IPRATROPIUM BROMIDE SALBUTAMOL

DUAVENT®

20 mcg /100 mcg per actuation
HFA Metered-dose Inhaler
Anticholinergic / Beta$_2$-agonist

FORMULATION
Each actuation delivers:
Ipratropium bromide monohydrate.....21 mcg
(equivalent to 20 mcg Ipratropium bromide)
Salbutamol sulfate.....120 mcg
(equivalent to 100 mcg Salbutamol)
Suspended in Propellant HFA-227..... q.s.

PRODUCT DESCRIPTION
Ipratropium + Salbutamol (Duavent) 20 mcg/100 mcg per actuation HFA Metered-dose Inhaler is a white homogenous suspension aerosol for inhalation, in propellant HFA-227, supplied in a pressurized container.

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 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 in chronic obstructive pulmonary disease (COPD) patients than when either drug is used alone.

The onset of bronchodilation is evident within 15 minutes, with peak effect in 1 hour after oral inhalation of ipratropium bromide-salbutamol sulfate combination in patients with COPD. Bronchodilation persists for 4 to 5 hours with the combination compared with 4 hours with ipratropium bromide alone and 3 hours for salbutamol alone.

PHARMACOKINETICS
Ipratropium's peak plasma concentration remains below detectable limits (less than 100 pg/mL) while maximum salbutamol concentration is 492± 132 pg/mL within 3 hours after administration; 27.1± 5.7% of the estimated mouthpiece dose of ipratropium-salbutamol combination is excreted in urine as unchanged drug within 24 hours.

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 disease (e.g., bronchial asthma)
- Management of patients with COPD on a regular inhaled bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator

DOSAGE AND ADMINISTRATION
Individualize dose based on patient's requirements.

Dosage:
Adults and children over 12 years: 2 actuations every 6 hours, or, as prescribed by a physician
Patients may have additional inhalations as required but should not exceed 12 actuations in 24 hours.

Directions for Use:
1. Before using the inhaler for the first time, or if it has not been used for a week or longer, shake it well and then "test fire" by releasing one actuation into the air.
   Avoid spraying in the eyes.
2. Shake the inhaler well before each use.
3. Remove the mouthpiece cover, and check if it is clean.
4. Hold the inhaler between the index finger and thumb. Breathe out deeply through the mouth and immediately place the mouthpiece in the mouth between the teeth and close lips around it.
5. Tilt head slightly backwards. Keep the eyes closed because ocular undesirable effects (i.e., temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma, eye pain) may result after contact of the aeorosol with the eyes.
6. Start breathing in slowly and deeply through the mouth. Press down the canister while breathing in to release one dose while continuing to breathe in steadily and deeply.
7. Remove the inhaler from the mouth and hold breath for 10 seconds, or for as long as comfortable. Breathe out slowly.
8. For the second dose, wait for at least one minute and repeat steps 4 to 7.
9. After use, replace the mouthpiece cover.

Cleaning Instructions:
Clean inhaler at least once a week.
1. Gently pull the metal canister out of the inhaler's adapter. Remove the mouthpiece cover.
2. Rinse the adapter and the mouthpiece cover in warm water. Do not put the metal canister in water.
3. Shake well to remove excess water.
4..Leave to dry in warm place. Avoid excess heat.
5. Replace the canister and mouthpiece cover correctly.

CONTRAINDICATIONS
- Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia
- Patients with known hypersensitivity to soya lecithin or related food products such as soybeans or peanuts; to atropine and its derivatives; or to any ingredient in the product

WARNINGS
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, frequently occurs with the first use of a new canister. 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.

PRECAUTIONS
Patients should avoid spraying the aerosol into the eyes since this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Consult a physician if any combination of these symptoms develops.

Use with caution in patients with the following conditions:
- Narrow-angle glaucoma
- Prostatic hypertrophy or bladder-neck obstruction
- Cardiovascular disorders including coronary insufficiency, cardiac arrhythmias or hypertension
- Convulsive disorders
- Hyperthyroidism
- Diabetes mellitus
- In patients who are unusually responsive to sympathomimetic amines
- 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 MEDICATIONS
- Although ipratropium is minimally absorbed systemically after inhalation, there is a possibility of an additive interaction when used concomitantly with anticholinergic medications. Care must be exercised in the co-administration of ipratropium and other anticholinergic-containing medicines.
- Do not use with other sympathomimetic aerosol bronchodilators or epinephrine. Administer with caution additional sympathomimetic agents by any route to patients using salbutamol aerosol to avoid deleterious cardiovascular effects.
- Concurrent administration with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants may increase the risk for cardiac arrhythmia, tachycardia, and increased or decreased blood pressure.
- Do not administer with beta-receptor blockers since these drugs inhibit salbutamol's effect.

PREGNANCY AND LACTATION
Pregnancy: The safe use of the product during pregnancy has not been established. Caution is advised when administering drugs in pregnancy, especially during the first trimester. 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
The most frequently reported undesirable effects of ipratropium bromide-salbutamol combination include bronchitis, dyspnea, cough, lower respiratory tract disorders, pneumonia, bronchospasm, upper respiratory tract disorders, sinusitis, pharyngitis, rhinitis, influenza, nasal congestion, wheezing, central nervous system stimulation, tremor, nervousness, dizziness, headache, sleeplessness or insomnia, tachycardia, palpitation, angina, chest pain, arthralgia, pain, weakness, nausea, vomiting, diarrhea, dyspepsia, dry mouth, dysphonia, increased sputum, unusual taste/taste perversion, and urinary tract infection/dysuria.

Cases of skin rash, angioedema of the tongue, lips, and face, urticaria, laryngospasm, oropharyngeal edema, anaphylactic reactions, and paradoxical bronchospasm have also been reported.

The following adverse effects have been noted after oral inhalation of ipratropium bromide: precipitation or worsening of narrow-angle glaucoma, blurred vision, acute eye pain, drowsiness, coordination difficulty, hypotension, exacerbation of respiratory symptoms, fatigue, paresthesia, pruritus, flushing, alopecia, irritation, drying of secretions, gastrointestinal distress, constipation, mucosal ulcers, and urinary retention/difficulty.

The following adverse effects have been observed after administration of inhaled salbutamol: edema, hypertension or hypotension, arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles), heartburn, sweating, and rarely muscle cramps. Potentially serious hypokalemia has also been reported.

OVERDOSE AND TREATMENT
Signs and symptoms of overdose are associated 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., angina, hypertension or hypotension, arrhythmias, palpitation, tachycardia, nervousness, dizziness, tremor, headache, sleeplessness or insomnia, dry mouth, 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.

STORAGE CONDITIONS
- Keep the product out of reach and sight of children
- Store at temperatures not exceeding 30°C
- Protect from direct sunlight or heat
- Do not freeze or refrigerate
- Exposure to temperatures above 48° C (120° F) may cause bursting
- Do not break, puncture or burn the canister even when apparently empty

AVAILABILITY: Metered-dose inhaler in 200 doses

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by Medispray Laboratories Pvt. Ltd.
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