

## **PRODUCT MONOGRAPH**

**PrDuovent<sup>®</sup> UDV**  
**(ipratropium bromide/fenoterol hydrobromide)**

### **NEBULIZER SOLUTION**

**Each plastic unit dose vial (UDV) contains a total of 0.5 mg of ipratropium bromide and 1.25 mg fenoterol hydrobromide in 4 mL of saline**

### **BRONCHODILATOR**

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## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>3</b>
SUMMARY PRODUCT INFORMATION .....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS .....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	8
DRUG INTERACTIONS .....	12
DOSAGE AND ADMINISTRATION .....	13
OVERDOSAGE .....	14
ACTION AND CLINICAL PHARMACOLOGY .....	15
STORAGE AND STABILITY .....	21
DOSAGE FORMS, COMPOSITION AND PACKAGING .....	21
<b>PART II: SCIENTIFIC INFORMATION .....</b>	<b>22</b>
PHARMACEUTICAL INFORMATION.....	22
CLINICAL TRIALS.....	23
DETAILED PHARMACOLOGY .....	24
TOXICOLOGY .....	27
REFERENCES .....	36
<b>PART III: CONSUMER INFORMATION.....</b>	<b>37</b>

## Duovent<sup>®</sup> UDV

(ipratropium bromide/fenoterol hydrobromide)

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
inhalation	Solution/0.5 mg of ipratropium bromide and 1.25 mg fenoterol hydrobromide in 4 mL of isotonic saline	sodium chloride, hydrochloric acid

#### INDICATIONS AND CLINICAL USE

DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) is indicated for:

- treatment of bronchospasm associated with acute severe exacerbations of bronchial asthma or chronic obstructive pulmonary disease (COPD).

DUOVENT UDV nebulizer solution must be administered by means of nebulizer using gas flow (oxygen or compressed air).

Concomitant use of DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) with other sympathomimetic agents is not recommended since the combined use may lead to deleterious cardiovascular effects. If concomitant use is necessary, this should take place only under strict medical supervision. (see [DRUG INTERACTIONS](#))

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved.

#### Pediatrics (< 12 years of age):

- DUOVENT UDV is not currently indicated for use in children under 12 years of age as the dosing regimen and evidence concerning its safety in this age group have not been established.

## CONTRAINDICATIONS

- Patients with a known hypersensitivity to the component drugs, sympathomimetic amines, atropinics or to any of the product components. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) is also contraindicated in patients with tachyarrhythmias and hypertrophic obstructive cardiomyopathy.

## WARNINGS AND PRECAUTIONS

### **General**

Like other nebulizer solutions that contain  $\beta_2$  agonists, DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) should not be used on a regular basis without appropriate concomitant anti-inflammatory therapy (see [DOSAGE AND ADMINISTRATION](#)).

Care should be taken in patients suffering from myocardial insufficiency, cardiac arrhythmias, recent myocardial infarction, severe organic heart and/or other vascular disorders, hypertension, hyperthyroidism, insufficiently controlled diabetes mellitus, or pheochromocytoma.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought in order to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Increasing use of  $\beta_2$  agonists to control symptoms of bronchial obstruction, especially administration on a regular basis or in high amounts, indicates deterioration of asthma control. Under these conditions, the patient's therapy plan has to be revised. It is inadequate simply to increase the use of bronchodilators under these circumstances, in particular over extended periods of time (see [DOSAGE AND ADMINISTRATION](#)).

Concomitant use of DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) with other sympathomimetic agents is not recommended since the combined use may lead to deleterious cardiovascular effects. If concomitant use is necessary, this should take place only under strict medical supervision (see [DRUG INTERACTIONS](#)).

The bronchodilating action of sympathomimetic drugs may be antagonized by  $\beta$  adrenergic blocking agents with the result that the respiratory status of patients may worsen when the two drugs are used concomitantly. In patients requiring concomitant treatment with DUOVENT UDV and a  $\beta$  adrenergic blocking agent, the use of a relatively cardioselective  $\beta$  blocker (e.g. metoprolol, atenolol, acebutolol) must be considered. During the concomitant treatment, patients should be monitored carefully for possible deterioration in pulmonary function or for the need to adjust the dosage of either drug.

Caution is advised against accidental release of the solution into the eyes.

DUOVENT UDV should be used with caution in patients predisposed to narrow-angle glaucoma or with pre-existing-urinary outflow tract obstruction (e.g. prostatic hyperplasia, or bladder neck obstruction) and in asthmatic or emphysematous patients who also have acute and recurring congestive heart failure or in patients sensitive to sympathomimetic amines.

To ensure the proper dosage administration, the patient should be instructed by the physician or other health professional on the proper use and maintenance of the nebulizer.

Failure to respond to a previously effective dose usually indicates a significant deterioration in the patient's asthmatic condition. The patient should be instructed to contact his/her physician immediately in these circumstances and warned on no account to exceed the recommended dose.

Three retrospective case-control studies, from one group in New Zealand, have suggested that there may be an increased risk of death in those patients using Berotec (fenoterol hydrobromide) whom the studies classified as 'severe' asthmatics. These conclusions have not been confirmed by other studies and are subject to considerable debate and ongoing studies.

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

### **Carcinogenesis and Mutagenesis**

Animal data only (see [TOXICOLOGY](#)).

### **Cardiovascular**

Cardiovascular effects may be seen with sympathicomimetic drugs, including DUOVENT. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving DUOVENT, should be warned to seek immediate 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.

Fatalities, the exact cause of which is unknown, have been reported following excessive use of sympathomimetic amines by inhalation. Cardiac arrest was noticed in several instances.

### **Endocrine and Metabolism**

In common with other  $\beta$  adrenergic agents, fenoterol hydrobromide can induce reversible metabolic changes. These are most pronounced during infusions of the drug and include hyperglycemia and hypokalemia.

Potentially serious hypokalemia may result from  $\beta_2$  agonist therapy, mainly from parenteral and nebulized administration. Particular caution is advised in acute severe asthma, as hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics; the adverse effects of hypokalemia may be exacerbated by hypoxia. It is recommended that serum

potassium levels be monitored in such situations (see [OVERDOSAGE](#)).

Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias.

### **Gastrointestinal**

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

### **Immune**

Immediate hypersensitivity reactions may occur after administration of DUOVENT, as demonstrated by rare cases of urticaria, angio-edema, bronchospasm, oropharyngeal edema and anaphylaxis.

### **Ophthalmologic**

#### **Glaucoma, Angle-Closure**

Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulizer solution does not escape into the eyes (e.g. use swimming goggles with the mask, or use a mouth piece). In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of DUOVENT UDV should be avoided unless measures (e.g. use of swimming goggles or mouthpiece) are taken to ensure that nebulized solution does not reach the eye. Exposure of the eyes of such patients to a nebulized combination of ipratropium bromide and a  $\beta_2$  agonist solution (e.g. DUOVENT UDV) has been reported to result in increased intraocular pressure and/or acute angle closure. There have been isolated reports of ocular complications (e.g. mydriasis, increased intraocular pressure, angle closure glaucoma, eye pain) when nebulized ipratropium bromide either alone or in combination with an adrenergic  $\beta_2$  agonist solution has escaped into the eyes. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition.

Eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema 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.

### **Respiratory**

**Paradoxical bronchospasm:** Some patients receiving inhaled  $\beta$  adrenergic agonists have developed severe paradoxical bronchospasm, which has been life-threatening. The cause of this refractory state is unknown. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

**Use of DUOVENT UDV in Conjunction with IPPV:** It has been reported in several cases that the use of intermittent positive-pressure ventilation in acute asthma attacks was related to lethal episodes of hypoxia and pneumothorax. This method of drug administration may be ineffective in patients with severe obstruction and greatly increased airway resistance, and it may induce severe

hypercapnia and hypoxia. During intermittent positive-pressure ventilation therapy, the monitoring of arterial blood gases is highly desirable.

In patients with bronchial asthma DUOVENT UDV should be used only on an as-needed basis. In patients with mild COPD, on-demand (symptom-oriented) treatment may be preferable to regular use.

### **Special Populations**

#### **Fertility:**

Clinical data on fertility are neither available for the combination of ipratropium bromide and fenoterol hydrobromide nor for each of the two components of the combination. Preclinical studies performed with the individual components ipratropium bromide and fenoterol hydrobromide showed no adverse effect on fertility (see [TOXICOLOGY](#)).

#### **Pregnant Women:**

The safety of DUOVENT UDV in pregnancy and lactation has not been established. It should be used with caution before childbirth in view of the inhibiting effect of fenoterol on uterine contractions.

Autoradiographic studies in gravid rats showed no detectable amounts of fenoterol in the fetus. Direct blood and tissue studies in several animal species and in man showed that the levels of fenoterol and its conjugates were 10 to 20 times lower in the fetus than in the maternal tissues.

#### **Nursing Women:**

Non-clinical studies have shown that fenoterol hydrobromide is excreted into breast milk. It is unknown whether ipratropium is excreted into breast milk. But it is unlikely that ipratropium would reach the infant to an important extent especially when administered to the mother by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when DUOVENT is administered to a nursing woman.

#### **Pediatrics (< 12 years of age):**

DUOVENT UDV is not currently indicated for use in children under 12 years of age as the dosing regimen and evidence concerning its safety in this age group have not been established.

