CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73045

DRAFT FINAL PRINTED LABELING

FORM 1264 **PRODUCT INFORMATION**

ALBUTEROL INHALATION AEROSOL

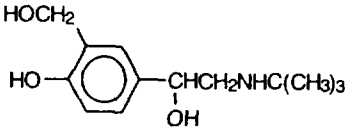
Bronchodilator Aerosol

FOR ORAL INHALATION ONLY

VC1252

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere

DESCRIPTION: The active component of Albuterol Inhalation Aerosol is albuterol (α^1-[(*tert*-butylamino)methyl] -4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective beta$_2$-adrenergic bronchodilator, having the following structural formula



Albuterol is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol. The molecular weight of albuterol is 239.32, and *the molecular formula is* $C_{13}H_{21}NO_3$. *Albuterol is a white to* off-white crystalline solid. It is soluble in alcohol, sparingly soluble in water, and very soluble in chloroform.

Albuterol Inhalation Aerosol is a metered-dose aerosol unit for oral inhalation. It contains a microcrystalline (95% ≤ 10μm) suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers from the mouthpiece 90 mcg of albuterol. Each canister provides at least 200 inhalations

CLINICAL PHARMACOLOGY: *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 indicate that there is a population of beta$_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells

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, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Albuterol 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 catecholamines nor for catechol-*O*-methyl transferase

Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation of recommended doses. *Studies undertaken with four subjects administered* inhaled albuterol resulted in maximum plasma concentrations *occurring within two to four hours. Due to the sensitivity of the* assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, urinary excretion provided data indicating that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted within 24 hours in the urine, and consists of 28% as unchanged drug and 44% as metabolite

Animal studies show that albuterol does not pass the blood-brain barrier

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that albuterol is one half to one quarter as active as isoproterenol in producing increases in heart rate. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

In controlled clinical trials involving adults with asthma, the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximum midexpiratory flow rate (MMEF) and forced expiratory volume in one second (FEV_1). MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following two inhalations of albuterol and that clinically significant improvement generally continues for three to four hours in most patients. Some patients showed a therapeutic response (defined by maintaining FEV_1 values 15% or more above baseline) that was still apparent at 6 hours. Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials.

In controlled clinical trials involving children 4 to 12 years of age, FEV_1 measurements showed that maximum improvement in pulmonary function occurs within 30 to 60 minutes. The onset of clinically significant (≥ 15%) improvement in FEV_1 was observed as soon as five minutes following 180 mcg of albuterol in 18 of 30 (60%) children in a controlled dose-ranging study. Clinically significant improvement in FEV_1 continued in the majority of patients for two hours and in 33% to 47% for four hours among 56 patients receiving inhalation aerosol in one pediatric study. In a second study, among 48 patients receiving inhalation aerosol, clinically significant improvement continued in the majority for up to one hour and in 23% to 40% for four hours. In addition, at least 50% of the patients in both studies achieved an improvement in forced expiratory flow rate between 25% and 75% of the forced vital capacity of at least 20% for two to five hours. Continued effectiveness of albuterol was demonstrated over the 12-week study period

In other clinical studies involving both children and adults, two inhalations of albuterol aerosol taken approximately 15 minutes before exercise prevented exercise-induced bronchospasm, as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients. Two of these studies, one of which involved adults and the other children, also evaluated the duration of the prophylactic effect to repeated exercise challenges, which was evident at four hours in ***a majority of the patients*** and at six hours in approximately one third of the patients.

INDICATIONS AND USAGE: Albuterol Inhalation Aerosol is indicated for the prevention and relief of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm in patients 4 years of age and older

Albuterol Inhalation Aerosol can be used with or without concomitant steroid therapy.

CONTRAINDICATIONS: Albuterol Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS: As with other inhaled beta-adrenergic agonists, albuterol inhalation aerosol can produce paradoxical bronchospasm that can be life-threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. The exact cause of death is unknown, but cardiac arrest following the unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate hypersensitivity reactions may occur after administration of albuterol inhalation aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

The contents of Albuterol Inhalation Aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of the reach of children.

PRECAUTIONS: General: Albuterol, as with all sympathomimetic amines, 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.

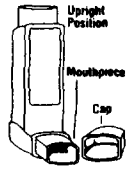
This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere

Patient's Instructions for Use

Before using your Albuterol Inhalation Aerosol, read complete instructions carefully.

Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

Figure 1



1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece.** (See Figure 1) Should the cap be dislodged or lost, the inhaler mouthpiece should be inspected for the presence of foreign objects before each use. Make sure the canister is fully and firmly inserted into the actuator

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (See Figure 1) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (See Figure 2).

