UNILAB

IPRATROPIUM SALBUTAMOL

DUA*VENT*®

500 mcg / 2.5 mg per 2.5 mL PULMONEB®
SOLUTION FOR NEBULIZATION
Chronic Obstructive Pulmonary Disease (Adrenergic Inhalant)

FORMULATION
Each 2.5 mL pulmoneb contains:
Ipratropium bromide (anhydrous).....500 mcg
Salbutamol (as sulfate) .....2.5 mg

PRODUCT DESCRIPTION
Ipratropium bromide-Salbutamol is a sterile, clear colorless aqueous solution filled in a 2.5 mL pulmoneb.

PHARMACODYNAMICS
Ipratropium bromide is an anticholinergic bronchodilator that reduces the formation of cyclic guanosine monophosphate (cGMP), a mediator of bronchospasm, thereby relaxing the smooth muscles of the bronchi and bronchioles. It is a potent bronchodilator, particularly in large bronchial airway; some evidence suggests that Ipratropium bromide also has bronchodilator activity in small airways.

Salbutamol is a selective short-acting beta$_2$-adrenergic agonist with preferential effect on beta$_2$-adrenergic receptors found in the respiratory tract. It stimulates adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP). cAMP mediates cellular responses such as bronchial smooth muscle relaxation resulting in bronchodilation.

Ipratropium bromide-Salbutamol combination maximizes the response to treatment in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD) by increasing bronchodilation through two distinctly different mechanisms, i.e., anticholinergic (parasympatholytic) and beta$_2$-agonist (sympathomimetic) effects. Simultaneous administration of both an anticholinergic (Ipratropium bromide) and a beta$_2$-agonist (Salbutamol) produces a greater bronchodilator effect than when either drug is used alone.

Bronchodilation occurs within 15 to 30 minutes with peak effect seen approximately 1 to 2 hours after oral inhalation via nebulization of 400 to 600 mcg of Ipratropium bromide. Bronchodilation generally persists for 4 to 5 hours, but may last up to 7 to 8 hours in some patients.

After concomitant administration via nebulization of Salbutamol and Ipratropium in patients with COPD, bronchodilation persists for 5 to 7 hours compared with 3 to 4 hours in patients given Salbutamol alone.

PHARMACOKINETICS
Only a small amount of Ipratropium reaches the systemic circulation after inhalation. Some Ipratropium is inadvertently swallowed but it is poorly absorbed from the gastrointestinal tract.

Pharmacokinetic studies in asthmatic patients receiving Salbutamol inhalation solution indicate that less than 20% of a single dose of the drug is absorbed when administered by nebulization. The remainder of the dose was recovered from the nebulizer and expired air.

Ipratropium is 0 to 9% bound to plasma albumin and α_1-acid glycoproteins *in vitro*. It is partially metabolized to N-isopropylnortropium methobromide, an inactive ester hydrolysis product.

Salbutamol is metabolized in the liver, being converted to Salbutamol 4'-O-sulfate which has little or no beta-adrenergic stimulating effect and no beta-adrenergic blocking effect.

Animal studies show that Salbutamol can cross the blood-brain barrier and the placenta. It may be secreted in breast milk, but the concentrations are not known.

INDICATIONS
·Management of reversible bronchospasm associated with obstructive airway diseases (e.g., bronchial asthma)
·For use in patients with chronic obstructive pulmonary disease (COPD) on a regular inhaled bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator

DOSAGE AND ADMINISTRATION
Dosage
Each pulmoneb of Ipratropium Bromide-Salbutamol contains 2500 mcg of salbutamol base (with each drop containing 50 mcg).
Children 2 to 12 years:
3 drops / kg / dose, maximum dose 2500 mcg (2.5 mg) of salbutamol every 6 to 8 hours
Adults (including elderly patients) and adolescents over 12 years of age:
Treatment of acute attacks:
· 1 pulmoneb (2.5 mL) is sufficient for prompt symptom relief in many cases
· 2 pulmonebs (5 mL) may be required in severe cases where an attack has not been relieved by 1 pulmoneb. Or, as prescribed by a physician.
Maintenance Treatment:
· 1 pulmoneb (2.5 mL) every 6-8 hours daily, or, as prescribed by a physician.
Administration
· The solution is intended only for inhalation with suitable nebulizing devices and should not be taken orally:
1. Prepare your nebulizer for use.
2. Remove the pulmoneb from the labeled strip by twisting and pulling.
3. Hold the pulmoneb upright and twist off the cap, transfer the contents to the reservoir of your nebulizer.
Note:
In most studies, a volume fill of 4 mL in the nebulizer chamber (using sterile normal saline as diluent) is recommended to ensure high aerosol output, small respirable particle size and acceptably short treatment time
4. Use your nebulizer, as instructed by the manufacturer.
5. After use, discard any remaining solution and thoroughly clean your nebulizer.
Other Information
· Since the solution contains no preservatives, it is important to use the content soon after opening. A new pulmoneb should be used for each administration to avoid microbial contamination. Discard partly used, opened or damaged pulmoneb.
· Do not mix the inhalation solution with other drugs in the same nebulizer.

CONTRAINDICATIONS
· Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia
· Patients with known hypersensitivity to any ingredient in the product or to atropine and its derivatives

WARNINGS AND PRECAUTIONS

If a previously effective dose fails to provide the usual relief, symptoms become worse, or the usual duration of action is reduced, consult a physician for medical advice as this would require reassessment of therapy.

Excessive use of sympathomimetic oral inhalations has been associated with fatalities in asthmatic patients. The exact cause of death is unknown but cardiac arrest following severe, acute asthmatic crisis and hypoxia is suspected.

Paradoxical bronchospasm, a potentially life-threatening event, has been observed with both inhaled Ipratropium and Salbutamol. If it occurs, discontinue use of the product immediately.

Therapy with Salbutamol and other beta$_2$-agonists may produce decrease in plasma potassium concentration possibly through intracellular shunting resulting in cardiovascular undesirable effects.

Immediate hypersensitivity reactions including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema may occur rarely after administration of the product.

Data from an observational study and another pooled analysis have shown an increased risk of mortality and/or cardiovascular events (e.g., myocardial infarction, stroke, transient ischemic attacks) in patients receiving inhaled anticholinergic agents, including ipratropium.

Concomitant administration of Ipratropium-Salbutamol has been reported to increase intraocular pressure and precipitate angle-closure glaucoma as a result of inadvertent contact to the eyes.

Patients should not expose the eyes to the nebulized solution of Ipratropium-Salbutamol since this may result in temporary pupillary dilation, precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Proper nebulizer techniques should be assured, particularly if a mask is used. Consult a physician if any combination of these symptoms develops.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances. Consult a physician in case of acute, rapidly worsening of dyspnea.

Use with caution in patients with the following conditions:
·Narrow-angle glaucoma
·Cardiovascular disorders including coronary insufficiency, cardiac arrhythmias or hypertension
·Convulsive disorders
·Hyperthyroidism
·Diabetes mellitus
·In patients who are unusually responsive to sympathomimetic amines
·Prostatic hypertrophy or bladder-neck obstruction
·Hepatic or renal disease

Use with caution in patients with severe airway obstruction where concomitant therapy with steroid, xanthine derivatives, or diuretics may result in hypokalemia; plasma potassium concentrations should be monitored.

INTERACTIONS WITH OTHER MEDICAMENTS
Anticholinergic agents: Although Ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications.

Beta-adrenergic agents: Co-administration with other sympathomimetic agents may increase risk of adverse cardiovascular events.

Beta-receptor blocking agents: Salbutamol and a beta-receptor blocking agent inhibit each other's effect.

Diuretics: The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (e.g., loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.