#### **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, tremor, accommodation disorder, mydriasis and blurred vision during treatment with DUOVENT UDV. 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 REACTIONS**

### **Adverse Drug Reaction Overview**

Frequent undesirable effects of DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) are fine tremor of skeletal muscles and nervousness, less frequent are tachycardia, increased heart rate, dizziness, palpitations or headache, especially in hypersensitive patients.

Potentially serious hypokalemia may result from beta<sub>2</sub> agonist therapy (see [OVERDOSAGE](#)).

In isolated cases there may be local reactions such as dryness of the mouth, throat irritation, pharyngitis or allergic reactions. As with use of other inhalation therapy, cough, local irritation (such as pharyngitis, throat irritation) and inhalation induced bronchospasm have been reported.

As with other β agonist containing products, nausea, vomiting, sweating, weakness and myalgia/muscle cramps may occur.

In rare cases, decrease in diastolic blood pressure, increase in systolic blood pressure, arrhythmias, particularly after higher doses, atrial fibrillation and supraventricular tachycardia and myocardial ischaemia may occur.

In individual cases, psychological alterations have been reported under inhalational therapy with β agonist containing products.

Because of the low systemic absorption of ipratropium bromide, ocular accommodation disturbances, gastrointestinal motility disturbances (vomiting, constipation, and diarrhea) and urinary retention are rare and reversible.

Ocular side effects (including accommodation disturbances and glaucoma) may occur (see [WARNINGS AND PRECAUTIONS](#)).

Skin reactions or allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*



The most frequent side effects reported in clinical trials were cough, dry mouth, headache, tremor, pharyngitis, nausea, dizziness, dysphonia, tachycardia, palpitations, vomiting, blood pressure systolic increased and nervousness.

**The adverse reactions noted for the individual components of DUOVENT UDV nebulizer solution are as follows:**

**Ipratropium Bromide**

The frequency of adverse reactions recorded in 214 patients receiving Atrovent (ipratropium bromide) solution was as follows (given by adverse effect: % of patients): Dry mouth or throat (9.3); Bad taste (5.1); Tremor (4.2); Exacerbation of symptoms (4.2); Burning eyes (0.9); Nausea (0.9); Sweating (0.9); Cough (0.9); Headache (0.5); Palpitations (0.5).

The adverse effect judged to be most severe was exacerbation of symptoms. This occurred in 8 patients treated with Atrovent solution alone, 6 of whom withdrew from the clinical studies.

Bronchospasm occurred in 3 patients with acute severe asthma who received Atrovent solution alone. In two patients, this was reversed after therapy with a  $\beta_2$  sympathomimetic solution. The third patient received no other therapy.

The following table compares the incidence of adverse effects of the combination of Atrovent and a  $\beta_2$  agonist solution with that of the  $\beta_2$  agonist alone.

ADVERSE EFFECT	ATROVENT - $\beta_2$ AGONIST (% of 94 patients)	$\beta_2$ AGONIST (% of 96 patients)
Tremor	31.9	26.0
Dry mouth	16.0	28.1
Bad taste	16.0	13.5
Vomiting	2.1	2.1
Palpitations	2.1	1.0
Headache	1.1	2.1
Cough	1.1	0.0
Flushing	1.1	0.0
Dizziness	0.0	1.0
Numbness in leg	0.0	1.0

There have been isolated reports of ocular effects such as mydriasis, increased intraocular pressure, and acute glaucoma associated with the escape of nebulized ipratropium bromide (alone or in combination with a  $\beta_2$  agonist) solution into the eyes.

**Fenoterol Hydrobromide**

At the most frequently used dosage of fenoterol hydrobromide solution of 0.5 to 1.0 mg, tremor occurred in 12% of patients. At higher doses of fenoterol hydrobromide solution (up to 2.5 mg), given for the treatment of severe asthma in a hospital emergency room, mild to moderate tremor occurred in 32% of patients. Other adverse reactions in decreasing order of frequency included nervousness, dizziness, headache, lightheadedness, and palpitations.

In 104 patients who received the highest recommended dosage of 2.5 mg of fenoterol hydrobromide solution, increases in heart rate of 10% or greater within 4 hours after drug administration were observed in 21% of the patients. However, at least an equal number of patients had decreased heart rate of a similar magnitude in the same time period. The remainder showed no significant pulse rate changes.

Local irritation or allergic reactions have been reported rarely. As with other bronchodilators, cough and, very rarely, paradoxical bronchospasm have been observed (see [WARNINGS AND PRECAUTIONS](#)). Potentially serious hypokalemia may result from  $\beta_2$  agonist therapy.

### **Post-Market Adverse Drug Reactions**

Many of the listed undesirable effects can be assigned to the anticholinergic and beta<sub>2</sub>-sympathomimetic properties of DUOVENT UDV. As with all inhalation therapy DUOVENT UDV 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.

#### Immune system disorders

- anaphylactic reaction
- hypersensitivity

#### Metabolism and nutritional disorders

- hypokalemia

#### Psychiatric disorders

- nervousness
- agitation
- mental disorder

#### Nervous system disorders

- headache
- tremor
- dizziness

#### Eye disorders

- glaucoma
- intraocular pressure increased
- accommodation disorder
- mydriasis
- vision blurred
- eye pain
- corneal edema
- conjunctival hyperaemia
- halo vision

### Cardiac disorders

- tachycardia, heart rate increased
- palpitations
- arrhythmia
- atrial fibrillation
- supraventricular tachycardia
- myocardial ischaemia

### Respiratory, thoracic and mediastinal disorders

- cough
- pharyngitis
- dysphonia
- bronchospasm
- throat irritation
- pharyngeal edema
- laryngospasm
- bronchospasm paradoxical
- dry throat

### Gastrointestinal disorders

- vomiting
- nausea
- dry mouth
- stomatitis
- glossitis
- gastrointestinal motility disorder
- diarrhoea
- constipation
- edema mouth

### Skin and subcutaneous tissue disorders

- urticaria
- rash
- pruritus
- angioedema
- hyperhidrosis

### Musculoskeletal and connective tissue disorders

- muscular weakness
- muscle spasms
- myalgia

### Renal and urinary disorders

- urinary retention

### Investigations

- blood pressure systolic increased
- blood pressure diastolic decreased

## DRUG INTERACTIONS

### Overview

Other  $\beta$  adrenergic agents, anticholinergics, xanthine derivatives (such as theophylline) and corticosteroids may enhance the effect of DUOVENT UDV nebulizer solution. The concurrent administration of other beta mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the adverse reactions.

A potentially serious reduction in bronchodilation may occur during concurrent administration of beta receptor blocking agents and fenoterol hydrobromide as these two agents inhibit the effects of one another (see [WARNINGS AND PRECAUTIONS](#)).

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

Hypokalemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. Additionally, hypoxia may aggravate the effects of hypokalemia on cardiac rhythm. It is recommended that serum potassium levels are monitored in such situations.

Avoid concomitant use of beta<sub>2</sub>-agonist containing medicinal products with monoamine oxidase inhibitors, tricyclic antidepressants or with other sympathomimetic agents since their combined effect on the cardiovascular system may be deleterious to the patient.

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

The chronic co-administration of DUOVENT UDV with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of DUOVENT UDV nebulizer solution with other anticholinergic drugs is not recommended.

### **Labour and Delivery**

Beta adrenergic agents have been shown to delay preterm labour in some reports.

There are no well-controlled studies which demonstrate that such agents will stop preterm labour or prevent labour at term. Cautious use of  $\beta$  adrenergics for the relief of bronchospasm is therefore required in pregnant patients to avoid interference with uterine contractility.

### **Lactation**

The safety of DUOVENT during lactation has not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved.

### **COPD: CHRONIC BRONCHITIS AND EMPHYSEMA**

DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) nebulizer solution dosage should be individualized and patient response should be monitored to determine the requirement for more than a single bronchodilator by the prescribing physician on an ongoing basis. Concomitant anti-inflammatory therapy should be considered for patients with steroid-responsive chronic obstructive pulmonary disease (COPD).

Counselling on smoking cessation should be the first step in treating patients with chronic obstructive pulmonary disease (COPD) who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema.

Smoking cessation produces symptomatic benefits and has been shown to confer a survival advantage by slowing or stopping the progression of chronic bronchitis and emphysema.

**ASTHMA:** DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide) nebulizer solution should be used only under medical supervision in patients with severe acute exacerbations of asthma who require more than a single bronchodilator.

**In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen if DUOVENT UDV is needed on a regular daily basis.**

**If a previously effective dosage regimen fails to provide the usual relief, or if the effects of a dose last for less than 3 hours, medical advice should be sought immediately; this is a sign of seriously worsening asthma that requires reassessment of therapy.**

### Recommended Dose and Dosage Adjustment

**Adults and adolescents 12 years of age or over:** The usual dose is 4 mL of DUOVENT UDV nebulizer solution (each plastic unit dose vial contains a total of 0.5 mg of ipratropium bromide and 1.25 mg fenoterol hydrobromide in 4 mL of isotonic saline).

Not recommended for children under 12 years of age.

## **Missed Dose**

If a dose is missed, the next scheduled dose should be taken. An extra dose must not be taken.

## **Administration**

This solution is ready for use and requires no dilution.

DUOVENT UDV nebulizing solution must be administered by means of nebulizer using gas flow (oxygen or compressed air).

DUOVENT UDV nebulizing solution can be administered using a range of commercially available nebulizing devices. The lung and systemic drug exposure is dependent on the nebulizer used.

Where wall oxygen is available the solution is best administered at a flow rate of 6 - 8 litres per minute.

Patients should follow the instructions provided by the manufacturer of the nebulizing device for proper care, maintenance and cleaning of the equipment.

