

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20950**

**DRAFT FINAL PRINTED LABELING**

# Approved Labeling

March 21, 2001

[NOTE: This version replaces Version 11 dated 03-14-00. This version reflects the changes requested in David Hilfiker's fax of 16 March 2001. Dey accepts all changes requested by the FDA]

**BEGIN PROPOSED PACKAGE INSERT TEXT  
VERSION 12: 16 MARCH 2001**

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**DuoNeb™ Inhalation Solution**

**DESCRIPTION**

The active components in DuoNeb™ Inhalation Solution are albuterol sulfate and ipratropium bromide.

Albuterol sulfate, is a salt of racemic albuterol and a relatively selective  $\beta_2$ -adrenergic bronchodilator chemically described as  $\alpha^1$ -[(tert-butylamino)methyl]-4-hydroxy-m-xylene- $\alpha$ ,  $\alpha'$ -diol sulfate (2:1) (salt). It has a molecular weight of 576.7 and the empirical formula is  $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ . It is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization recommended name for albuterol base is salbutamol.

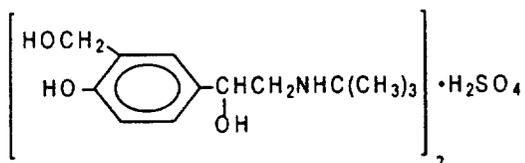


Figure 3.1-1. Chemical structure of albuterol sulfate.

Ipratropium bromide is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo [3.2.1]-octane,3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8methyl-8-(1-methylethyl)-, bromide, monohydrate (endo,syn)-, ( $\pm$ )-; a synthetic quaternary ammonium compound, chemically related to atropine. It has a molecular weight of 430.4 and the empirical formula is  $C_{20}H_{30}BrNO_3 \cdot H_2O$ . It is a white crystalline substance, freely soluble in water and lower alcohols, and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

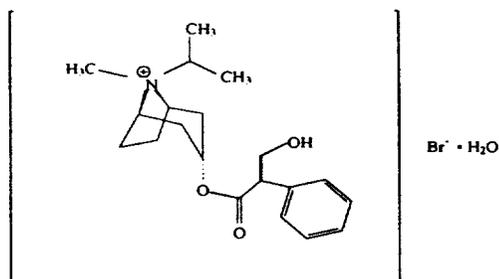


Figure 3.1-2. Chemical structure of ipratropium bromide.

Each 3 mL vial of DuoNeb contains 3.0 mg (0.1%) of albuterol sulfate (equivalent to 2.5 mg (0.083%) of albuterol base) and 0.5 mg (0.017%) of ipratropium bromide in an isotonic, sterile, aqueous solution containing sodium chloride, hydrochloric acid to adjust to pH 4, and edetate disodium, USP (a chelating agent).

DuoNeb is a clear, colorless solution. It does not require dilution prior to administration by nebulization. For DuoNeb Inhalation Solution, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONEB™ compressor system, under in vitro conditions, the mean delivered dose from the mouth piece (% nominal dose) was approximately 46% of albuterol and 42% of ipratropium bromide at a mean flow rate of 3.6 L/min. The mean nebulization time was 15 minutes or less. DuoNeb should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

## CLINICAL PHARMACOLOGY

DuoNeb Inhalation Solution is a combination of the  $\beta_2$ -adrenergic bronchodilator, albuterol sulfate, and the cholinergic bronchodilator, ipratropium bromide.

### Albuterol sulfate

**Mechanism of Action.** The prime action of  $\beta$ -adrenergic drugs is to stimulate adenylyl cyclase, the enzyme that catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The cAMP thus formed mediates the cellular responses. In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on  $\beta_2$ -adrenergic receptors compared with isoproterenol. While it is recognized that  $\beta_2$ -adrenergic

receptors are the predominant receptors in bronchial smooth muscle, recent data indicated that 10% to 50% of the  $\beta$ -receptors in the human heart may be  $\beta_2$ -receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other  $\beta$ -adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients.

*Pharmacokinetics:* Albuterol sulfate is longer acting than isoproterenol in most patients by any route of administration, because it is not a substrate for the cellular uptake processes for catecholamine nor for the metabolism of catechol-O-methyl transferase. Instead the drug is conjugatively metabolized to albuterol 4'-O-sulfate.

