

BROVANA™ (arformoterol tartrate) Inhalation Solution

15 mcg*/2 mL

*potency expressed as arformoterol

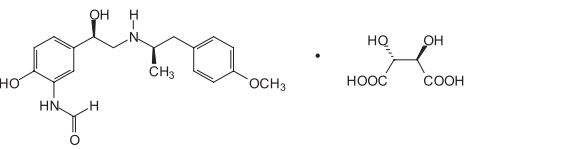
For oral inhalation only

WARNING:
Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to arformoterol (a long-acting beta₂-adrenergic agonist), the active ingredient in BROVANA (see WARNINGS).

DESCRIPTION

BROVANA (arformoterol tartrate) Inhalation Solution is a sterile, clear, colorless, aqueous solution of the tartrate salt of arformoterol, the (R,R)-enantiomer of formoterol.

Arformoterol is a selective beta₂-adrenergic bronchodilator. The chemical name for arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-2R,3R)-2,3-dihydrobutanedioate (1:1 salt), and its established structural formula is as follows:



The molecular weight of arformoterol tartrate is 494.5 g/mol, and its empirical formula is C₁₉H₂₃N₂O₄ • C₄H₆O₆ (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

Arformoterol tartrate is the United States Adopted Name (USAN) for (R,R)-formoterol L-tartrate.

BROVANA is supplied as 2 mL of arformoterol tartrate solution packaged in 2.1 mL unit-dose, low-density polyethylene (LDPE) vials. Each unit-dose vial contains 15 mcg of arformoterol (equivalent to 22 mcg of arformoterol tartrate) in a sterile, isotonic saline solution, pH-adjusted to 5.0 with citric acid and sodium citrate.

BROVANA requires no dilution before administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend upon patient factors, the nebulizer used, and compressor performance. Using the PARI LC PLUS® nebulizer (with mouthpiece) connected to a PARI DURA-NEB® 3000 compressor under *in vitro* conditions, the mean delivered dose from the mouthpiece (% nominal) was approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization time was 6 minutes or less. BROVANA should be administered from a standard jet nebulizer at adequate flow rates via face mask or mouthpiece (see Dosage and Administration).

Patients should be carefully instructed on the correct use of this drug product (please refer to the accompanying Medication Guide).

CLINICAL PHARMACOLOGY

Mechanism of Action

Arformoterol, the (R,R)-enantiomer of formoterol, is a selective long-acting beta₂-adrenergic receptor agonist (beta₂-agonist) that has two-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer is about 1,000-fold less potent as a beta₂-agonist than the (R,R)-enantiomer. While it is recognized that beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, data indicate that there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that arformoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Arformoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these *in vitro* and animal findings to humans is unknown.

Animal Pharmacology

In animal studies investigating its cardiovascular effects, arformoterol induced dose-dependent increases in heart rate and decreases in blood pressure consistent with its pharmacology as a beta₂-adrenergic agonist. In dogs, at systemic exposures higher than anticipated clinically, arformoterol also induced exaggerated pharmacologic effects of a beta-adrenergic agonist on cardiac function as measured by electrocardiogram (sinus tachycardia, atrial premature beats, ventricular escape beats, PVCs).

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

Pharmacokinetics

The pharmacokinetics (PK) of arformoterol have been investigated in healthy subjects, elderly subjects, renally and hepatically impaired subjects, and chronic obstructive pulmonary disease (COPD) patients following the nebulization of the recommended therapeutic dose and doses up to 96 mcg.

Absorption

In COPD patients administered 15 mcg arformoterol every 12 hours for 14 days, the mean steady-state peak (R,R)-formoterol plasma concentration (C_{max}) and systemic exposure (AUC_{0-12h}) were 4.3 pg/mL and 34.5 pg*hr/mL, respectively. The median steady-state peak (R,R)-formoterol plasma concentration time (t_{max}) was observed approximately one half hour after drug administration.

Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks.