## **DILUTION INSTRUCTIONS:**

If the full content of DUOVENT UDV is to be nebulized, squeeze the plastic vial to empty its contents into the nebulizer chamber. If instructions were given to use a dose less than one complete vial, use a syringe to transfer the necessary amount to the nebulizer chamber. Where wall oxygen is available, the solution is best administered at a flow rate of 6-8 L/min. **Any solution left in the plastic vial must be discarded because DUOVENT UDV does not contain preservatives.** In most cases, dilution of the dose with sterile preservative-free saline is not necessary. However, volumes of DUOVENT solution less than 2 mL are not appropriate for nebulization and must be diluted with sterile preservative-free saline or another suitable nebulizer solution to make-up a total fill volume of 2-5 mL.

## **OVERDOSAGE**

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

The effects of overdosage are expected to be primarily related to fenoterol. Overdosage resulting in excessive  $\beta$  adrenergic stimulation may cause tachycardia, palpitations, tremor, hypotension, widening of the pulse pressure, anginal pain, flushing, arrhythmia, hypertension and in extreme cases, sudden death. Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disturbances) are mild because the systemic availability of inhaled ipratropium is very low. Metabolic acidosis and hypokalaemia have also been observed with fenoterol when applied in doses higher than recommended for the approved indications of DUOVENT UDV. If DUOVENT UDV (ipratropium bromide/fenoterol hydrobromide)

overdosage occurs, cardiac and respiratory support should be provided as required.

Treatment with DUOVENT UDV should be discontinued. Acid base and electrolyte monitoring should be considered.

Administration of sedatives, tranquilizers, or in severe cases, intensive therapy may be appropriate for the treatment of overdosage. 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 or COPD because of the risk of precipitating severe bronchospasm, which may be fatal.

Furthermore, an increase in mucociliary clearance has been demonstrated after administration of higher doses of fenoterol.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

DUOVENT UDV nebulizer solution is a combination of the anticholinergic bronchodilator ipratropium bromide and the  $\beta_2$  adrenergic bronchodilator fenoterol hydrobromide. Ipratropium bromide is a quaternary ammonium derivative of atropine and is an anticholinergic drug which has bronchodilator properties. Each unit dose vial contains a total of 0.5 mg ipratropium bromide and 1.25 mg fenoterol hydrobromide in 4 mL of normal saline.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve.

Anticholinergics prevent the increase in intracellular concentration of  $Ca^{++}$  which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.  $Ca^{++}$  release is mediated by the second messenger system consisting of IP<sub>3</sub> (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilatation following inhalation of ipratropium bromide is primarily a local, site-specific effect, not a systemic one.

Preclinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance or gas exchange.

Fenoterol hydrobromide is a direct acting sympathomimetic agent, selectively stimulating  $\beta_2$ -receptors in the therapeutic dose range. The stimulation of  $\beta_1$ -receptors comes into effect at a higher dose range. Occupation of  $\beta_2$ -receptors activates adenyl cyclase via a stimulatory  $G_s$ -protein.

The increase in cyclic AMP activates protein kinase A which then phosphorylates target proteins in smooth muscle cells. This in turn leads to the phosphorylation of myosin light chain kinase, inhibition of phosphoinositide hydrolysis, and the opening of large-conductance calcium-activated potassium channels.

Fenoterol hydrobromide relaxes bronchial and vascular smooth muscle and protects against bronchoconstricting stimuli such as histamine, methacholine, cold air, and allergen (early response). After acute administration the release of bronchoconstricting and pro-inflammatory mediators from mast cells is inhibited. Further, an increase in mucociliary clearance has been demonstrated after administration of doses of fenoterol (0.6 mg).

The bronchodilating effect of fenoterol hydrobromide is produced primarily by stimulation of  $\beta_2$  receptors in the bronchial smooth muscles. When administered by inhalation, fenoterol exerts a significant increase in pulmonary function 5 minutes after administration with a maximal effect in 30 to 60 minutes. This effect remains at the same level for 2-3 hours before gradually declining. A significant degree of bronchodilation has been reported in some studies for 6-8 hours.

The concurrent administration of ipratropium bromide and fenoterol hydrobromide results in dilatation of the bronchi by affecting different pharmacologic sites of action. The two active substances thus complement each other in their spasmolytic action on the bronchial muscles. The complementary action is such that only a very low proportion of the  $\beta$ -adrenergic component is needed to obtain the desired effect, facilitating individual dosage suited to each patient with a minimum of adverse reactions.

### **Pharmacodynamics**

Large single inhaled doses of ipratropium bromide have been given to man without any signs of toxicity. After administration of 400  $\mu\text{g}$  by inhaler (10 times the recommended single dose) to 10 normal subjects, no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in another study, no changes in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhalation to 12 normal volunteers.

Higher plasma concentrations, which are more frequently achieved with oral, or even more so, with intravenous administration inhibit uterine motility. Also at higher doses, metabolic effects are observed: lipolysis, glycogenolysis, hyperglycaemia and hypokalaemia, the latter caused by increased  $\text{K}^+$ -uptake primarily into skeletal muscle.

Beta-adrenergic effects on the heart such as increase in heart rate and contractility, are caused by the vascular effects of fenoterol, cardiac  $\beta_2$ -receptor stimulation, and at supratherapeutic doses by  $\beta_1$ -receptor stimulation. As with other beta-adrenergic agents, QTc prolongations have been reported. For fenoterol pressurized inhalation solution these were discrete and observed at doses higher than recommended. However, systemic exposure after administration with nebulizers (nebulizer solution, nebulizer solution in UDV) might be higher than with recommended pressurized inhalation solution doses. The clinical significance has not been established. Tremor is a more frequently observed effect of beta-agonists. Unlike the effects on the bronchial smooth



muscle, the systemic effects on skeletal muscle of  $\beta$ -agonists are subject to the development of tolerance.

Special studies utilizing therapeutic doses in asthmatic and chronic bronchitic patients, again did not reveal any systemic anticholinergic effects. In one study, 14 patients were treated for 45 days with either Atrovent inhaler 40  $\mu$ g qid or Atrovent inhaler 40  $\mu$ g plus oral Berotec 5 mg qid. No changes in visual acuity, intraocular pressure, pupil size or accommodation of vision occurred. Micturition function studies in 20 male patients showed no differences in urinary flow, total flow time and time until maximum flow between placebo and ipratropium bromide inhaler 40  $\mu$ g tid administered for 3 days.

Deterioration in pulmonary function in patients treated in all clinical trials with therapeutic doses of Atrovent solution was examined. The following table shows the number of patients who showed a 15% or greater fall in FEV<sub>1</sub> at any time within 2 hours following the administration of the drug. Also shown are the figures for comparative agents used.

<b>Treatment</b>	<b>Incidence</b>
Normal saline	15/90 (16.7%)
Atrovent Solution	14/214 (6.5%)
Atrovent Inhaler	4/78 (5.1%)
Berotec Solution	4/83 (4.8%)
Atrovent Solution + Berotec Solution	1/81 (1.2%)

Dose titration studies in stable asthmatic patients with Atrovent solution have indicated that maximal improvement in pulmonary function occurs at approximately 250  $\mu$ g for adults and 125  $\mu$ g for children over 5 years.

A clinical pharmacology study comparing single doses of Atrovent inhaler (80  $\mu$ g) and Atrovent solution (250  $\mu$ g) in 16 stable adult asthmatics was performed. No difference between the regimens was found, based on an improvement in pulmonary function over a 2 hour period. A wide variety of challenge studies have been conducted using ipratropium bromide as a protective agent. In pharmacologically induced bronchospasm, ipratropium bromide, in clinical doses, was very effective against metacholine and acetylcholine, moderately effective against propranolol but had little or no effect against histamine or serotonin. Studies in exercise induced bronchospasm have yielded variable results. Some investigations have indicated that ipratropium bromide has little or no effect but other studies have shown that some patients are protected against bronchospasm induced by exercise. Likewise, the protective effects of ipratropium bromide against cold air induced bronchospasm have been variable.

Antigen challenge studies have demonstrated that Atrovent offers some protection against the “early” allergic asthma response, but has no effect on the “late” response.

In patients with asthma and COPD, better efficacy compared to its components ipratropium or fenoterol was demonstrated. Two studies (one with asthma patients, one with COPD patients)

have shown that DUOVENT is as efficacious as double the dose of fenoterol administered without ipratropium but was better tolerated in cumulative dose response studies.

In acute bronchoconstriction DUOVENT is effective shortly after administration and is therefore also suitable for treating acute episodes of bronchospasm.

### **Pharmacokinetics**

The pharmacokinetics of ipratropium bromide and fenoterol are not altered when the two drugs are administered concurrently.

The therapeutic effect of the combination ipratropium bromide and fenoterol hydrobromide is produced by a local action in the airway. The pharmacodynamics of the bronchodilation are therefore not related to the pharmacokinetics of the active constituents of the preparation.

Following inhalation 10 to 39% of a dose is generally deposited in lungs, depending on the formulation, inhalation technique and device, while the remainder of the delivered dose is deposited in the mouthpiece, mouth and the upper part of the respiratory tract (oropharynx).

There is no evidence that the pharmacokinetics of both ingredients in the combination differ from those of the mono-substance.

