USER INFORMATION
NEBULISER SOLUTION
COMBINEB
Nebuliser Solution Unit Dose Vial
Ipratropium Bromide 0.5mg and Salbutamol 2.5mg

Composition:
Each 2.5 mL COMBINEB contains:
Ipratropium bromide 0.5 mg corresponding to Ipratropium bromide monohydrate 0.525 mg and salbutamol 2.5 mg corresponding to salbutamol sulphate 3.0 mg.

Characteristic:
COMBINEB is a clear and colourless nebuliser solution.

Pharmacodynamics:
Ipratropium bromide has 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.
The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.
Salbutamol is a beta2-adrenergic agent which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.
COMBINEB provide the simultaneous delivery of ipratropium bromide and salbutamol sulphate allowing effects on both muscarinic and beta2-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

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 halflife 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 COMBINEB is due to the combined local effect on the lung following inhalation.

Indications:
The management of bronchospasm in patients suffering from chronic obstructive pulmonary disease who require regular treatment with both ipratropium and salbutamol.

Recommended Dosage:
The recommended dose is :
Adults (including elderly patients and children over 12 years): 1 single dose unit three or four times daily.
Children under 12 years: No data for usage in children under 12 years.

Route of Administration:
Unit Dose Vial: The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

Contraindications:
Known to be hypersensitivity to any components of the formulation or to atropine. COMBINEB are contraindicated in patients with hypertrophic obstructive cardio-myopathy or tachyarrhythmia. COMBINEB are also contraindicated in patients with a history of hypersensitivity to ipratropium bromide, salbutamol sulphate or to atropine or its derivatives.

Warnings and Precautions:
Immediate hypersensitivity reactions may occur after administration such as urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.
Ocular complications (i.e. mydriasis, blurring of vision, narrow-angle glaucoma and eye pain) may occur when the contents of metered aerosols containing ipratropium bromide have been sprayed inadvertently into the eye.
The solution or mist should not be allowed to enter the eyes.
This is particularly important in patients who may be predisposed to glaucoma. Such patients 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 congestion and corneal oedema may be signs of acute arrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.
In the following conditions COMBINEB should only be used after careful risk/benefit assessment: insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, risk of narrowangle glaucoma, prostatic hypertrophy or bladder-neck obstruction.
Cardiovascular effects may be seen with sympathomimetic drugs including COMBINEB.
Rare occurences of myocardial ischaemia associated with salbutamol has been reported. 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 such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.
Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in severe airway obstruction as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving digoxin). It is recommended that serum potassium levels are monitored in such situations.
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.
The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea. In addition, the patient should be warned to seek medical advice should a reduced response become apparent.
The use of COMBINEB may lead to positive results with regards to salbutamol in tests for non clinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Interactions with Other Medicaments:
The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of COMBINEB.
The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the severity of side effects. A potentially serious reduction in 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.

Adverse Effects/Undesirable Effects:
The most frequent side effects reported 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: Nervousness, Mental disorder.
Nervous system disorders: Headache, Tremor, Dizziness.
Eye disorders: Accommodation disorder, Corneal oedema, Angle closure, Glaucoma, Intraocular pressure increased, Mydriasis, blurred Vision, Eye pain, Conjunctival hyperaemia, Halo vision.
There have been isolated reports of ocular complications with symptoms mentioned above when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist, has escaped into the eyes.
Cardiac disorders: Palpitations, Tachycardia, Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, Myocardial ischaemia, Blood pressure diastolic decreased Blood pressure systolic increased.
Respiratory, thoracic and mediastinal disorders: Cough, Dysphonia, Dry throat, Bronchospasm, Paradoxical Bronchospasm, Laryngospasm, Pharyngeal oedema, Throat irritation.
Gastrointestinal disorders: Dry mouth, Nausea, Throat irritation, Diarrhoea, Vomiting, Constipation, Gastrointestinal motility disorder, Mouth Oedema, 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.

Statement on Usage During Pregnancy and Lactation:
Ipratropium bromide has been in general use for several years and there is no definite evidence of ill-consequence during pregnancy; animal studies have shown no hazard.
Salbutamol has been in widespread use for many years without apparent ill-consequence during pregnancy. There is inadequate published evidence of safety in the early stages of human pregnancy but in animal studies there has been evidence of some harmful effects on the foetus at very high dose levels.
As with all medicines, COMBINEB should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus. Similarly, COMBINEB should not be administered to breast-feeding mothers unless the expected benefit is thought to outweigh any possible risk to the neonate.

Overdosage and Treatment:
Acute effects of overdosage with ipratropium bromide are unlikely due to its poor systemic absorption after either inhalation or oral administration. Any effects of overdosage are therefore likely to be related to the salbutamol component.
Manifestations of overdosage with salbutamol may include anginal pain, hypertension, hypokalaemia and tachycardia. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent but caution should be used in administering these drugs in patients with a history of bronchospasm.

Caution:
COMBINEB contains no preservative. It should be opened immediately before administration. Do not use if ampoule is damaged. Single dose container. Discard all unused contents.

Storage Condition:
Do not store above 30°C. Protect from light.

Shelf life:
2 years from manufacturing date in the proposed storage condition.
Do not use after expiry.

Dosage form and packaging available:
2.5mL X 60 LDPE plastic ampoule per box.

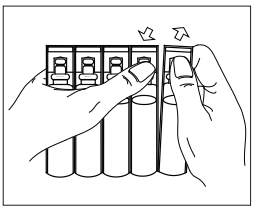
Manufacturer/Product Registration Holder:

AIN MEDICARE SDN. BHD.
Lot 4933, 4934 & PT2464, Jalan 6/44,
Kaw. Perindustrian Pengkalan Chepa 2,
16100 Kota Bharu, Kelantan, MALAYSIA

HANDLING INSTRUCTION

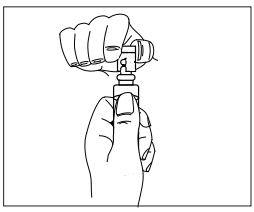
AIN MEDICARE NEBULISER SOLUTION IN POLYETHYLENE (LDPE) AMPOULE

1)



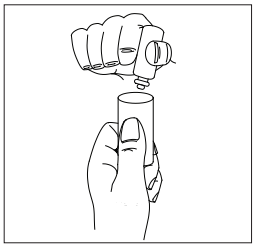
Detach ampoule along parting line

2)



Twist off tab

3)



Squeeze the content of the unit dose vial into the nebuliser reservoir. Assemble the nebuliser and use as directed. After use, throw away any solution left in the reservoir and clean the nebuliser according to the manufacturer's instructions.

Date of Revision: 01.03.2020