In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil® Aerolizer™) was administered twice daily for 2 weeks, the accumulation index was approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three treatments. At steady state, geometric means of systemic exposure (AUC_{0-12h}) to (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of formoterol fumarate inhalation powder were 39.33 pg*hr/mL and 33.93 pg*hr/mL, respectively (ratio 1.16; 90% CI 1.00, 1.35), while the geometric means of the C_{max} were 4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

In a study in patients with asthma, treatment with arformoterol 50 mcg with pre- and post-treatment with activated charcoal resulted in a geometric mean decrease in (R,R)-formoterol AUC_{0-6h} by 27% and C_{max} by 23% as compared to treatment with arformoterol 50 mcg alone. This suggests that a substantial portion of systemic drug exposure is due to pulmonary absorption.

Distribution

The binding of arformoterol to human plasma proteins *in vitro* was 52-65% at concentrations of 0.25, 0.5 and 1.0 ng/mL of radiolabeled arformoterol. The concentrations of arformoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of multiple doses of 50 mcg arformoterol.

Metabolism

In vitro profiling studies in hepatocytes and liver microsomes have shown that arformoterol is primarily metabolized by direct conjugation (glucuronidation) and secondarily by O-demethylation. At least five human uridine diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation *in vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily CYP2C19) catalyze the O-demethylation of arformoterol. Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes at >1,000-fold higher concentrations than the expected peak plasma concentrations following a therapeutic dose.

Arformoterol was almost entirely metabolized following oral administration of 35 mcg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol with glucuronic acid was the major meta-

bolic pathway. Most of the drug-related material in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol. O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor metabolites accounting for less than 17% of the dose recovered in urine and feces.

Elimination

After administration of a single oral dose of radiolabeled arformoterol to eight healthy male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces within 48 hours. A total of 89% of the total radioactive dose was recovered within 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was recovered as unchanged arformoterol in urine over 14 days. Renal clearance was 8.9 L/hr for unchanged arformoterol in these subjects.

In COPD patients given 15 mcg inhaled arformoterol twice a day for 14 days, the mean terminal half-life of arformoterol was 26 hours.

Special Populations

Gender

A population PK analysis indicated that there was no effect of gender upon the pharmacokinetics of arformoterol.

Race

The influence of race on arformoterol pharmacokinetics was assessed using a population PK analysis and data from healthy subjects. There was no clinically significant impact of race upon the pharmacokinetic profile of arformoterol.

Geriatric

The pharmacokinetic profile of arformoterol in 24 elderly subjects (aged 65 years or older) was compared to a younger cohort of 24 subjects (18-45 years) that were matched for body weight and gender. No significant differences in systemic exposure (AUC and C_{max}) were observed when the two groups were compared.

Pediatric

The pharmacokinetics of arformoterol have not been studied in pediatric subjects.

Hepatic Impairment

The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild, moderate, and severe hepatic impairment. The systemic exposure (C_{max}) and AUC to arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to 16 demographically matched healthy control subjects. No clear relationship between drug exposure and the severity of hepatic impairment was observed. BROVANA should be used cautiously in patients with hepatic impairment.

Renal Impairment

The impact of renal disease upon the pharmacokinetics of arformoterol was studied in 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure (AUC and C_{max}) to arformoterol was similar in renally impaired patients compared with demographically matched healthy control subjects.

Pharmacogenetics

Arformoterol is eliminated through the action of multiple drug metabolizing enzymes. Direct glucuronidation of arformoterol is mediated by several UGT enzymes and is the primary elimination route. O-Desmethylation is a secondary route catalyzed by the CYP enzymes CYP2D6 and CYP2C19. In otherwise healthy subjects with reduced CYP2D6 and/or UGT1A1 enzyme activity, there was no impact on systemic exposure to arformoterol compared to subjects with normal CYP2D6 and/or UGT1A1 enzyme activities.

Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The predominant adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of systemic beta₂-adrenergic receptors. The most common adverse effects may include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Changes on Serum Potassium and Serum Glucose Levels

Effects on serum potassium and serum glucose were evaluated in a dose ranging study of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily (15 mcg, 25 mcg, or 50 mcg; 101 patients with COPD) BROVANA in COPD patients. At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum potassium ranging from 0 to -0.3 mEq/L were observed in the BROVANA groups with similar changes observed after 2 weeks of treatment. Changes in mean serum glucose levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL, were observed for BROVANA dose groups at both 2 and 6 hours post dose, both after the first dose and 14 days of daily treatment.

Electrophysiology

The effect of BROVANA on QT interval was evaluated in a dose ranging study following multiple doses of BROVANA 5 mcg, 15 mcg, or 25 mcg twice daily or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with COPD. ECG assessments were performed at baseline, time of peak plasma concentration and throughout the dosing interval. Different methods of correcting for heart rate were employed, including a subject-specific method and the Friederich method.

Relative to placebo, the mean change in subject-specific QT_c averaged over the dosing interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA on cardiac repolarization after 2 weeks of treatment. The maximum mean change in subject-specific QT_c for the BROVANA 15 mcg twice daily dose was 17.3 msec, compared with 15.4 msec in the placebo group. No apparent correlation of QT_c with arformoterol plasma concentration was observed.

Electrocardiographic Monitoring in Patients with COPD

The effect of different doses of BROVANA on cardiac rhythm was assessed using 24-hour Holter monitoring in two 12-week double-blind, placebo-controlled studies of 1,456 patients with COPD (873 received BROVANA at 15 or 25 mcg twice daily or 50 mcg once daily doses; 293 received placebo; 290 received salmeterol). The 24-hour Holter monitoring occurred once at baseline, and up to 3 times during the 12-week treatment period. The rates of new-onset cardiac arrhythmias not present at baseline over the double-blind 12-week treatment period were similar (approximately 33-34%) for patients who received BROVANA 15 mcg twice daily to those who received placebo. There was a dose-related increase in new, treatment emergent arrhythmias seen in patients who received BROVANA 25 mcg twice daily and 50 mcg once daily, 37.6% and 40.1%, respectively. The frequencies of new, treatment emergent events of non-sustained (3-10 beat run) and sustained (>10 beat run) ventricular tachycardia were 7.4% and 1.1% in BROVANA 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients who received BROVANA 25 mcg twice daily and 50 mcg once daily the frequencies of non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0% and 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported as adverse events (1 in BROVANA 15 mcg twice daily and 4 in placebo), with two of these events leading to discontinuation of treatment (2 in placebo).

There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour Holter monitoring in patients treated with BROVANA 15 mcg twice daily or placebo. New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of patients who received BROVANA 15 mcg twice daily and 0.3% of patients who received placebo. There was a dose-related increase in the frequency of atrial fibrillation/ flutter reported in the BROVANA 25 mcg twice daily and 50 mcg once daily dose groups of 0.7% and 1.4%, respectively. Two cases of atrial fibrillation/ flutter were reported as adverse events (1 in BROVANA 15 mcg twice daily and 1 in placebo).

Dose-related increases in mean maximum change in heart rate in the 12 hours after dosing were also observed following 12 weeks of dosing with BROVANA 15 mcg twice daily (8.8 bpm), 25 mcg twice daily (9.9 bpm) and 50 mcg once daily (12 bpm) versus placebo (8.5 bpm).

Tachyphaxixis/Tolerance

In two placebo-controlled clinical trials in patients with COPD involving approximately 725 patients in each, the overall efficacy of BROVANA was maintained throughout the 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as measured by FEV₁, FEV₂ improvement at the end of the 12-hour dosing interval decreased by approximately one third (22.1% mean improvement after the first dose compared to 14.6% at week 12). Tolerance to the FEV₁ bronchodilator effect of BROVANA was not accompanied by other clinical manifestations of tolerance in these trials.

