PACKAGE INSERT

SCHEDULING STATUS **S3**

PROPRIETARY NAME AND DOSAGE FORM

ADCO-COMBINEB

Inhalant Solution

COMPOSITION

Each 2,5 ml ampoule of ADCO-COMBINEB contains ipratropium bromide equivalent to 0,50 mg ipratropium bromide anhydrous and salbutamol sulphate equivalent to 2,50 mg salbutamol base. The solution is isotonic and preservative free.

PHARMACOLOGICAL CLASSIFICATION

A 10.2.1 Brochodilators - Inhalants

PHARMACOLOGICAL ACTION

Ipratropium bromide is a competitive muscarinic receptor antagonist at the neuroeffector sites, preventing the effects of acetylcholine by competing with and blocking its binding at neuroeffector sites.
Ipratropium is a synthetic quaternary ammonium compound that does not cross the blood-brain barrier.
When ipratropium is inhaled, its action is primarily confined to the mouth and airways.
Salbutamol is a short-acting beta-two ($ß_2$) selective agonist that relaxes bronchial smooth muscle and airway muscle. Beta-adrenergic agonists activate pulmonary beta–two receptors that relax bronchial smooth muscle and decrease airway resistance.

Pharmacokinetics:

Systemic absorption of inhaled ipratropium is minimal. After inhalation,maximal responses usually develop over 30 to 90 minutes, lasting for four to six hours.

The elimination half-life of ipratropium is approximately 3 to 4 hours after inhalation.

Salbutamol is well and completely absorbed. Significant bronchodilation occurs within minutes of inhalation of a therapeutic dose, persisting for three to four hours. Salbutamol is excreted in the urine as an inactive metabolite and unchanged drug. The elimination half-life of salbutamol is estimated to range from 4 to 6 hours. Only about 10 % of an inhaled dose reaches the lungs, the remainder is swallowed and ultimately may be absorbed.

INDICATIONS

ADCO-COMBINEB is indicated for the treatment of reversible bronchospasm associated with obstructive pulmonary disease.

CONTRA-INDICATIONS

Hypersensitivity to any of the ingredients.

Hypersensitivity to atropine or its derivatives.

Tachyarrhythmias.

Hypertrophic Obstructive Cardiomyopathy.

Safety in children under 12 years has not been established (see **DOSAGE AND DIRECTION FOR USE).**

WARNINGS and SPECIAL PRECAUTIONS

Do not exceed the recommended maximum doses.

Fatalities have been reported following excessive use of inhaled $ß_2$ agonists.

$ß_2$ agonists should be given with caution in patients with:-

- Cardiovascular disorders - such as ischaemic heart disease, severe cardiac decompensation, arrhythmias, severe hypertension - may require special care and supervision, with particular emphasis on dosage limits.
- Hyperthyroidism - patients with uncontrolled hyperthyroidism are unusually more sensitive to beta-2- agonists.
- Diabetes mellitus – close blood glucose monitoring may be required.

Ipratropium bromide should be administered with caution in patients with:-

- Urinary retention, bladder neck obstruction and prostatic hypertrophy
- Glaucoma (narrow angle) – An acute attack may be precipitated if the inhalation is inadvertently sprayed into the eyes.

Porphyria: Safety has not been established.

Immediate hypersensitivity reactions may occur after administration of ADCO-COMBINEB solution for inhalation (see **Side–effects**).

Paradoxical bronchospasm has been reported following bronchodilator therapy.

In addition, regular use of inhaled, short-acting $ß_2$ agonists such as salbutamol (as opposed to on an as-needed basis) has been shown to increase airway hyperresponsiveness to various stimuli and leads to the possible development of tolerance to the bronchoprotective effect.
There have been reports of ocular complications (see **Side- effects**), when aerosolised ipratropium bromide either alone, or in conjunction with a $ß_2$-receptor agonist has 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 must be instructed in the correct use of ADCO-COMBINEB.

Care must be taken not to expose the eyes to the solution or mist of ADCO-COMBINEB. It is recommended that the nebulised solution be 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.

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

In the case of acute, rapidly worsening dyspnoea a medical practitioner should be consulted immediately. If higher than recommended doses of ADCO-COMBINEB are required to control symptoms, the patient's therapy plan should be reviewed by a medical practitioner.

Potentially serious hypokalaemia may result from $ß_2$-receptor agonist therapy.
Particular caution is advised in severe airway obstruction, as the hypokalaemic effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia and acidosis may aggravate the effects of hypokalaemia on cardiac rhythm. Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin.

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

INTERACTIONS

- Concurrent use of other anticholinergics or other medicines with anticholinergic effects may potentiate the effects of ipratropium bromide or vice-versa.
- Concurrent use of beta–blockers may result in mutual inhibition of therapeutic effects.
- Diuretics (non-potassium sparing), digitalis glycosides, methylxanthines, corticosteriods – may increase the hypokalaemic effect of $ß_2$ agonists and lead to an increased disposition to arrhythmias in patients treated with digitalis glycosides. Monitor serum potassium levels.