*Animal Pharmacology/Toxicology:* Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of plasma concentrations. In structures outside of the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those found in whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

#### Ipratropium bromide

*Mechanism of Action:* Ipratropium bromide is an anticholinergic (parasympatholytic) agent, which blocks the muscarinic receptors of acetylcholine, and, based on animal studies, appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cGMP), resulting from the interaction of acetylcholine with the muscarinic receptors of bronchial smooth muscle.

*Pharmacokinetics:* The bronchodilation following inhalation of ipratropium is primarily a local, site-specific effect, not a systemic one. Much of an inhaled dose is swallowed as shown by fecal excretion studies. Following nebulization of a 1-mg dose to healthy volunteers, a mean of 4% of the dose was excreted unchanged in the urine.

Ipratropium bromide is minimally (0% to 9% in vitro) bound to plasma albumin and  $\alpha_1$ -acid glycoproteins. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one-half is excreted unchanged in the urine. The half-life of elimination is about 1.6 hours after intravenous administration. Ipratropium bromide that reaches the systemic circulation is reportedly removed by the kidneys rapidly at a rate that exceeds the glomerular filtration rate. The pharmacokinetics of DuoNeb Inhalation Solution or ipratropium bromide have not been studied in the elderly and in patients with hepatic or renal insufficiency (see PRECAUTIONS).

*Animal Pharmacology/Toxicology:* Autoradiographic studies in rats have shown that ipratropium does not penetrate the blood-brain barrier.

#### DuoNeb™

*Mechanism of Action:* DuoNeb is expected to maximize the response to treatment in patients with chronic obstructive pulmonary disease (COPD) by reducing bronchospasm through two distinctly different mechanisms: sympathomimetic (albuterol sulfate) and anticholinergic/parasympatholytic (ipratropium bromide). Simultaneous administration of both an anticholinergic and a  $\beta_2$ -sympathomimetic is designed to produce greater bronchodilation effects than when either drug is utilized alone at its recommended dosage.

#### *Animal Pharmacology/Toxicology:*

In 30-day studies in Sprague-Dawley rats and Beagle dogs, subcutaneous doses of up to 205.5 mcg/kg of ipratropium administered with up to 1000 mcg/kg albuterol in rats and 3.16 mcg/kg ipratropium and 15 mcg/kg albuterol in dogs (less than the maximum recommended daily inhalation dose for adults on a  $\text{mg}/\text{m}^2$  basis) did not cause death or potentiation of the cardiotoxicity induced by albuterol administered alone.

#### *Pharmacokinetics:*

In a double blind, double period, crossover study, 15 male and female subjects were administered single doses of DuoNeb or albuterol sulfate inhalation solution at two times the recommended single doses as two inhalations separated by 15 minutes. The total nebulized dose of albuterol sulfate from both treatments was 6.0 mg and the total dose of ipratropium bromide from DuoNeb was 1.0 mg. Peak albuterol plasma concentrations occurred at 0.8 hours after dosing for both treatments. The mean peak albuterol concentration following administration of albuterol sulfate alone was 4.86 ( $\pm$  2.65) mg/mL and it was 4.65 ( $\pm$  2.92) mg/mL for DuoNeb. Mean AUC values for the two treatments were 26.6 ( $\pm$  15.2) ng•

hr/mL (albuterol sulfate alone) versus 24.2 ( $\pm$  14.5) ng•hr/mL (DuoNeb). The mean  $t_{1/2}$  values were 7.2 ( $\pm$  1.3) hours (albuterol sulfate alone) and 6.7 ( $\pm$  1.7) hours (DuoNeb). A mean of 8.4 ( $\pm$  8.9)% of the albuterol dose was excreted unchanged in urine following administration of two vials of DuoNeb which is similar to 8.8 ( $\pm$  7.3)% that was obtained from albuterol sulfate inhalation solution. There were no statistically significant differences in the pharmacokinetics of albuterol between the two treatments. For ipratropium, a mean of 3.9 ( $\pm$  5.1)% of the ipratropium bromide dose was excreted unchanged in urine following two vials of DuoNeb Inhalation Solution, which is comparable with previously reported data.

*Clinical Trials:* In a 12 week, randomized, double-blind, positive-control, crossover study of albuterol sulfate, ipratropium bromide, and DuoNeb, 863 COPD patients were evaluated for bronchodilator efficacy comparing DuoNeb with albuterol sulfate and ipratropium bromide alone.