### **IPRATROPIUM BROMIDE**

**Absorption:** Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 µg administered from a pressurized metered dose inhaler. The peak plasma concentration (mean  $C_{max}$  = 32 pg/mL) is reached within 5 minutes after inhalation. The therapeutic effect of ipratropium bromide is produced by a local action in the airways. Therefore time courses of bronchodilation and systemic pharmacokinetics do not run in parallel. The time to reach peak plasma concentration was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited in the pharyngeal mucosa and swallowed. The absolute bioavailability after oral administration is approximately 2%.

**Distribution:** Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues (half-life of alpha phase approximately 5 minutes), and a terminal half-life (beta phase) of 3-4 hours. Plasma concentrations after inhaled ipratropium bromide were 1000 times lower than equipotent oral or intravenous doses (15 and 0.15 mg, respectively).

The half-life of the terminal elimination phase is about 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.

Radio-labelled technetium was administered with Atrovent (ipratropium bromide) solution in an adult dose finding study. The following table outlines the doses reaching the patient. The figures for Atrovent inhaler are published estimates.

Dose Available (µg)	Amount Reaching Patient (µg)	Lung Dose (µg)
500	53	17.0
250	27	8.5
125	13	4.3
40 (Atrovent Inhaler)	40	4.4

The drug is minimally (less than 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the quaternary amine structure of the molecule. It is not known if the placental barrier is crossed.

**Metabolism:** Up to eight metabolites of ipratropium have been detected in man, rat and dog. However, the main metabolites bind poorly to the muscarinic receptor.

**Excretion:** In man, about 70% of the <sup>14</sup>C labelled drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination of ipratropium and its metabolites occurs primarily via the kidneys with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the radiolabelled dose is detectable in the feces, suggesting relatively low lung deposition and poor absorption of the swallowed portion.

Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose via DUOVENT metered dose inhaler. Based on these data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (V<sub>dss</sub>) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Preclinical studies with rats and dogs revealed that the quaternary amine ipratropium does not cross the blood-brain barrier.

The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. Binding of the main

urinary metabolites to the muscarinic receptor is negligible and the metabolites have to be regarded as ineffective.

## FENOTEROL

**Absorption:** In man, fenoterol is rapidly absorbed from the gastrointestinal tract, with an absorption level of 60%. After administration of tritium labelled fenoterol, peak plasma levels (2.5% of the oral dose) are reached in two hours, the half-life of radioactivity being 6 to 7 hours. When given from a pressured container, absorption proceeds in two phases: the first one is essentially independent of the dose and apparently takes place between the first and fourth subdivisions of the bronchial tree. The second phase appears to be identical to oral absorption. After inhalation, blood levels remain almost unchanged for 7 hours (0.3-0.4 ng/mL fenoterol).

Following intravenous administration, three phases were observed, whereby the half-life of the terminal phase was approximately 3 hours.

**Distribution:** Fenoterol is very rapidly taken up by the tissues, where it conjugated to the extent of 99% (as sulphates).

**Metabolism:** Unlike isoproterenol, fenoterol is not metabolized by catechol-O-methyl transferase.

After intravenous administration, free fenoterol and conjugated fenoterol are approximated to 15% and 27% of the administered dose in the cumulative 24-hour urine. After inhalation via DUOVENT metered dose inhaler approximately 1% of an inhaled dose is excreted as free fenoterol in the 24-hour urine. Based on these data, the total systemic bioavailability of inhaled doses of fenoterol hydrobromide is estimated at 7%.

Kinetic parameters describing the disposition of fenoterol were calculated from plasma concentrations after i.v. administration. Following intravenous administration, plasma concentration-time profiles can be described by a 3-compartment model, whereby the terminal half-life is approximately 3 hours. In this 3-compartment model the apparent volume of distribution of fenoterol at steady state ( $V_{dss}$ ) is approximately 189 L ( $\approx 2.7$  L/kg).

**Excretion:** The resulting metabolites are excreted via the kidneys (40% within the first 48 hours after oral administration) and the bile (fecal excretion: 40% of the oral dose).

About 40 % of the drug is bound to plasma proteins.

Preclinical studies with rats revealed that fenoterol and its metabolites do not cross the blood-brain barrier. Fenoterol has a total clearance of 1.8 L/min and a renal clearance of 0.27 L/min.

In an excretion balance study cumulative renal excretion (2 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 65% of dose after intravenous administration and total radioactivity excreted in faeces was 14.8% of dose. Following oral administration, total radioactivity excreted in urine was approximately 39% of dose and total radioactivity excreted in faeces was 40.2% of dose within 48 hours.

## **STORAGE AND STABILITY**

Unopened unit dose vials of DUOVENT UDV should be stored at room temperature (15-25°C) and protected from heat and light. If necessary, the solution may be diluted with preservative-free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

DUOVENT nebulizer solution is provided as plastic single unit dose vials (UDV) filled with 4 mL of clear, colourless, isotonic aqueous solution containing 0.5 mg of ipratropium bromide and 1.25 mg fenoterol hydrobromide.

Each millilitre of the solution contains 0.125 mg of ipratropium bromide and 0.3125 mg of fenoterol hydrobromide. Non-medicinal ingredients include sodium chloride and hydrochloric acid to adjust the pH.

Each carton contains 2 strips of 10 x 4 mL UDVs. Each UDV strip is packaged in an aluminum/Low Density Polyethylene (LDPE) pouch.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: ipratropium bromide

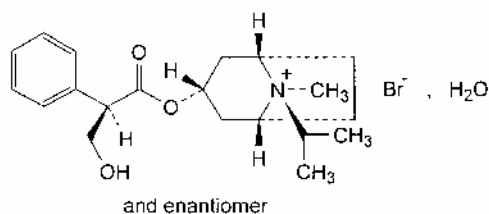
Chemical name:

(1) 8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide;

(2) (8*r*)-3α-Hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate.

Molecular formula and molecular mass: C<sub>20</sub>H<sub>30</sub>NO<sub>3</sub>Br, 412.37

Structural formula:



Physicochemical properties:

White crystalline powder with bitter taste. Freely soluble in water and alcohol; insoluble in chloroform and ether. In neutral and acid solutions the substance is rather stable; in alkaline solutions the ester bond is rapidly hydrolyzed. Melting point, 230°C with decomposition.

#### Drug Substance

Proper name: fenoterol hydrobromide

Chemical name:

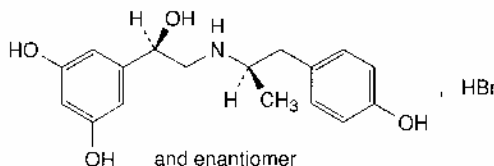
(1) 1,3-Benzenediol,5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-,hydrobromide;

(2) 3,5-Dihydroxy-α-[[*p*-hydroxy-α-methyl-

phenethyl)amino]methyl]benzyl alcohol-,hydrobromide.

Molecular formula and molecular mass:  $C_{17}H_{21}NO_4HBr$ , 384.28

Structural formula:



Physicochemical properties:

White crystalline powder, odorless with bitter taste; soluble in water and in alcohol, practically insoluble in chloroform. Melting point of approximately 230°C.

## CLINICAL TRIALS

The effect of q.i.d. domiciliary nebulized DUOVENT for 3 weeks was assessed in a placebo-controlled, randomized, double blind, cross-over study in 20 patients with a low bronchodilator response and steroid resistant chronic obstructive pulmonary disease. Home expiratory flow rate rose from 164L/min on saline to 196L/min on DUOVENT. Secondary end-point analysis revealed a fall in home inhaler usage and a rise in visual analogue scales for symptoms.

### The Lung Health Study

The Lung Health study is a randomized multicentre clinical trial carried out from October 1986 to April 1994 in North America. It was designed to test the effectiveness of intervention-smoking cessation and bronchodilator administration in smokers aged 35-60 years who have mild obstructive pulmonary disease. The main outcome or end point was the rate of change and cumulative change in FEV<sub>1</sub> over a 5-year period.

A total of 5887 male and female smokers, aged 35 to 60 years, with spirometric signs of early chronic obstructive pulmonary disease were recruited. Participants were randomized to one of the following groups: (1) smoking intervention plus bronchodilator, (2) smoking intervention plus placebo, or (3) no intervention.

Smoking intervention consisted of an intensive 12-session smoking cessation program combining behavior modification and use of nicotine gum, with continuing 5-year maintenance program to minimize relapse. Two puffs ipratropium bromide were prescribed three times daily from a metered-dose-inhaler.

The results showed that participants in the two smoking intervention groups showed significantly smaller declines in FEV<sub>1</sub> than did those in the control group. Most of this difference occurred during the first year following entry into the study and was attributable to smoking cessation, with those who achieved sustained smoking cessation experiencing the largest benefit. The small

noncumulative benefit associated with the use of the ipratropium bromide vanished after the ipratropium bromide was discontinued at the end of the study.

In summary the results showed that smoking intervention reduced the rate of decline in FEV<sub>1</sub> in middle aged smokers with mild airways obstruction who remained non-smokers throughout the 5 years. The other intervention, administration of ipratropium bromide, did not alter the rate of decline in lung function. There was a small one time improvement in lung function associated with the onset of ipratropium use, but this disappeared rapidly when ipratropium use was discontinued at the end of the study. Otherwise, the regular use of ipratropium bromide had no effect on the rate of decline of lung function over 5 years in patients studied.