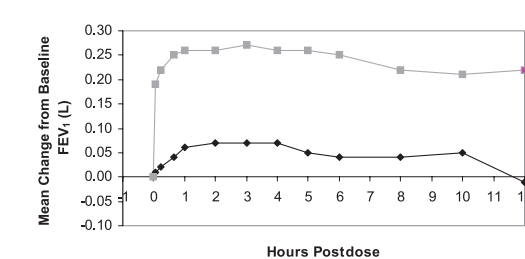
CLINICAL TRIALS

Adult COPD Trials

BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical, 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD who had a mean FEV₁ of 1.3 L (42% of predicted) were enrolled in the two clinical trials. The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline FEV₁ <65% of predicted value and <0.70 L, and a FEV₁/forced vital capacity (FVC) ratio <70%). About 80% of patients in these studies had bronchodilator reversibility, defined as a 10% or greater increase FEV₁ after inhalation of 2 actuations (180 mcg racemic albuterol from a metered dose inhaler). Both trials compared BROVANA 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily

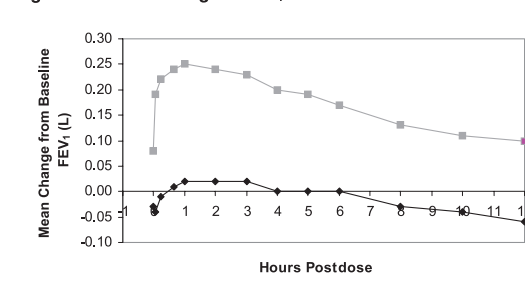
(293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation aerosol, 42 mcg twice daily as an active comparator (290 patients). In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by percent change from study baseline FEV₁ at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily, BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient additional benefit on a variety of endpoints, including FEV₁, to support the use of higher doses. Plots of the mean change in FEV₁ values obtained over the 12 hours after dosing for the BROVANA 15 mcg twice daily dose group and for the placebo group are provided in Figures 1 and 2 for Clinical Trial A, below. The plots include mean FEV₁ change observed after the first dose and after 12 weeks of treatment. The results from Clinical Trial B were similar.

Figure 1 Mean Change in FEV₁ Over Time for Clinical Trial A at Week 0 (Day 1)



Placebo (ITT n=143) Baseline FEV₁ = 1.20(L)
 15 mcg BROVANA BID (ITT n=141) Baseline FEV₁ = 1.15 (L)

Figure 2 Mean Change in FEV₁ Over Time for Clinical Trial A at Week 12



Placebo (ITT n=143) Baseline FEV₁ = 1.20 (L)
 15 mcg BROVANA BID (ITT n=141) Baseline FEV₁ = 1.15 (L)

BROVANA 15 mcg twice daily significantly improved bronchodilation compared to placebo over the 12 hours after dosing (FEV₁, AUC_{0-12h}). This improvement was maintained over the 12-week study period. Following the first dose of BROVANA 15 mcg, the median time to onset of bronchodilation, defined by an FEV₁ increase of 15%, occurred at 6.7 min. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours of dosing. In both clinical trials, compared to placebo, patients treated with BROVANA demonstrated improvements in peak expiratory flow rates, supplemental ipratropium and rescue albuterol use.

INDICATIONS AND USAGE

BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA is for use by nebulization only.

CONTRAINDICATIONS

BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product.

WARNINGS

- **Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.**
- A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13, 176 in patients treated with salmeterol vs. 3/13, 179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting beta₂-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma related death is increased in patients treated with BROVANA has been conducted.
- Clinical studies with racemic formoterol (Foradil® Aerolizer™) suggested a higher incidence of serious asthma exacerbations in patients who received racemic formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

- **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, i.e., rescue therapy.**
- **BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate.**
- **BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients.**
- **BROVANA should not be used in conjunction with other inhaled, long-acting beta₂-agonists. BROVANA should not be used with other medications containing long-acting beta₂-agonists.**
- **When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.**
- **See PRECAUTIONS, Information for Patients and the accompanying Medication Guide.**

Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, BROVANA can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted.

Deterioration of Disease

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalations of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

Cardiovascular Effects

BROVANA, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after

administration of BROVANA at the recommended dose, 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 QT interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see PRECAUTIONS, General).

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm.