DuoNeb demonstrated significantly better changes in FEV<sub>1</sub>, as measured from baseline to peak response, when compared with either albuterol sulfate or ipratropium bromide. DuoNeb was also shown to have the rapid onset associated with albuterol sulfate, with a mean time to peak FEV<sub>1</sub> of 1.5 hours, and the extended duration associated with ipratropium bromide with a duration of 15% response in FEV<sub>1</sub> of 4.3 hours.

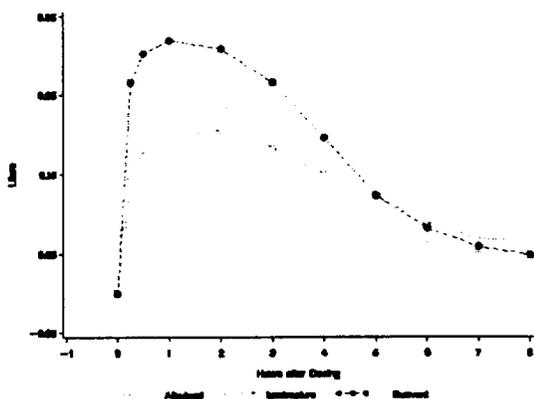


Figure 3.1-3. Mean Change in FEV<sub>1</sub> — Measured on Day 14

This study demonstrated that each component of DuoNeb contributed to the improvement in pulmonary function, especially during the first 4 to 5 hours after dosing, and that DuoNeb was significantly more effective than albuterol sulfate or ipratropium bromide alone.

### INDICATIONS AND USAGE

DuoNeb is indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator.

### CONTRAINDICATIONS

DuoNeb is contraindicated in patients with a history of hypersensitivity to any of its components, or to atropine and its derivatives.

### WARNINGS

**Paradoxical Bronchospasm:** In the clinical study of DuoNeb, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with both inhaled ipratropium bromide and albuterol products and can be life-threatening. If this occurs, DuoNeb should be discontinued immediately and alternative therapy instituted.

**Do Not Exceed Recommended Dose:** Fatalities have been reported in association with excessive use of inhaled products containing sympathomimetic amines and with the home use of nebulizers.

**Cardiovascular Effect:** DuoNeb, like other beta adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon for DuoNeb at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, DuoNeb, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**Immediate Hypersensitivity Reactions:** Immediate hypersensitivity reactions to albuterol and/or ipratropium bromide may occur after the administration of DuoNeb as demonstrated by rare cases of urticaria, angioedema, rash, pruritis, oropharyngeal edema, bronchospasm, and anaphylaxis.

## PRECAUTIONS

### General

1. Effects Seen with Sympathomimetic Drugs: As with all products containing sympathomimetic amines, DuoNeb should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Additionally,  $\beta$ -agonists may cause a decrease in serum potassium in some patients, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation.
2. Effects Seen with Anticholinergic Drugs: Due to the presence of ipratropium bromide in DuoNeb, it should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder-neck obstruction.
3. Use in Hepatic or Renal Diseases: DuoNeb has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in these patient populations.

### Information for Patients

The action of DuoNeb should last up to 5 hours. DuoNeb should not be used more frequently than recommended. Patients should be instructed not to increase the dose or frequency of DuoNeb without consulting their healthcare provider. If symptoms worsen, patients should be instructed to seek medical consultation.

Patients must avoid exposing their eyes to this product as temporary papillary dilation, blurred vision, eye pain, or precipitation or worsening of narrow-angle glaucoma may occur, and therefore proper nebulizer technique should be assured, particularly if a mask is used.

If a patient becomes pregnant or begins nursing while on DuoNeb, they should contact their healthcare provider about use of DuoNeb.

See the illustrated Patient's Instruction for Use in the product package insert.

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Dey L.P.  
03-16-01

### **Drug Interactions**

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is, therefore, advised in the co-administration of DuoNeb with other drugs having anticholinergic properties.

$\beta$ -adrenergic agents: Caution is advised in the co-administration of DuoNeb and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

$\beta$ -receptor blocking agents: These agents and albuterol sulfate inhibit the effect of each other.  $\beta$ -receptor blocking agents should be used with caution in patients with hyperreactive airways, and if used, relatively selective  $\beta_1$  selective agents are recommended.