## **DETAILED PHARMACOLOGY**

### **Ipratropium bromide**

Ipratropium bromide is an anticholinergic agent which, when delivered by aerosol, exerts its effect primarily in the bronchial tree. It abolishes acetylcholine induced bronchospasm in the guinea pig and dog after intravenous administration of ED<sub>50</sub> of 0.15 - 0.40 µg/kg with a transient effect on blood pressure. By inhalation, approximately 25 µg ipratropium bromide produces a 50% inhibition of acetylcholine-induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to intravenous administration. Histologic evaluation of human bronchial mucosa following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 µg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from a s.c. dose of about 0.011 mg/kg, equipotent to atropine, but the equipotent oral dose of ipratropium was 58 times greater. By inhalation, no increase in heart rate or pathologic changes in ECG pattern were recorded at dose up to 8 mg. In another study, blood pressure and heart rate in the dog could be modulated after i.v. administration of low doses of ipratropium but metered aerosol administration of 100 puffs (40 µg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in the rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 µg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration to dogs of about 65 puffs (40 µg/puff) produced a 50% decrease in salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between effective enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after s.c. doses but were 10-20 times less after oral administration. Tests of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system.

Ipratropium bromide, subcutaneously, inhibited the secretory effects of the cholinergic agonist, oxxtremorine, in mice. It also inhibited spasmolytic effects equivalent to or greater than atropine in



isolated guinea pig gut. In vitro tests with isolated rectum of the guinea pig demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride induced spasm. Ipratropium bromide exerted anticholinergic effects on the in situ bladder and intestine preparations of the dog. Intravenous doses were 500 times more potent than oral or intraduodenal administration. Ipratropium bromide was administered by inhalation in combination with a  $\beta_2$  sympathomimetic agent (fenoterol hydrobromide). In both the dog and guinea pig, these agents were additive in antagonizing acetylcholine induced bronchospasm with ED50 being 19.8  $\mu\text{g}$  (ipratropium), 49.25  $\mu\text{g}$  (fenoterol) and 11.05  $\mu\text{g}$  + 27.63  $\mu\text{g}$  (ipratropium + fenoterol). In the dog, 50  $\mu\text{g}$  of fenoterol by inhalation produced an 8% increase in heart rate and a 16% increase in left ventricular dp/dt. When 20  $\mu\text{g}$  ipratropium was added to the above, the corresponding increases were 8% and 9%.

### **Fenoterol hydrobromide**

Fenoterol has been shown by pharmacologic studies in animals to exert a preferential effect on  $\beta_2$  adrenergic receptors, such as those located in bronchial smooth muscles.

#### *In Vitro Studies*

Studies with isolated guinea pig trachea and atria were performed to evaluate the effects of isoproterenol, salbutamol and fenoterol using cumulative concentration-effect curves. In vitro, the agonists were similar in potency in relaxing guinea pig trachea but the order of potency for the chronotropic response of guinea pig trachea was isoproterenol, > fenoterol, > salbutamol.

#### *In Vivo Studies*

Effect on acetylcholine-induced bronchoconstriction:

Guinea Pig:

- a) Simultaneous recordings of the effects of intravenous administration of several adrenergic agents on bronchomotor tone and on cardiac rate were made following bronchospastic challenge with acetylcholine. In these experiments the  $\beta$  selectivity of fenoterol was superior to isoproterenol and orciprenaline and comparable to salbutamol and terbutaline.
- b) Bronchospasm induced with i.v. acetylcholine was counteracted by sympathomimetic agents previously administered in aerosol form in varying concentrations. The maximum protective effect declined by 50% at 12 minutes (isoproterenol), 14 minutes (orciprenaline), 18 minutes (terbutaline), 25 minutes (salbutamol) and 27 minutes (fenoterol). The associated increases in heart rate at doses producing equal protection were respectively, 25 beats/min (isoproterenol), 15 beats/min (orciprenaline), 13 beats/min (terbutaline), 10 beats/min (fenoterol) and 1 beat/min (salbutamol).

Effect of Histamine-induced Bronchoconstriction:

Guinea Pig: The heart rate and protective effect of sympathomimetic agents were measured in guinea pigs continuously exposed to histamine aerosol (0.01%) for 10 minutes. Two hours after intraperitoneal administration of 200  $\mu\text{g}/\text{kg}$  of drug, the time to collapse following histamine provocation were 6.3 minutes for fenoterol, 3.2 minutes for salbutamol, 3.1 minutes for isoproterenol and 2.2 minutes for saline. When given 15 minutes before histamine, all beta agonists at low aerosol concentrations (0.3 mg/mL) delayed collapse time significantly and only

minor changes in heart rate were produced.

At higher aerosol concentrations (6 mg/mL), isoproterenol produced greater tachycardia than either of the other two agonists. Finally, when given by the oral route the dose required to completely prevent collapse during histamine administration was 10 mg/kg for fenoterol, 5 mg/kg for salbutamol and 10 mg/kg for isoproterenol. The tachycardia produced by salbutamol or fenoterol was of short duration, while that produced by isoproterenol persisted over the 90-minute period of the experiment.

Dog: In the anesthetized dog with histamine-induced bronchospasm, isoproterenol, salbutamol and fenoterol were given i.p. and measurements of pulmonary resistance, as well as of heart rate, were made. The bronchoconstrictor effects of histamine were significantly reduced by i.v. administration of the adrenergic agents tested. Isoproterenol-induced bronchodilatation was shorter than that of either fenoterol or salbutamol. Fenoterol and salbutamol produced long-lasting bronchodilatation with less cardiac stimulation than did isoproterenol.

		% PROTECTION IN RESISTANCE		
DRUG	DOSE µg/kg i.p.	(15 min)	(60 min)	HEART RATE (beats/min)
Saline		8.7 ± 6.2	9.2 ± 7.0	-0.2 ± 1.11
Isoproterenol	3.12	38.3 ± 7.6*	7.7 ± 7.7	41.4 ± 11.3*
	6.25	71.8 ± 3.2*	41.0 ± 15.0	46.5 ± 7.3*
	12.50	82.0 ± 6.9*	29.5 ± 5.5	43.1 ± 11.1*
Salbutamol	0.39	33.0 ± 16.6	7.7 ± 7.7	1.0 ± 1.0
	1.56	74.0 ± 3.3*	32.0 ± 1.1*	6.0 ± 6.0
	3.12	85.0 ± 3.4*	48.1 ± 10.0*	17.4 ± 4.6*
	6.25	82.3 ± 2.8*	64.1 ± 6.9*	28.0 ± 6.9*
Fenoterol	0.39	70.2 ± 7.2*	53.0 ± 15.2*	7.0 ± 7.0
	0.78	67.6 ± 10.4*	63.9 ± 10.4*	11.5 ± 6.0
	1.56	76.5 ± 4.9*	79.8 ± 5.7*	36.0 ± 14.5*
	3.12	85.9 ± 4.1*	83.7 ± 6.6*	45.6 ± 14.2*

\*Significantly different from saline treated group, p < 0.05

Metabolic Effects: In common with other β adrenergic agents, fenoterol exerts glycolytic, lipolytic, hypoglycemic effects and hypokalemic effects.

Effect on Ciliary Activity of the Respiratory Tract: In the rat airway preparation, fenoterol and isoproterenol were shown to augment, in a dose-dependent fashion, the frequency of ciliary movement, with a concomitant increase in the rate of mucus transport.

### **Ipratropium bromide and fenoterol hydrobromide (1:2.5)**

Ipratropium, fenoterol and the combination (1:2.5) inhalation aerosols were evaluated against acetylcholine-induced bronchospasm in the dog. The inhalation ED50 values were 19.8 µg (1.98

puffs of 10 µg ipratropium), 49.25 µg (1.97 puffs of 25 µg fenoterol) and 38.68 µg (2.21 puffs of 5 µg ipratropium + 12.5 µg fenoterol) for ipratropium, fenoterol and the combination, respectively. These results indicated the presence of an additive effect of the combination.

## TOXICOLOGY

### ACUTE TOXICITY

#### Ipratropium Bromide

LD <sub>50</sub> Values for Ipratropium		
Species	Route	LD50(mg/kg)
Mice	IV	13.5
Mice-males	IV	12.3
Mice-females	IV	15.0
Mice	SC	322
Mice	SC	300
Mice	Oral	2010
Mice	Oral	1038
Rats	IV	15.8
Rats	SC	1500
Rats	Oral	>4000
Rats	Oral	1722

The signs of toxicity were apathy, reduced mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after i.v. administration and for 8 days after oral administration.

Acute dose tolerance studies were performed in dogs. No deaths occurred at doses of up to 400 mg/kg oral or 50 mg/kg s.c. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature and death from respiratory failure.

An acute inhalation toxicity study of ipratropium bromide administered as a 4% and 8% solution to guinea pigs was performed. No toxic signs were observed with the 4% solution and death occurred five hours after administration of the 8% solution (approximately 200 mg/kg).

An acute inhalation tolerance study in rats with benzalkonium chloride (0.025%) or benzalkonium chloride (0.025%) plus ipratropium bromide (0.025%) administered over 8 hours was performed. No clinical signs of intolerance were observed. Necropsy and histological findings (16 hours and 14 days after administration) were also negative.

Anesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given IV infusions (10 mg/kg/min) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

An acute inhalation dose tolerance study in rats using doses up to 160 puffs (3.2 mg) from an Atrovent inhaler was performed. No deaths occurred. A combination of ipratropium bromide (up to 3.2 mg/kg) with fenoterol hydrobromide (up to 8 mg/kg) was administered by inhaler (up to 320 puffs) to rats. There were no deaths or clinical signs observed.