Do Not Exceed Recommended Dose

Fatality has been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta₂-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long-acting beta-agonists.

PRECAUTIONS

General

BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta₂-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated (see Information for Patients and the accompanying Medication Guide).

BROVANA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be given the following information:

1. Patients should be informed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death.
2. BROVANA is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting, beta₂-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).
3. Patients should be informed that treatment with beta₂-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness.
4. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution.
5. Patients should protect BROVANA single-use low-density polyethylene (LDPE) vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2°C and 8°C (36°-46°F). They should not be used after the expiration date stamped on the container. Patients should be instructed that once the foil pouch is opened, the contents of the vial should be used immediately and to discard any vial if the solution is not colorless.
6. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established.
7. Women should be advised to contact their physician if they become pregnant or if they are nursing.
8. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking (see the accompanying Medication Guide and the Instructions for Using BROVANA).

Drug Interactions

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated. When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given



STW-SP06-42-0001

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MEDICATION GUIDE


STW-SP06-42-0001

BROVANA™ (arformoterol tartrate) Inhalation Solution
MEDICATION GUIDE
MEDICATION GUIDE
BROVANA [Brō vā´-nah]
 (arformoterol tartrate) Inhalation Solution

IMPORTANT USE INFORMATION

1. BROVANA is for use with a standard jet nebulizer machine connected to an air compressor. Read the complete instructions for use at the end of this Medication Guide before starting BROVANA.

2. Do not swallow or inject BROVANA. BROVANA is for inhalation use only.

Read the Medication Guide that comes with BROVANA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about BROVANA?

BROVANA is a medicine called a long-acting beta₂-agonist or LABA. BROVANA is used to treat chronic obstructive pulmonary disease (COPD).

- In patients with asthma, LABA medicines such as BROVANA may increase the chance of asthma-related death from asthma problems.
- It is not known if LABA medicines, such as BROVANA, increase the chance of death in patients with chronic obstructive pulmonary disease (COPD).
- BROVANA does not relieve sudden symptoms of COPD. Always have a short-acting beta₂-agonist medicine with you to treat sudden symptoms. If you do not have an inhaled short-acting bronchodilator, call your healthcare provider to have one prescribed for you.
- Get emergency medical care if:
 - breathing problems worsen quickly
 - you use your short-acting beta₂-agonist medicine, but it does not relieve your breathing problems
- Do not stop using BROVANA unless told to do so by your healthcare provider because your symptoms might get worse.
- BROVANA should not be used in children. BROVANA has not been studied in children.

What is BROVANA?

BROVANA is used long term, twice a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD.

LABA medicines such as BROVANA help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath.

What should I tell my healthcare provider before using BROVANA?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- are pregnant or planning to become pregnant. It is not known if BROVANA can harm your unborn baby.
- are breastfeeding. It is not known if BROVANA passes into your milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. BROVANA and certain other medicines may interact with each other. This may cause serious side effects.

Know the medicines you take. Keep a list of them to show your health-

care provider and pharmacist each time you get a new medicine.

How should I use BROVANA?

Read the step-by-step instructions for using BROVANA at the end of this Medication Guide.

- Use BROVANA exactly as prescribed. One ready-to-use vial of BROVANA is one dose. The usual dose of BROVANA is 1 ready-to-use vial, twice a day (morning and evening) breathed in through your nebulizer machine. The 2 doses should be about 12 hours apart. **Do not use more than 2 vials of BROVANA a day.**
- Do not mix other medicines with BROVANA in your nebulizer machine.
- If you miss a dose of BROVANA. Just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- While you are using BROVANA twice a day:
 - do not use other medicines that contain a long-acting beta₂-agonist (LABA) for any reason.
 - do not use your short-acting beta₂-agonist medicine on a regular basis (four times a day).
- Make sure you always have a short-acting beta₂-agonist medicine with you. Use your short-acting beta₂-agonist medicine if you have breathing problems between doses of BROVANA.
- Do not change or stop any of your medicines to control or treat your COPD breathing problems. Your healthcare provider will adjust your medicines as needed.