- Beta–adrenergic agonists should be administered with caution in patients taking monoamine oxidase inhibitor or tricyclic antidepressants.
- Inhalation of halogenated hydrocarbon anaesthetics such as halothane,trichloroethylene and enflurane may increase the susceptibility to cardiovascular effects of beta-agonists.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

ADCO-COMBINEB solution for inhalation may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

Do not exceed recommended doses.

There is no experience in the use of ADCO-COMBINEB in children under the age of 12 years.

In the case of acute or rapidly worsening dyspnoea, a medical practitioner should be consulted immediately.

Treatment of acute symptoms:

Adults and children over the age of 12 years:

One unit dose provides prompt relief in most cases.

In servere cases if an attack has not been relieved by one unit dose vial, two unit doses may be required.

In this situation, the patient should seek prompt medical attention.

Maintenance treatment:

Adult and children over the age of 12 years:

One unit dose three or four times a day.

Instruction for Use:

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or your doctor.

2. Remove one ampoule by detaching from the strip.

3. Flick the top of the ampoule to dispel any fluid in the neck.

4. Detach top portion by twisting.

5. Squeeze the contents of the ampoule into the nebuliser reservoir.

6. Assemble the nebuliser and use as directed.

7. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

Since the ampoules do not contain a preservative, it is important that the contents of each ampoule are used up immediately after opening and that a fresh ampoule is used for each administration to avoid microbial contamination. Partly used, opened or damaged ampoules should be discarded.

It is strongly recommended not to mix ADCO-COMBINEB inhalant solution with other medicines in the same nebuliser reservoir. If necessary, dilution should be made using only sterile sodium chloride 0,9 % solution under medical supervision.

SIDE EFFECTS

Gastro–intestinal system:

Frequent: Dry mouth.

Less Frequent: Nausea, vomiting, dyspepsia, abdominal pain, constipation.

Skin and appendages:

Less Frequent: Rash, urticaria, pruritus.

Respiratory system:

Less Frequent: Bronchospasm (cough, shortness of breath, chest tightness, wheezing).

Central Nervous System:

Less Frequent: Dizziness, headache, agitation, restlessness, anxiety, sleep disturbances, nervousness.

Musculoskeketal system:

Frequent: Skeletal muscle tremor.

Less Frequent: Muscle cramps.

Cardiovascular system:

Less Frequent: Palpitations, tachycardia, arrhythmias, increases in blood pressure.

Genitourinary system:

Less Frequent: Urinary retention.

Metabolic system:

*L*ess Frequent: Hyperglycaemia (with large doses).

Potentially serious hypokalaemia has been reported after large doses.

Hypokalaemia may lead to arrhythmias.

Vision:

Less Frequent: Mydriasis, increased intraocular pressure, narrow–angle glaucoma, eye pain, blurred vision, visual halos or coloured images when solution for inhalation has escaped into the eyes in patients with narrow-angle glaucoma.

Hypersensitivity reaction:

Less Frequent: Hypersensitivity reactions have occurred, including paradoxical bronchospasm, angioedema, oropharyngeal oedema, urticaria, rash, hypotension and collapse.

Other:

Frequent: Dysphonia.

Less Frequent: Sweating.

Infection and inflammation have been reported to occur in children and includes viral infection, rhinitis, tonsillitis and gastroenteritis.

Dizziness, tremor or agitation may affect the ability to drive a vehicle or to operate machinery.

KNOWN SYMPTOMS OF OVER-DOSE AND PARTICULARS OF ITS TREATMENT

Expected symptoms of overdose are primarily related to salbutamol and are those of excessive beta-adrenergic stimulation.

The most prominent effects are headache, hyperglycaemia (blurred vision, increased hunger or thirst, increased urination), hypotension, hypertension, metabolic acidosis (shortness of breath), skeletal muscle tremor, tachycardia, palpitation, anginal pain, arrythmias and flushing.
Expected symptoms of overdose with ipratopium bromide (such as dry mouth and visual accommodation disturbances) are mild and transient.

Treatment of overdose:

Administration of sedatives, tranquillizers.

Beta-receptor blockers, preferably beta 1-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.

FURTHER TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

IDENTIFICATION

ADCO-COMBINEB low density polyethylene ampoules contain a clear, colourless or almost colourless solution, free from visible particulate matter.

PRESENTATION

Strips of 10 ampoules enclosed in packs of 60 ampoules. Each colourless, transparent, plastic low density polyethylene ampoule contains 2,5 ml of solution.

STORAGE INSTRUCTIONS

Store the ampoules in the outer packaging, below 25 °C, until required for use.
Protect from light. Do not freeze. Do not use if the solution is discoloured.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

A39/10.2.1/0373

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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