Diuretics: The electrocardiogram (ECG) changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by  $\beta$ -agonists, especially when the recommended dose of the  $\beta$ -agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of  $\beta$ -agonist-containing drugs, such as DuoNeb, with non-potassium sparing diuretics.

Monoamine oxidase inhibitors or tricyclic antidepressants: DuoNeb should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents because the action of albuterol sulfate on the cardiovascular system may be potentiated.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Albuterol Sulfate: In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.

In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 20 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleous assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 25 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

Ipratropium bromide: In 2-year studies in Sprague-Dawley rats and CD-1 mice, ipratropium bromide showed no evidence of tumorigenicity at oral doses up to 6 mg/kg (approximately 15 times and 8 times the maximum recommended daily inhalation dose for adults in rats and mice respectively, on a mg/m<sup>2</sup> basis).

Ipratropium bromide was not mutagenic in the Ames test and mouse dominant lethal test. Ipratropium bromide was not clastogenic in a mouse micronucleus assay.

A reproduction study in rats demonstrated decreased conception and increased resorptions when ipratropium bromide was administered orally at a dose of 90 mg/kg (approximately 240 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). These effects were not seen with a dose of 50 mg/kg (approximately 140 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

### **Pregnancy**

*TERATOGENIC EFFECTS: Pregnancy Category C*

Albuterol sulfate: *Pregnancy Category C.* Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum

recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). Cleft palate formation also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg isoproterenol (positive control).

A reproduction study in Stride rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Ipratropium bromide: Pregnancy Category B. Reproduction studies in CD-1 mice, Sprague-Dawley rats and New Zealand rabbits demonstrated no evidence of teratogenicity at oral doses up to 10, 100, and 125 mg/kg, respectively (approximately 15, 270, and 680 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). Reproduction studies in rats and rabbits demonstrated no evidence of teratogenicity at inhalation doses up to 1.5 and 1.8 mg/kg, respectively (approximately 4 and 10 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). There are no adequate and well-controlled studies of the use of DuoNeb, albuterol sulfate, or ipratropium bromide in pregnant women. DuoNeb should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **Labor and Delivery**

Oral albuterol sulfate has been shown to delay preterm labor in some reports. Because of the potential of albuterol to interfere with uterine contractility, use of DuoNeb during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

**Nursing Mothers**

It is not known whether the components of DuoNeb are excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken as a nebulized solution. Because of the potential for tumorigenicity shown for albuterol sulfate in some animals, a decision should be made whether to discontinue nursing or discontinue DuoNeb, taking into account the importance of the drug to the mother.

**Pediatric Use**

The safety and effectiveness of DuoNeb in patients below 18 years of age have not been established.

**Geriatric Use**

Of the total number of subjects in clinical studies of DuoNeb, 62 percent were 65 and over, while 19 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**ADVERSE REACTIONS**

Adverse reaction information concerning DuoNeb was derived from the 12-week controlled clinical trial.

<b>ADVERSE EVENTS OCCURRING IN ≥ 1% OF ≥ 1 TREATMENT GROUP(S) AND WHERE THE COMBINATION TREATMENT SHOWED THE HIGHEST PERCENTAGE</b>			
<b>Body System COSTART Term</b>	<b>Albuterol n (%)</b>	<b>Ipratropium n (%)</b>	<b>DuoNeb n (%)</b>
<b>NUMBER OF PATIENTS</b>	761	754	765
<b>N (%) Patients with AE</b>	327 (43.0)	329 (43.6)	367 (48.0)
<b>BODY AS A WHOLE</b>			
Pain	8 (1.1)	4 (0.5)	10 (1.3)
Pain chest	11 (1.4)	14 (1.9)	20 (2.6)
<b>DIGESTIVE</b>			
Diarrhea	5 (0.7)	9 (1.2)	14 (1.8)
Dyspepsia	7 (0.9)	8 (1.1)	10 (1.3)
Nausea	7 (0.9)	6 (0.8)	11 (1.4)
<b>MUSCULO-SKELETAL</b>			
Cramps leg	8 (1.1)	6 (0.8)	11 (1.4)
<b>RESPIRATORY</b>			
Bronchitis	11 (1.4)	13 (1.7)	13 (1.7)
Lung Disease	36 (4.7)	34 (4.5)	49 (6.4)
Pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
Pneumonia	7 (0.9)	8 (1.1)	10 (1.3)
<b>UROGENITAL</b>			
Infection urinary tract	3 (0.4)	9 (1.2)	12 (1.6)

Additional adverse reactions reported in more than 1% of patients treated with DuoNeb included constipation and voice alterations.