### Fenoterol Hydrobromide

TOXICITY		
Acute Toxicity		
Species	Route	LD <sub>50</sub> (mg/kg)
Rat (adult) 21 days observation	Oral	2500
Rat (adult) 14 days observation	Oral	3750
Rat (newborn)	Oral	1360
Rat (adult)	i.v.	65
Mouse	i.v	60.0

The signs of toxicity consisted of irritability, tachycardia, hyperpnea, ataxia, coma or convulsion and death.

An acute dose tolerance study in dogs was performed using oral and intravenous administration. No deaths occurred with doses up to 300 mg/kg orally or 35 mg/kg i.v. At higher doses, death was attributable to cardiac failure, as documented by ECG and pathologic findings.

IPRATROPIUM BROMIDE + FENOTEROL HYDROBROMIDE (RATIO 1:2.5)			
Species	Sex	Route	LD <sub>50</sub> (mg/kg)
Mouse	M	i.v.	23.6
Mouse	F	i.v.	26.2
Mouse	M	oral	630
Mouse	F	oral	650
Rat	M	i.v.	32.5
Rat	F	i.v.	32.5
Rat	M	oral	3200
Rat	F	oral	2450

The signs of toxicity were spasmodic breathing, tonic, clonic and saltatory convulsions, sedation, ataxia, spasms, exophthalmus, chromolacryorrhoea, reduced motility, tremor and positive sliding test. Late mortality occurred only after oral administration.

Single-dose toxicity studies with the combination ipratropium bromide and fenoterol hydrobromide in a ratio of 1/2.5 (ipratropium bromide/fenoterol hydrobromide) in mice and rats after oral, intravenous and inhalation administration revealed a low level of acute toxicity. In comparison to the individual components, the LD<sub>50</sub> values of the combination were determined more by the ipratropium bromide component than by fenoterol hydrobromide without any indication of potentiation.

## SUBACUTE

### Ipratropium Bromide

#### Oral:

A subacute toxicity study of nine weeks duration in rats, utilizing doses of 10, 100 and 500 mg/kg, revealed no pathologic findings apart from a dose related decrease in food consumption and growth rate.

A four week study in dogs using doses of 3, 30 and 150 mg/kg (for three weeks) increased to 300 mg/kg, showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of six dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study of 13 weeks using doses of 1.5, 3.0 and 15 mg/kg revealed no pathologic changes apart from a dose related inhibition of lacrimal secretion and associated keratoconjunctivitis and dryness of the mouth.

#### Intravenous:

A 32 day study in rats was conducted with the combination of ipratropium bromide and fenoterol hydrobromide at doses of 1.32 + 3.32 µg/kg (Group 1), 8 + 20 µg/kg (Group 2) and 24 + 60 µg/kg (Group 3) respectively. Fenoterol 60 µg/kg (Group 4) and ipratropium 24 µg/kg (Group 5) were also administered. Increases in heart rate (dose related in all treated animals) and dry mouth and nose (Groups 3 and 5) were seen. Increases in LDH (Groups 3 and 4), creatine kinase (all treated Groups), potassium (Groups 2, 3 and 4) and cholesterol (Groups 3 and 4) were observed. Myocardial scars were seen in one animal in Groups 3 and fatty changes in the liver were noted in one animal in Group 4.

#### Subcutaneous:

Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg group from paralytic ileus. Inflammatory changes were noted at the injection site.

A 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last five days) was conducted. Dryness of oral and nasal mucosal membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and body weight also occurred. One dog died in the high dose group. Signs of liver damage were noted in 2 of the high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

#### Inhalation:

Twelve rats were exposed to aerosolized ipratropium bromide at a concentration of 11.5 µg/L for 1 hour, 4 times per day for 7 days. No drug toxicity was observed.

In another study, administration of ipratropium bromide in doses of 128, 256 and 384 µg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and

areas of fibrosis and hemorrhage in the parametrium of 2 of 9 females in the high dose group. This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 µg of ipratropium bromide twice a day (total dose 1 mg/day) for 7 days without the appearance of any drug induced toxicity.

In another rhesus monkey study, the animals were given ipratropium bromide at doses of 200, 400 and 800 µg/day of inhalation for 6 weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

## **Fenoterol Hydrobromide**

### **Rat:**

A 13 week study was carried out in 120 rats. The animals being dose by gavage five days per week at 0.5 mg/kg, 5 mg/kg, 50 mg/kg and 150 mg/kg. Of the animals, 109 survived; mortality showed no drug or dosage correlation, with the highest death rate occurring in the control group. The males in the highest dosage group showed a slower weight gain in comparison to the control. The high dose group showed increased, water consumption, and the animals became quite agitated for a short while following each administration of the drug. Out of the 40 animals in this group, 23 had focal necrosis of the myocardium or myocardial scars; one animal had hemorrhage in the adrenal gland, three had focal necrosis and another three animals central globular atrophy in the liver.

### **Dog:**

The drug was also given for 13 weeks to 18 dogs, seven days a week, in capsules at doses of 0.3 mg/kg, 3 mg/kg and 30 mg/kg. All animals survived and no weight alterations occurred. There was a slight drop in the hemoglobin and hematocrit values in both the middle and high level groups. Elevation of serum potassium levels occurred in the middle and high dosage group. There was also a lowering of non-esterified fatty acids. Post-dose tachycardia was common. A consistent shortening of the P-T interval was seen shortly after administration. In animals of the mid and high dose group, drug-related changes in the heart included: dilatation and/or hypertrophy with numerous subendocardial foci of myocardial necrosis, as well as areas of recent and old scars.

A four week study in dogs was performed using 0.003 mg/kg and 0.03 mg/kg intravenously. In the high dose group there was an elevation of blood urea and non-esterified fatty acids were lowered. Post-dose tachycardia and shortening of the P-T interval also occurred in this group. In two high dose animals there was moderate hypertrophy of the left ventricle associated with small areas of necrosis. Three high dose animals demonstrated hypertrophy of the myocardial fibers.

### **Monkey:**

Monkeys were administered fenoterol hydrobromide 0.5 mg/kg, 2.5 mg/kg, and 5.0 mg/kg as an aerosol 6 hours daily for 6 weeks. All the animals survived and of all the parameters studied, only focal lesions of myocarditis were seen in one or two (low dose) animals per group including the control. In a second similar study, no lesions of myocarditis were observed.

### **Ipratropium Bromide and Fenoterol Hydrobromide**

Rats were exposed to a combination of fenoterol and ipratropium twice, 4 times and 8 times per day. Metered dose inhalers containing 50 µg fenoterol and 20 µg ipratropium per actuation were discharged into the exposure chamber at a rate of 6 doses per minute for 25 minutes over a 7 day period. No changes apart from a reduction in food consumption in the first 2 days in the high dose group were noted.

A 28 day study in dogs was conducted using fenoterol and ipratropium in the following doses respectively: 350 + 140 µg (Group 3); 1050 + 420 µg (Group 4); 3150 + 1260 µg (Group 5). Vasodilation occurred in Groups 4 and 5 and heart rate was increased in the treated animals. Potassium levels were raised in Group 5. Liver glycogen content was raised in 4 (of 6) animals in Group 5 and 2 in Group 4.

A further 13 week combination study was done in dogs using doses of 23 + 9 µg (Group 1), 160 + 64 µg (Group 2) and 1100 + 440 (Group 3) fenoterol + ipratropium respectively. Peripheral hyperaemia and dry mucous membranes were observed in all treated animals. Increases in heart rate were seen in Groups 1 to 3, and 5 of 6 dogs in Group 3 had disturbances of impulse formation and conduction. Slight increases in GPT in Groups 2 and 3, as well as increases in AP in individual animals of Groups 1 to 3 were noted. Histological findings consisted of a scar in the papillary muscle of the left ventricle of one dog in Group 3 as well as centrolobular fatty infiltration of hepatocytes in dogs of Groups 2 and 3.

Repeat-dose toxicity studies with the combination ipratropium bromide and fenoterol hydrobromide were performed in rats (oral, inhalation) and dogs (intravenous, inhalation) for up to 13 weeks. Only minor toxic effects at concentrations up to several hundred times greater than that recommended in man were observed. Left ventricular myocardial scars were seen only in one animal from the highest treatment group (84µg/kg/day) of the 4-week intravenous study in dogs. The 13-week oral study in rats and the 13-week inhalation study in dogs did not show any toxicological changes beyond that proportional to the individual components.

There was no indication of potentiation with the combination in comparison to the individual components. All of the adverse effects observed are well known for fenoterol hydrobromide and ipratropium bromide.

## CHRONIC

### Ipratropium bromide

#### Oral:

A 6 month and a 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after 14 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostitis and dilatation of the intestines was observed in the highest dose group. A toxic hepatitis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs at doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions, the latter leading to keratoconjunctivitis, was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in two dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver which varied from animal to animal, was also seen.

#### Inhalation:

A 6 month study in rats was performed using doses of 128, 256 and 384 µg per rat per day. Measurements included ciliary beat frequency, lung mechanics and blood gas. The only finding was a dose related decrease in growth rate of the male animals.

A 6 month inhalation toxicity study was performed in rhesus monkeys utilizing daily doses of 20, 800 and 1600 µg. All findings were negative including measurements of lung mechanics, ciliary beat frequency and blood gases.

### Fenoterol Hydrobromide

#### Rat:

A 78-week chronic toxicity study was performed with 400 SPF rats, receiving oral daily doses of 0.4 mg/kg, 2 mg/kg, 10 mg/kg or 50 mg/kg of fenoterol. Because of the absence of toxic symptoms, the dosage in the high-dose group of animals was gradually increased to 100 mg/kg. No toxic symptoms were observed in any of the groups. An excessive increase in body weight, particularly in the females, was dose-dependent and correlated with an increased in food and water consumption. A reduction in the glycogen was seen in the liver (high dose) and muscles (mid and high dose).