For Oral Inhalation Only

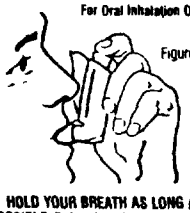


Figure 2

4. HOLD YOUR BREATH AS LONG AS POSSIBLE. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

5. Wait one minute and **SHAKE** the inhaler again. Repeat steps 2 through 4 for each inhalation prescribed by your physician.

6. CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm, running water, at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister into the case with a twisting motion and replace the cap

7. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

8. DISCARD THE CANISTER AFTER YOU HAVE USED THE LABELED NUMBER OF INHALATIONS. The correct amount of medication in each inhalation cannot be assured after this point.

(continued)

PHARMACIST - DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT. THIS LEAFLET SHOULD ACCOMPANY EACH ALBUTEROL INHALATION AEROSOL OR REFILL DISPENSED

THE REFILL CANISTER IS TO BE USED WITH THE CCL INDUSTRIES LTD. ADAPTER

DOSAGE: Use only as directed by your physician.

WARNINGS: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without consulting your physician. If recommended dosage does not provide relief of symptoms or symptoms become worse, seek immediate medical attention. While taking Albuterol Inhalation Aerosol, other inhaled medicines should be used only as prescribed by your physician.

Contents Under Pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of the reach of children.

Store between 15° and 30°C (59° and 86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc
Baltimore, MD 21244
USA

FORM NO 1264-P
Rev.8/96

PHARMACIST - DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT. THIS LEAFLET SHOULD ACCOMPANY EACH ALBUTEROL INHALATION AEROSOL OR REFILL DISPENSED

Large doses of intravenous albuterol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, inhaled and intravenous albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Although there have been no reports concerning the use of Albuterol Inhalation Aerosol during labor and delivery, it has been reported that high doses of albuterol administered intravenously inhibit uterine contractions. Although this effect is extremely unlikely as a consequence of aerosol use, it should be kept in mind.

Information for Patients: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without medical consultation. If recommended dosage does not provide relief of symptoms or symptoms become worse, seek immediate medical attention. While taking Albuterol Inhalation Aerosol, other inhaled drugs should not be used unless prescribed.

In general, the technique for administering Albuterol Inhalation Aerosol to children is similar to that for adults, since children's smaller ventilatory exchange capacity automatically provides proportionally smaller aerosol intake. Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

See illustrated **Patient's Instructions For Use.**

Drug Interactions: Other sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a two-year study in the rat at oral doses of 2, 10, and 50 mg/kg, corresponding to 93, 463, and 2,315 times, respectively, the maximum inhalational dose for a 50 kg human. In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18 month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C: Albuterol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25, and 2.5 mg/kg, corresponding to 1.15, 11.5, and 115 times, respectively, the maximum inhalational dose for a 50 kg human) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None was observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Str de Dutch rabbits revealed cranioschisis in 7 of 19 (37% fetuses at 50 mg/kg, corresponding to 2,315 times the maximum inhalational dose for a 50 kg human.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below 4 years of age have not been established.

ADVERSE REACTIONS

The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents, although the incidence of certain cardiovascular effects is lower with albuterol.

A 13-week, double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients aged 12 years and older. The results of this study showed that the incidence of cardiovascular effects was: palpitations, fewer than 10 per 100 with albuterol and fewer than 15 per 100 with isoproterenol; tachycardia 10 per 100 with both albuterol and isoproterenol; and increased blood pressure, fewer than 5 per 100 with both albuterol and isoproterenol. In the same study, both drugs caused tremor or nausea in fewer than 15 patients per 100, and dizziness or heartburn in fewer than 5 per 100 patients. Nervousness occurred in fewer than 10 per 100 patients receiving albuterol and in fewer than 15 per 100 patients receiving isoproterenol.

In 12-week, double-blind studies involving the use of Albuterol Inhalation Aerosol 180 mcg qid by 104 asthmatic children aged 4 to 11 years showed the following side effects.

Central Nervous System: Headache, 3 of 104 patients (3%), nervousness, lightheadedness, agitation, nightmares, hyperactivity, and aggressive behavior, each in 1%.

Gastrointestinal: Nausea and/or vomiting, 6 of 104 (6%); stomachache, 3 of 104 (3%); diarrhea in 1%.

Oropharyngeal: Throat irritation, 6 of 104 (6%); discoloration of teeth in 1%.

Respiratory: Epistaxis, 3 of 104 (3%); coughing, 2 of 104 (2%).

Musculoskeletal: Tremor and muscle cramp, each in 1%.

Rare cases of urticaria, angioedema, rash, bronchospasm, hoarseness and oropharyngeal edema have been reported after the use of inhaled albuterol.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, and unusual taste.

OVERDOSAGE: Manifestations of overdosage may include seizures, anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute, and exaggeration of the pharmacologic effects listed in ADVERSE REACTIONS.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse.