In the clinical trial, there was a 0.3% incidence of possible allergic-type reactions, including skin rash, pruritis, and urticaria.

Additional information derived from the published literature on the use of albuterol sulfate and ipratropium bromide singly or in combination includes precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, paradoxical bronchospasm, wheezing, exacerbation of COPD symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, elevated heart rate, sinusitis, back pain and sore throat.

## OVERDOSAGE

The effects of overdosage with DuoNeb are expected to be related primarily to albuterol sulfate, since ipratropium bromide is not well-absorbed systemically after oral or aerosol administration. The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of symptoms such as seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmia, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, and exaggeration of pharmacological effects listed in ADVERSE REACTIONS. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of DuoNeb. Treatment consists of discontinuation of DuoNeb together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DuoNeb.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 540 times the maximum recommended daily inhalation dose of DuoNeb on a mg/m<sup>2</sup> basis). The subcutaneous median lethal dose of albuterol sulfate in mature rats and small young rats is approximately 450 and 2000 mg/kg respectively (approximately 240 and 1100 times the maximum recommended daily inhalation dose of DuoNeb on a mg/m<sup>2</sup> basis, respectively). The inhalation median lethal dose has not been determined in animals. The oral median lethal dose of ipratropium bromide in mice, rats and dogs is greater than 1000 mg/kg, approximately 1700 mg/kg and approximately 400 mg/kg, respectively (approximately 1400, 4600, and 3600 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis, respectively).

## DOSAGE AND ADMINISTRATION

The recommended dose of DuoNeb is one 3 mL vial administered 4 times per day via nebulization with up to 2 additional 3 mL doses allowed per day, if needed. Safety and efficacy of additional doses or increased frequency of administration of DuoNeb beyond these guidelines has not been studied and the safety and efficacy of extra doses of albuterol sulfate or ipratropium bromide in addition to the recommended doses of DuoNeb have not been studied.

The use of DuoNeb can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of worsening COPD, which would require reassessment of therapy.

A Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONEB™ compressor was used to deliver DuoNeb to each patient in one U.S. clinical study. The safety and efficacy of DuoNeb delivered by other nebulizers and compressors have not been established.

DuoNeb should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.

## HOW SUPPLIED

DuoNeb is supplied as a 3-mL sterile solution for nebulization in sterile low-density polyethylene unit-dose vials. Cards of five vials are placed into a foil pouch. Supplied in cartons of twenty-five vials; NDC 49502-672-03.

Store between 36°F and 77°F (2°C and 25°C). Protect from light.

DEY LP  
Napa, CA  
03-485-00

16 March 2001

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Dey L.P.  
03-16-01

**DuoNeb™ Inhalation Solution**

**Albuterol Sulfate 3.0 mg\*/Ipratropium Bromide 0.5 mg**

**\*equivalent to 2.5 mg albuterol base**

**Patient's Instructions for Use**

Read this patient information completely every time your prescription is filled as information may have changed. Keep these instructions with your medication as you may want to read them again.

DuoNeb should only be used under the direction of a physician. Your physician and pharmacist have more information about DuoNeb and the condition for which it has been prescribed. Contact them if you have additional questions.

**Storing your Medicine**

Store DuoNeb between 2° and 25° C (36° and 77° F). Vials should be protected from light before use, therefore, keep unused vials in the foil pouch or carton. Do not use after the expiration (EXP) date printed on the carton.

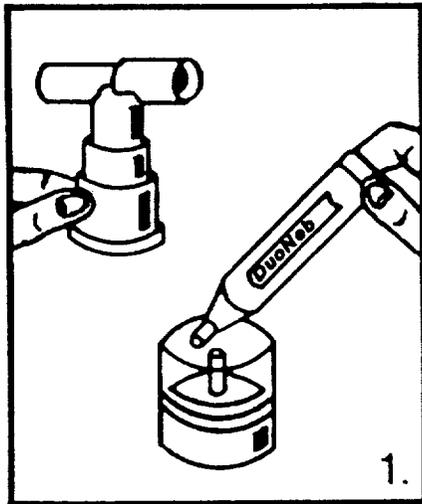
**Dose**

DuoNeb is supplied as a single-dose, ready-to-use vial containing 3 mL of solution. No mixing or dilution is needed. Use one new vial for each nebulizer treatment.