#### Dog:

A one year toxicity study was performed in 24 dogs at dosages of 0.3 mg/kg, 1.5 mg/kg or 7.5 mg/kg daily. A retardation of body weight gain was noticeable in the high dose male animals. A reduction of non-esterified fatty acids was seen in the mid and high dose groups. ECG, hearing and eye examinations remained within normal limits. Gross findings were essentially normal and microscopic examination of only two different sections of myocardium revealed no abnormality.



## MUTAGENICITY

### **Ipratropium Bromide**

Three Ames tests, a micronucleus test in mice, a cytogenic study in Chinese hamsters, and a dominant lethal test were performed to assess the mutagenic potential of ipratropium bromide. Two positive tests (one Ames and the micronucleus study) were apparently spurious as they could not be reproduced with subsequent exhaustive experimentation. In the cytogenic study, a dose-related increase in the number of chromatid gaps, but not of other aberrations, was seen. The significance of this finding is not known. All other test results were negative.

### **Fenoterol Hydrobromide**

A number of short term in vitro and in vivo mutagenicity studies were conducted with fenoterol including several Ames tests (with and without metabolic activation), a HGPRT-test with V79 Chinese hamster cells (with and without metabolic activation), a mouse lymphoma L5178Y test (with and without metabolic activation), one chromosomal aberration study using V79 hamster cells and two chromosomal aberration studies using cultured human lymphocytes (with and without metabolic activation), a micronucleus test in mice and an unscheduled DNA synthesis assay in Hela S3 cells (with and without metabolic activation).

In the mouse lymphoma L5178Y assays, marginal increases in mutation frequency were observed at cytotoxic concentrations of fenoterol hydrobromide (between 2,000 and 3,000 µg/mL) in the absence of S9 activation.

The clastogenic potential of fenoterol hydrobromide was evaluated in cultured human lymphocytes in vitro. In the absence of metabolic activation, increases in the incidence of aberration frequency were recorded following a 45 hour exposure period. A repeat of this study in the same concentrations ranges and at the same exposure levels (up to 45 hours) demonstrated no clastogenic activity of fenoterol hydrobromide in the absence or in the presence of metabolic activation.

In all the other tests performed there was no evidence to show a mutagenic or clastogenic potential of fenoterol hydrobromide.

## CARCINOGENICITY

### **Ipratropium Bromide**

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. These studies demonstrated that ipratropium bromide does not have a tumorigenic or carcinogenic effect.

### **Fenoterol Hydrobromide**

Mice:

A 78 week toxicity study was performed in male and female Charles-River (France) CD-1 mice with doses of 0, 25, 50 or 100 mg/kg/day of fenoterol administered in drinking water. Throughout the study, there were no overt clinical signs of drug toxicity. Mortality rates were similar among treated and control groups. There was a dose related increase in lung weights in the mid and high

dose groups. Heart weights were increased in high dose males and in low and high dose females; there was also an increase of myocarditis in high dose males.

An increased incidence of uterine tumors in the treated female mice was observed although this finding appeared to be unrelated to dose (control, 1%; low, 18%; mid, 22%; high, 7.5%). These tumors were predominantly leiomyomas; 3 of the lesions (one in each dose group) were leiomyosarcomas. It has been postulated that these findings were not related to a directed effect of the drug, but rather to a receptor mediated secondary mechanism; these results are similar to the findings seen in rats with fenoterol and with other  $\beta$  adrenergic drugs. The incidence of bronchioalveolar tumors of the lungs were also increased (15%) in the high dose female mice. These tumors were evident only at necropsy, following a histological examination, and no evidence of decreased latency, multiplicity, or increased incidence of macroscopically recognizable tumors were observed. Neither hyperplasia nor other preneoplastic lesions was present. As historical control data on CD-1 mice indicates a spontaneous incidence of up to 40% for bronchioalveolar lung tumors, the incidences reported in this study were within an expected range for this species at this age.

In a two year peroral toxicity study in Sprague-Dawley rats given 25, 50 or 100 mg/kg of fenoterol, there was an increased incidence of mesovarian leiomyomas seen in the female of the low (4%) and high (11%) animals sacrificed at the end of the study. No such tumors were observed in the control and mid dose animals nor in the dosed animals which died or were sacrificed during the study. Similar tumors were seen previously in long term studies carried out in this and other strains of rats using other  $\beta$  adrenergic agonists. No such tumors have been found at the analogous site (cremaster muscle) in male rats with any of these substances. All leiomyomas were histologically benign.

Carcinogenicity studies for the combination were not performed. No tumorigenic or carcinogenic effects were demonstrated in long term studies in mice and rats with ipratropium bromide. For fenoterol hydrobromide, carcinogenicity studies were performed after oral (mouse, 18 months rat, 24 months) and inhalation administration (rat, 24 months). At oral doses of 25 mg/kg/day an increased incidence of uterine leiomyomas with variable mitotic activity in mice and mesovarial leiomyomas in rats were observed. These findings are recognized effects caused by the local action of beta-adrenergic agents on the uterine smooth muscle cell in mice and rats. Taking into account the present level of research, these results are not applicable to man. All other neoplasms found were considered to be common types of neoplasm spontaneously occurring in the strains used and did not show a biologically relevant increased incidence resulting from treatment with fenoterol hydrobromide.

## REPRODUCTIVE STUDIES

### **Ipratropium Bromide**

Three teratology studies, one in mice using oral doses of 2 and 10 mg/kg, and two in rats, were performed. The first study used the same doses and the second employed 10 and 20 mg/kg and revealed no drug induced fetal abnormalities.

A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again demonstrated no teratogenic or embryotoxic effects of ipratropium bromide.

An inhalation teratology study in rabbits using doses of 0.3, 0.9 and 1.8 mg/kg demonstrated no effects on litter parameters and no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at the 500 mg/kg dose and spurious pregnancy in 5 of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

### **Fenoterol Hydrobromide**

Fertility and general reproductive performance have been evaluated in male and female rats at doses of up to 150 mg/kg given orally. Doses above 2.5 mg/kg produced signs of toxicity in the parent generation, but did not influence fertility, reproductive performance or fetal development.

Teratology and peri/postnatal studies have also been performed in rats given oral doses of fenoterol up to a maximum dose of 100 mg/kg. The substance was not shown to be teratogenic. A slight delay in delivery was caused by fenoterol, but F1 generation development, behaviour and reproductive capability were unaffected by the substance.

Teratology studies were performed in rabbits using oral doses up to 100 mg/kg. Decrease in body weight gain of the dose (100 mg/kg), increase in miscarriage rate (100 mg/kg) and an increased number of runts (100 mg/kg) were seen. No teratogenic effects were observed.

### **Ipratropium Bromide and Fenoterol Hydrobromide**

After inhalation administration of the combination ipratropium bromide and fenoterol hydrobromide in rats and rabbits no teratogenic effects occurred. Also no teratogenic effects were seen after ipratropium bromide, and after inhalation administration of fenoterol hydrobromide. After oral dosing, at doses >25 mg/kg/day (rabbits) and >38.5 mg/kg/day (mice) fenoterol hydrobromide induced an increase rate of malformations.

The malformations observed are considered a class effect for beta-agonists. Fertility was not impaired in rats at oral doses up to 90 mg/kg/day ipratropium bromide [166] and up to 40 mg/kg/day fenoterol hydrobromide.

## **GENTOXICITY STUDIES**

Genotoxicity studies for the combination were not performed. *In vitro* and *in vivo* assays revealed that neither fenoterol hydrobromide nor ipratropium bromide have a mutagenic potential.

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## PART III: CONSUMER INFORMATION

**Pr Duovent® UDV**  
**Ipratropium Bromide/Fenoterol Hydrobromide**  
**Nebulizer Solution**

This leaflet is part III of a three-part "Product Monograph" published when DUOVENT UDV was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DUOVENT UDV. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

Your doctor has prescribed DUOVENT UDV for your medical condition. It can relieve wheezing, coughing, chest tightness and/or shortness of breath if you have an acute attack of asthma or COPD (Chronic Obstructive Pulmonary Disease) which includes chronic bronchitis and emphysema.

It is important to know that the treatment of asthma and COPD may be different for each patient. Your doctor will discuss with you the best plan for the treatment of your particular condition. This plan may include taking other medication(s) in addition to DUOVENT UDV. It is necessary that you follow your doctor's directions for the treatment of your condition. If you have any questions about how you should treat your condition at home, you should consult your doctor.

#### What it does:

DUOVENT UDV belongs to a group of medicines known as "bronchodilators" which works by relaxing the muscles surrounding the bronchioles (airways in the lungs) and therefore helps to ease breathing problems.