The oral LD_{50} in male and female rats and mice was greater than 2,000 mg/kg. The inhalational LD_{50} could not be determined.

Dialysis is not appropriate treatment for overdosage of albuterol inhalation aerosol. The judicious use of a cardioselective beta-receptor blocker, such as metoprolol tartrate, is suggested, bearing in mind the danger of inducing an asthmatic attack.

DOSAGE AND ADMINISTRATION: For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years and older is two inhalations repeated every four to six hours; in some patients, one inhalation every four hours may be sufficient. More frequent administration or a larger number of inhalations are not recommended.

The use of Albuterol Inhalation Aerosol can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and children 4 years and older is two inhalations 15 minutes before exercise.

For treatment, see above.

HOW SUPPLIED: Albuterol Inhalation Aerosol is supplied in 17-g canisters in boxes of one with patient's instructions and an oral adaptor or as refills, without oral adaptor. Each actuation delivers 90 mcg of Albuterol from the mouthpiece. Each canister provides 200 metered inhalations.

Store at controlled room temperature 15°-30°C (59°-86°F). As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Shake well before using.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc
Baltimore, MD 21244
USA

FORM NO 1264 Rev.8/96 VC1252

A.L. LABORATORIES, INC.

ANDA #73-045

Albuterol Inhalation Aerosol 17 g

200 metered Inhalations

Final Printed Labeling

THE REFILL CANISTER IS TO BE USED WITH THE CCL INDUSTRIES LTD. ADAPTER.

USUAL DOSAGE: Use only as directed by your physician

WARNINGS: The action of Albuterol Inhalation Aerosol may last up to six hours, and therefore it should not be used more frequently than recommended. Do not increase the number or frequency of doses without consulting your physician. If symptoms get worse, discontinue use and consult your physician immediately. Other inhaled medicines should be used only as prescribed by your physician.

Shake well before using.

Manufactured by
CCL Industries Limited
Runcorn WA7 1NU
UK

Distributed by
Barre-National Inc
Baltimore, MD 21244
USA

12640994

Barre®

17 g

For oral inhalation with CCL Industries Ltd. Albuterol Inhalation Aerosol adapter only.

Contents: Each canister contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers 90 mcg of albuterol from the mouthpiece.

Attention Pharmacist: Detach patient's leaflet of instructions from package insert and dispense with inhaler.

This product contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.

APPROVED
AUG 19 1997

CAUTION: Federal law prohibits dispensing without prescription.

See package insert for full prescribing information

Important: Read accompanying directions carefully

Store between 15° and 30°C (59° and 86°F) As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold

Shake well before using.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator Keep out of the reach of children

04721 26463 6

Barre®

PATIENT'S INSTRUCTIONS FOR USE

Before using your Albuterol Inhalation Aerosol, read complete instructions carefully. Children should use Albuterol Inhalation Aerosol under adult supervision, as instructed by the patient's physician.

1. SHAKE THE INHALER WELL immediately before each use **Then remove the cap from the mouthpiece.** (See Figure 1) Should the cap be dislodged or lost, the inhaler mouthpiece should be inspected for the presence of foreign objects before each use. Make sure the canister is fully and firmly inserted into the actuator.

2. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (see Figure 1) and closing the lips around it.

3. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger. (See Figure 2).

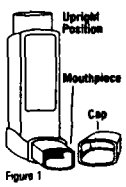


Figure 1

4. HOLD YOUR BREATH AS LONG AS POSSIBLE. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

5. Wait one minute and **SHAKE** the inhaler again. Repeat steps 2 through 4 for each inhalation prescribed by your physician.

6. CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm, running water, at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister into the case with a twisting motion and replace the cap.

7. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

8. DISCARD THE CANISTER AFTER YOU HAVE USED THE LABELED NUMBER OF INHALATIONS. The correct amount of medication in each inhalation cannot be assured after this point.

Figure 2

Carton 17 g (refill)

12640994

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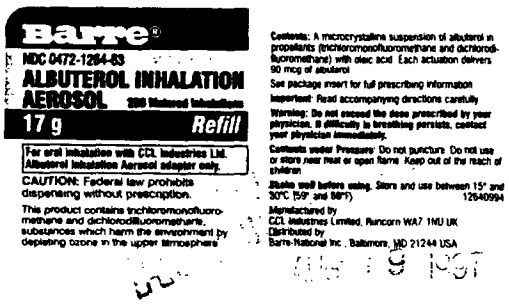
A.L. LABORATORIES, INC.

ANDA #73-045

Albuterol Inhalation Aerosol 17 g

200 metered Inhalations

Final Printed Labeling



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Label 17 g (refill)
12640994