**FOLLOW THESE DIRECTIONS FOR USE OF YOUR NEBULIZER/COMPRESSOR OR THE DIRECTIONS GIVEN BY YOUR HEALTHCARE PROVIDER. A TYPICAL EXAMPLE IS SHOWN BELOW.**

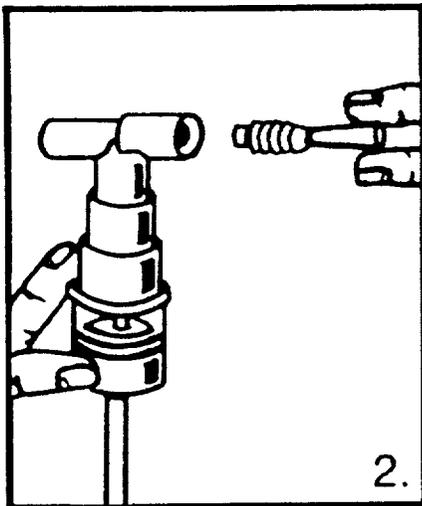
**Instructions for Use**

1. Remove one vial from the foil pouch. Place remaining vials back into pouch for storage.
2. Twist the cap completely off the vial and squeeze the contents into the nebulizer reservoir (Figure 1)



**Figure 1**

3. Connect the nebulizer to the mouthpiece or face mask (Figure 2)



**Figure 2**

4. Connect the nebulizer to the compressor.

5. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 3) or put on the face mask (Figure 4); and turn on the compressor.