Call your healthcare provider or get emergency medical care right away if:

- your breathing problems worsen with BROVANA
- you need to use your short-acting beta₂-agonist medicine more often than usual
- your short-acting beta₂-agonist medicine does not work as well for you at relieving symptoms

What are the possible side effects with BROVANA?

- In patients with asthma, LABA medicines such as BROVANA may increase the chance of asthma-related death from asthma problems.
- serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems. Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.

- chest pain
- increased or decreased blood pressure
- a fast and irregular heartbeat
- headache
- tremor
- nervousness
- dry mouth
- muscle cramps
- nausea, vomiting
- dizziness
- tiredness
- low or high blood potassium
- high blood sugar
- high blood acid
- trouble sleeping

Tell your healthcare provider if you get any side effect that bothers you or that does not go away.

These are not all the side effects with BROVANA. Ask your healthcare provider or pharmacist for more information.

How should I store BROVANA?

- Store BROVANA in a refrigerator between 36° to 46°F (2° to 8°C) in the protective foil pouch. Protect from light and excessive heat. **Do not open a sealed pouch until you are ready to use a dose of BROVANA. Once a sealed pouch is opened, BROVANA must be used right away.** BROVANA may be used directly from the refrigerator.

- BROVANA may also be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 6 weeks (42 days). If stored at room temperature, discard BROVANA if it is not used after 6 weeks or if past the expiration date, whichever is sooner. Space is provided on the packaging to record room temperature storage times.

- Do not use BROVANA after the expiration date provided on the foil pouch and vial.
- BROVANA should be colorless. Discard BROVANA if it is not colorless.

- **Keep BROVANA and all medicines out of the reach of children.**

General Information about BROVANA

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use BROVANA for a condition for which it was not prescribed. Do not give BROVANA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about BROVANA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BROVANA that was written for healthcare professionals.

- For customer service, call 1-888-394-7377.
- To report side effects, call 1-877-737-7226.
- For medical information, call 1-800-739-0565.

Instructions for Using BROVANA (arformoterol tartrate) Inhalation Solution

BROVANA is used only in a standard jet nebulizer machine connected to an air compressor. Make sure you know how to use your nebulizer machine before you use it to breathe-in BROVANA or other medicines.

Do not mix BROVANA with other medicines in your nebulizer machine.

BROVANA comes sealed in a foil pouch. Do not open a sealed pouch until you are ready to use a dose of BROVANA.

1. Open the foil pouch by tearing on the rough edge along the seam of the pouch. Remove the unit-dose vial of BROVANA and use it right away.
2. Carefully twist open the top of the unit-dose vial (Figure 1).

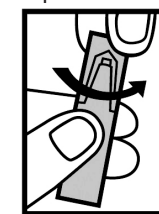


Figure 1

3. Squeeze all of the medicine from the vial into the nebulizer medicine cup (reservoir) (Figure 2).



Figure 2

4. Connect the nebulizer reservoir to the mouthpiece (Figure 3) or face mask (Figure 4).

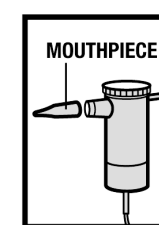


Figure 3



Figure 4

5. Connect the nebulizer to the compressor (Figure 5).

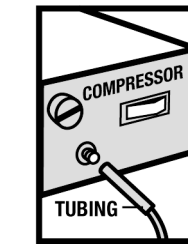


Figure 5

6. Sit in a comfortable, upright position. Place the mouthpiece in your mouth (Figure 6) (or put on the face mask) and turn on the compressor.

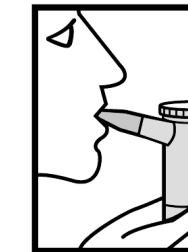


Figure 6

7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer reservoir. It takes about 5 to 10 minutes for each treatment.

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

Rx Only

This Medication Guide has been approved by the Food and Drug Administration.



Manufactured for:
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 Marlborough, MA 01752 USA

October 2006
 901005R0