Monoamine oxidase inhibitors (MAOIs) or Tricyclic antidepressant (TCAs): Concomitant administration with these agents may potentiate Salbutamol's effect on the cardiovascular system.

PREGNANCY AND LACTATION
Pregnancy: The safe use of the product during pregnancy has not been established. Therefore, the product should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The inhibitory effect of the product on uterine contraction should be taken into account.

Labor and Delivery: Since beta$_2$-agonists may interfere with uterine contraction, the product should be used in labor only if the potential benefit justifies the potential risk.

Lactation: Ipratropium bromide and Salbutamol may be secreted in breast milk. Therefore, do not administer to breastfeeding women unless, in the opinion of a physician, the potential benefits of the product justify the possible risk.

UNDESIRABLE EFFECTS
Nasopharyngeal/Respiratory: Bronchitis, dyspnea, cough, lower respiratory tract disorders, pneumonia, bronchospasm, upper respiratory tract disorders, sinusitis, pharyngitis/sore throat, rhinitis, flu-like symptoms, nasal congestion, wheezing, lung disease, dysphonia/voice alterations, increased sputum, exacerbation of respiratory symptoms, hemoptysis, oropharyngeal edema, laryngospasm, bronchospasm, and anaphylactic reactions . Paradoxical bronchospasm, a potentially life-threatening event, has also been reported.

Cardiovascular: Tachycardia, palpitation, angina, chest pain, hypotension or hypertension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles), vasodilation, heartburn

Neurological: Tremor, nervousness, dizziness, headache, drowsiness, coordination difficulty, paresthesia, hypertonia, flushing, reduced appetite, insomnia, migraine, anxiety, vertigo, central nervous system stimulation

Gastrointestinal: Dry mouth, throat, and tongue, mucosal ulcers, thirst, diarrhea, dyspepsia, gastrointestinal distress, constipation, paralytic ileus, nausea, vomiting

Endocrine/Metabolic: Slight elevation of serum alanine aminotransferase, increased sweating. Potentially serious hypokalemia has also been reported.

Musculoskeletal, Connective Tissue and Bone Disorder: Arthralgia, pain, back pain, leg cramps, asthenia/muscle weakness, myalgia, muscle cramps

Dermatologic: Cases of skin rash, angioedema of the tongue, lips, and face, urticaria, pruritus, contact dermatitis

Ophthalmic: Precipitation or worsening of narrow-angle glaucoma, temporary pupillary dilation, blurred vision, acute eye pain

Genitourinary: Urinary tract infection/dysuria, urinary retention/difficulty

Otic: Otitis media, tinnitus

Others: Viral infection, local irritation, unusual taste/taste perversion, fatigue

OVERDOSAGE AND MANAGEMENT

Signs and symptoms of overdose are associated primarily with Salbutamol. Acute overdosage with Ipratropium bromide is unlikely after oral inhalation because of the drug's low systemic absorption. Manifestations of overdosage include extensions of Salbutamol's common undesirable effects (e.g., seizure, angina, hypertension or hypotension, arrhythmias, palpitation, tachycardia, nervousness, dizziness, tremor, headache, sleeplessness or insomnia, dry mouth, fatigue, malaise, and nausea). Hypokalemia has also been reported; thus, plasma potassium concentrations should be monitored.

Discontinue use of the product and institute appropriate symptomatic therapy in cases of overdosage. Administration of a beta-adrenergic blocking agent may be appropriate, but use with caution if the patient is asthmatic. There is no adequate evidence to support the use of dialysis in the treatment of Salbutamol overdose.

AVAILABILITY: Pulmonebs in box of 20's x 2.5 mL
CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.
STORE AT TEMPERATURES NOT EXCEEDING 30°C. KEEP THE PRODUCT OUT OF REACH AND SIGHT OF CHILDREN. PROTECT FROM LIGHT. DO NOT FREEZE. DO NOT USE IF THE SOLUTION IS DISCOLORED.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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