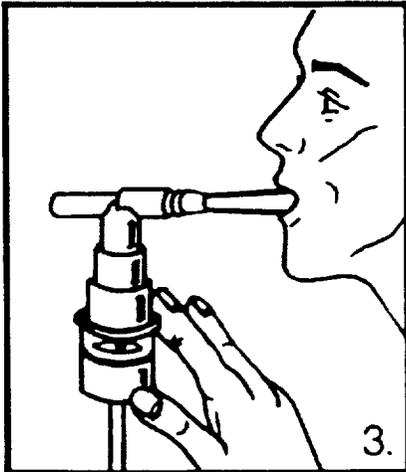


Figure 3

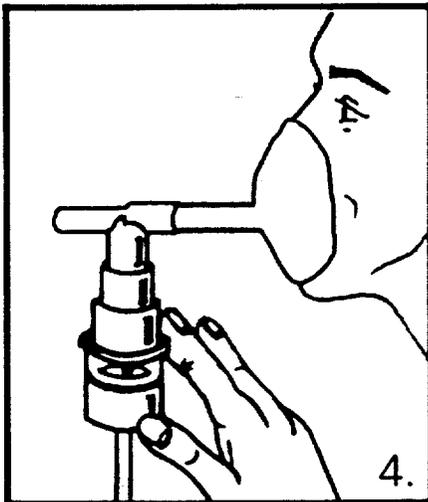


Figure 4

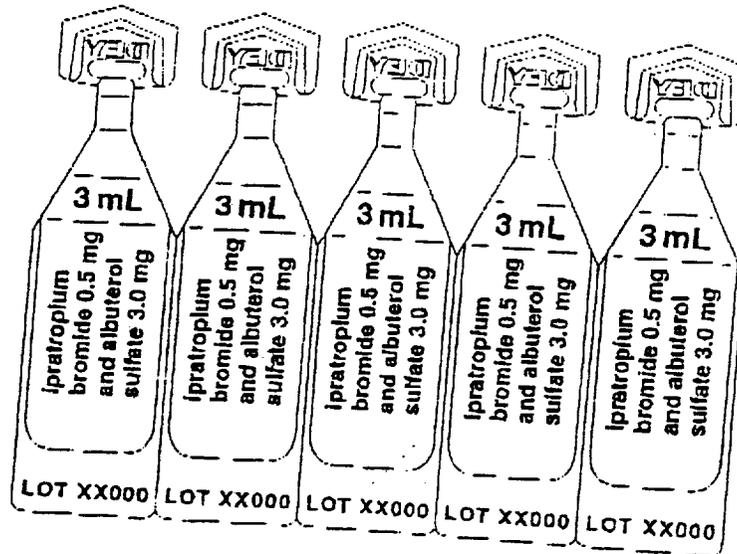
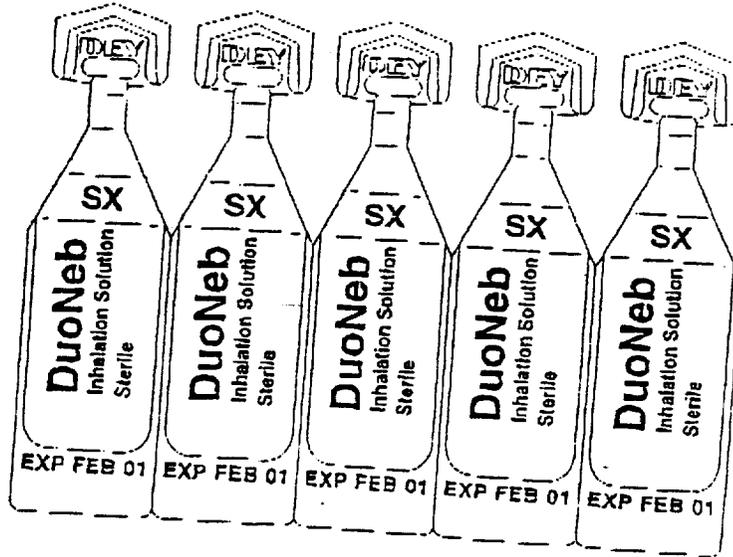
6. Breathe as calmly, deeply and evenly as possible through your mouth until no more mist is formed in the nebulizer chamber (about 5-15 minutes). At this point, the treatment is finished.

7. Clean the nebulizer (see manufacturer's instructions).

DEY, Napa California 94558

03-485-00

16 March 2001



3/1/01 FINAL. Agreed w/ FDA. P. Reilly

01 005

316-2001



Black

01 023

 **DuoNeb™**  
(ipratropium bromide and albuterol sulfate)  
INHALATION SOLUTION

Sterile Unit Dose Vials For Inhalation Only	LOT / EXPIRES:
Each 3 mL Vial Contains:	
Active: 0.5mg ipratropium bromide and 3.0 mg albuterol sulfate*	
Inactive: Sodium chloride, edetate disodium, and hydrochloric acid (to adjust the pH between 3 and 5) and purified water.	
<b>STORAGE CONDITIONS: PROTECT FROM LIGHT.</b> Unit-dose vials should remain stored in the protective foil pouch at all times. Once removed from the foil pouch, the individual vials should be used within one week. Discard if the solution is not colorless. Store between 2°C and 25°C (36°F and 77°F).	
<b>USUAL DOSAGE:</b> See accompanying prescribing information.	
Rx only.	
*Equivalent to 2.5 mg albuterol base.	
03-609-00	Pouch Contains: five 3 mL vials
 DEY*, Napa, California 94558	



**DEY**

INHALATION SOLUTION  
(ipratropium bromide  
and albuterol sulfate)

**DuoNeb**

NDC 4950247230

**DuoNeb**  
(ipratropium bromide and albuterol sulfate)  
INHALATION SOLUTION

**INGREDIENTS:**  
Active: 0.5 mg ipratropium bromide and 3.0 mg albuterol sulfate\*.  
Inactive: Sodium chloride, edetate disodium, and hydrochloric acid (to adjust the pH between 3 and 5) and purified water.

**STORAGE CONDITIONS:** PROTECT FROM LIGHT. STORE IN POUCH UNTIL TIME OF USE. Store between 2°C and 25°C (36°F and 77°F).

**USUAL DOSAGE:** See accompanying prescribing information. USE ONLY AS DIRECTED BY YOUR PHYSICIAN. DO NOT EXCEED RECOMMENDED DOSAGE.

Rx only.

\*Equivalent to 2.5 mg albuterol base.