**If you have asthma and you find that you need to use DUOVENT UDV on a regular, daily basis, but you are not taking other medication(s) that control the inflammation of the airways called Inhaled Corticosteroids (ICS), you should contact your doctor so that your treatment can be re-evaluated.**

**If DUOVENT UDV does not relieve your symptoms within 10 minutes after the nebulization is finished, if the dosage of medication(s) recommended by your doctor does not provide relief for longer than 3 hours, or if you experience a change of your symptoms, for example, more coughing, chest tightness, waking up at night, or increased usage of other relief medication (for example Ventolin®), you should contact your doctor or go to the nearest hospital. These are signs that your condition may be worsening, and that you need to be re-assessed by a doctor.**

**If you have COPD and DUOVENT UDV does not relieve your symptoms within 10 minutes after the nebulization is finished, or if the dosage of medication(s) recommended by your doctor does not provide relief for longer than 3 hours, you should contact your doctor or go to the nearest hospital. These are signs that your condition may be worsening, and that you need to be re-assessed by a doctor.**

#### When it should not be used:

DUOVENT UDV should not be used if you:

- are allergic to ipratropium bromide, fenoterol hydrobromide, atropine, any other sympathomimetic amines or to any non-medicinal ingredient in the formulation
- have the following heart conditions:
  - tachyarrhythmia
  - hypertrophic obstructive cardiomyopathy

#### Please remember:

- **DO NOT use a higher dose of DUOVENT UDV than your doctor has recommended**
- **DO NOT use your nebulizer more often than your doctor has recommended**
- **Contact your doctor if you feel that you need more medication than he/she has recommended**
- **DUOVENT UDV contains a beta agonist, and the taking of additional doses in the form of other single agent, beta agonists (fenoterol, salbutamol [Ventolin®] etc.) could lead to poor heart related effects. If these medications need to be taken together, it should only be under the supervision of your doctor.**

#### What the medicinal ingredients are:

ipratropium bromide and fenoterol hydrobromide

#### What the non-medicinal ingredients are:

hydrochloric acid, sodium chloride

#### What dosage forms it comes in:

DUOVENT UDV is a combination of two bronchodilators (airway openers) in a solution that is inhaled using a nebulizer. Each plastic unit dose vial (UDV) contains 0.5 mg of ipratropium bromide and 1.25 mg fenoterol hydrobromide in four milliliters (4 mL) of sodium chloride solution.

### WARNINGS AND PRECAUTIONS

**BEFORE you use DUOVENT UDV talk to your doctor or pharmacist if:**

- you are pregnant or intend to become pregnant.
- you are breast feeding.
- you have eye problems such as glaucoma or eye pain.
- you are taking other medications, including those you can buy without a prescription and including eye drops, or herbal medicines.

- you have special allergies or reactions to foods or drugs.
- you have other health problems such as difficult urination, enlarged prostate, blood vessel disease, high blood pressure, diabetes mellitus.
- you have a history of heart disease, irregular heart rhythm (heart skips a beat) or angina (chest pain).

Your doctor will recommend when and how often you should use DUOVENT UDV. You must follow any other directions that your doctor has given you for the treatment and/or monitoring of your condition. This may include taking other medication(s) in addition to DUOVENT UDV.

DUOVENT UDV may cause dizziness, tremor, difficulty in focusing the eye, dilated pupils, and blurred vision. You should not drive or operate machinery if this occurs.

The use of DUOVENT UDV may test positive for performance enhancement (doping) in athletic competition.

### INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with DUOVENT UDV include:** Other beta adrenergic agents, anticholinergics, xanthine derivatives (such as theophylline) and corticosteroids may enhance the effect of DUOVENT UDV nebulizer solution. The concurrent administration of other beta mimetics, systemically available anticholinergics and xanthine derivatives (e.g. theophylline) may increase the side effects.

### PROPER USE OF THIS MEDICATION

Treatment with DUOVENT UDV is to be initiated and administered under medical supervision (e.g. in the hospital setting). Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved

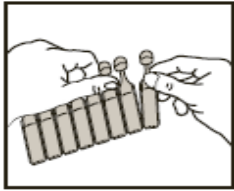
Since DUOVENT UDVs contain no preservatives, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged UDVs should be discarded. In most cases, dilution of the DUOVENT UDV dose with sterile preservative-free saline is not necessary. However, volumes of DUOVENT solution less than 2 mL are not appropriate for nebulization and must be diluted with saline or another suitable nebulizer solution to make-up a total fill volume of 2-5 mL. Dilute your dose immediately before you plan to use the solution.

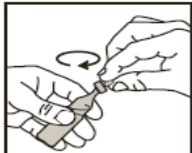
#### Usual dose:


*Adults and adolescents (12 years of age or older)*

The usual dose is 4 mL of DUOVENT UDV.

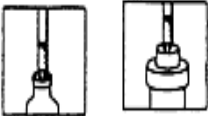
It is not recommended for use in children under 12 years of age.


- 1)  Detach one plastic unit dose vial (UDV) by pulling it firmly from the strip


- 2)  Open the unit dose vial (UDV) by twisting off the top. It is important that you use the contents of the vial as soon as possible after opening it.

- 3)  Squeeze the plastic unit dose vial (UDV) to empty its contents into your nebulizer chamber. If your doctor has instructed you to use less than the contents of one complete vial, use a syringe to transfer the necessary amount from the vial to the nebulizer chamber.

Any solution left in the plastic vial must be thrown away.

- 4)  If you have been directed by your pharmacist or doctor to add sterile preservative free 0.9% sodium chloride to the chamber, add this solution by means of a syringe.

- 5)  Gently swirl the nebulizer chamber to mix the liquid, and connect it to the mouthpiece or face mask. Then connect the nebulizer tube to the air pump or oxygen supply.

- 6)  Begin therapy. Sit upright in a comfortable position. Breathe calmly and deeply through the mask or mouthpiece until no more mist is formed in the nebulizer chamber. This usually takes 10-15 minutes.

It is very important to adjust the face mask, if required, to prevent the mist from getting in your eyes.

- 7) Follow the instructions provided by the nebulizer and air pump manufacturers for the proper care, maintenance and cleaning of the equipment. Keep the nebulizer, nebulizer tube and face mask clean to minimize microbial contamination.
- 8) Store the unit dose vials (UDV) at room temperature (15-25°C) and protect from light and heat.

**You must remember:**

- DUOVENT UDV has been prescribed to treat your current condition. Do not give this medication to other people.
- DO NOT take any other medication without your doctor’s advice. Tell any other doctor, dentist, or pharmacist with whom you consult that you are using DUOVENT UDV.

**The solution is to be administered only using a nebulizer. DO NOT inject it or drink it.**

- **Do not let the nebulized mist get into your eyes. Patients with glaucoma should use a mouthpiece or swimming goggles to prevent nebulizer solution from getting into the eyes.**
- **Keep this medication out of the reach of children.**

**Overdose:**

In case of an overdose, contact your doctor, or the Regional Poison Control Center, or go to the nearest hospital emergency department (do not drive yourself). Always take the labelled medicine container with you.

**Missed Dose:**

If you forget to take your dose, don’t worry. Take your next dose as usual. Do not double your dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

If you experience a dry mouth or bad taste, sucking a sour candy or rinsing your mouth may help. Check with your doctor if the dry mouth or bad taste persists, or if you experience constipation.

Like any medication, DUOVENT UDV may cause unwanted effects along with the good effects. The most common side effects of DUOVENT UDV are cough, tremor (shakiness), dry mouth, headache, sore throat, nausea, dizziness, hoarseness/impaired voice, vomiting, changes in blood pressure, feeling nervous, increased heart rate and a feeling that your heart is beating fast. If you experience any unusual or unwanted effects while you are using DUOVENT UDV, you should contact your doctor.

Other side effects include: decreased blood flow to the heart, heart problems such as fast or irregular heart beat or rate, eye disorders such as difficulty in focusing the eye, seeing halos, swelling of the cornea, build up or increased pressure in the eye, dilated pupils,

swelling of the blood vessels in the conjunctiva (outermost layer of the eye and inner surface of the eyelids), blurred vision, eye pain; muscle problems such as muscle spasms, muscle weakness, muscle pain; agitation, mental disorder; difficulty in passing urine; increased sweating; low potassium levels in the blood; breathing problems such as difficulty in breathing, coughing bouts, swelling of the throat, and choking due to swelling of the muscles around the voice box; irritation of throat, dry throat, wheezing after inhalation, swelling of the mouth, tongue and throat, tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation (bronchospasm) and digestive problems like constipation, diarrhoea and vomiting.

Stop taking the medication and tell your doctor immediately if you notice any of the following:

- you are wheezy or have any other difficulties in breathing;
- you are having an allergic reaction – the signs may include rash, itching and nettle rash. In severe cases the signs include swelling of your tongue, lips and face, sudden difficulties in breathing and reduction of your blood pressure.

DUOVENT UDV is a combination of two bronchodilators. Excessive use of bronchodilators may cause unwanted side effects (increased heart rate, low blood pressure, and/or irregular heart beat). Therefore do not take additional bronchodilators by inhalation with DUOVENT UDV unless instructed to do so by your doctor or pharmacist.

*Do not be alarmed by this list of possible side effects. You may not experience any of them.*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug. Seek emergency medical assistance
		Only if severe	In all cases	
Uncommon	Fast or irregular heart beat/Chest pain			✓
Rare	Increased /Sudden wheezing or tightness in the chest			✓
	Swelling of eyelids, face, lips, tongue or throat			✓
	Difficulty in swallowing			✓
	Blurred vision or pain in the eyes			✓
	Difficult or painful urination			✓
	Lumpy skin rash or “hives” anywhere on the body			✓

*This is not a complete list of side effects. For any unexpected effects while taking DUOVENT UDV, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Unopened unit dose vials of DUOVENT UDV should be stored at room temperature (15-25°C) and protected from heat and light. If necessary, the solution may be diluted with preservative-free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.boehringer-ingenheim.ca> or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103 Ext. 84633 (Medical Information).

Please visit our website to see if more up-to-date information has been posted.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

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