatives, tranquillisers, in severe cases intensive therapy.

Beta-receptor blockers, preferably beta1-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.

Pharmaceutical Precautions

Store below 30 °C.

Medicines Classification

Prescription Only Medicine

Package Quantities

Arrow – Combipramol Ampoule: 2.5ml, 20's.

Further Information

Arrow – Combipramol contains the following excipients: sodium chloride, hydrochloric acid, purified water.

Name and Address of Sponsor

Arrow Pharmaceuticals (NZ) Limited
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