**DEY** Napa, CA 94558

LOT:                      EXPRES

ATTENTION PHARMACIST: Detach Pouch's instructions for Use from package insert and dispense with solution.

**DuoNeb**  
(ipratropium bromide  
and albuterol sulfate)  
INHALATION SOLUTION

**UPC FPO**

0 12345 67890 5

0220820

NDC 4950247230

**DuoNeb**  
(ipratropium bromide  
and albuterol sulfate)  
INHALATION SOLUTION

*Sterile Unit-Dose Vial  
For Inhalation Only*

*Sterile Unit-Dose Vial  
For Inhalation Only*

*Carton contains 6 pouches of 5.5 ml vials each.  
Vial contains 0.5 mg ipratropium bromide  
3.0 mg albuterol sulfate.*

**DEY**

**FPO ONLY**

1 2 3 4 5 6 7 8

**FPO ONLY**

1 2 3 4 5 6 7 8

316-2001 (round 3)



INHALATION SOLUTION  
(ipratropium bromide and albuterol sulfate)  
**DuoNeb**<sup>™</sup>

NDC 49502-672-60

**DuoNeb**<sup>™</sup>

(ipratropium bromide and albuterol sulfate)  
INHALATION SOLUTION

**INGREDIENTS:**  
Active: 0.5 mg ipratropium bromide and 3.0 mg albuterol sulfate\*.  
Inactive: Sodium chloride, edetate disodium, and hydrochloric acid (to adjust the pH between 3 and 5) and purified water.

**STORAGE CONDITIONS:** PROTECT FROM LIGHT. STORE IN POUCH UNTIL TIME OF USE. Store between 2°C and 25°C (36°F and 77°F).

**USUAL DOSAGE:** See accompanying prescribing information. USE ONLY AS DIRECTED BY YOUR PHYSICIAN. DO NOT EXCEED RECOMMENDED DOSAGE.

Rx only.

\*Equivalent to 2.5 mg albuterol base.



DEY, Napa, CA 94558

LOT: DPRES

ATTENTION PHARMACIST: Detach Patient's Instructions for Use\* from package insert and dispense with solution.

**DuoNeb**<sup>™</sup>

(ipratropium bromide  
and albuterol sulfate)  
INHALATION SOLUTION



DEY, Napa, CA 94558

**DuoNeb**<sup>™</sup>

(ipratropium bromide and  
albuterol sulfate)  
INHALATION SOLUTION

*Sterile Unit-Dose Vial  
For Inhalation Only*



*Contains 1.25 mg ipratropium bromide and 3.0 mg albuterol base.*



3162001 (round 4)



One Sample Pouch Per Patient

**DuoNeb**

(ipratropium bromide  
and albuterol sulfate)  
INHALATION SOLUTION

PLACE DEY REPRESENTATIVE'S CARD HERE

1 800 755 7560  
www.duoneb.com

REMOVE TAB FOR EASIER DISPENSING

LOT: EXPRES

ATTENTION PHARMACEUT: Search Patient's Instructions for  
"Use" from package insert and dispense with solution.

REMOVE FLAP FOR EASIER DISPENSING

**DuoNeb**

Professional Sample Not For Sale

(ipratropium bromide and albuterol sulfate)  
INHALATION SOLUTION

**INGREDIENTS:**

Active: 0.5mg ipratropium bromide and 3.0 mg albuterol sulfate\*  
Inactive: Sodium chloride, edetate disodium, and hydrochloric acid (to adjust the pH between 3 and 5) and purified water

**STORAGE CONDITIONS:** PROTECT FROM LIGHT. STORE IN POUCH UNTIL TIME OF USE. Store between 2°C and 25°C (36°F and 77°F)

**USUAL DOSAGE:** See accompanying prescribing information. USE ONLY AS DIRECTED BY YOUR PHYSICIAN. DO NOT EXCEED RECOMMENDED DOSAGE.

Rx only.

\*Equivalent to 2.5 mg albuterol base.



DEY, Napo, CA 94558

www.duoneb.com

**DuoNeb**

(ipratropium bromide  
and albuterol sulfate)  
INHALATION SOLUTION



0 12345 67890 5

**DuoNeb**  
(ipratropium bromide and  
albuterol sulfate)  
INHALATION SOLUTION



www.duoneb.com



Contains 12 pouches of 5.4 mL each



1 2 3 4 5 6 7 8