CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-912

LABELING

BROVANA™
(arformoterol tartrate) Inhalation Solution
15 mcg*/2 mL

*potency expressed as arformoterol

For oral inhalation only

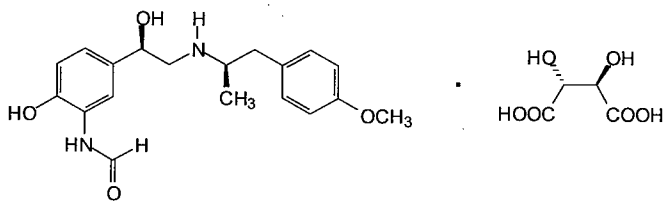
WARNING:

Long-acting beta$_2$-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 beta$_2$-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 beta$_2$-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 beta$_2$-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-dihydroxybutanedioate (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 $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (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 beta$_2$-adrenergic receptor agonist (beta$_2$-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 beta$_2$-agonist than the (R,R)-enantiomer. While it is recognized that beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, data indicate that there are also beta$_2$-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 beta$_2$-agonists may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenyl 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 beta-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 ($AUC_{0\text{-}12h}$) 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 ($AUC_{0\text{-}12h}$) 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 $AUC_{0\text{-}6h}$ 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 metabolic 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.

145 **Geriatric**

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

150 **Pediatric**

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

152 **Hepatic Impairment**

153 The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild,
154 moderate, and severe hepatic impairment. The systemic exposure (C_{max} and AUC) to
155 arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to
156 16 demographically matched healthy control subjects. No clear relationship between
157 drug exposure and the severity of hepatic impairment was observed. BROVANA should
158 be used cautiously in patients with hepatic impairment.

159 **Renal Impairment**

160 The impact of renal disease upon the pharmacokinetics of arformoterol was studied in
161 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure
162 (AUC and C_{max}) to arformoterol was similar in renally impaired patients compared with
163 demographically matched healthy control subjects.

164 **Pharmacogenetics**

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

172 **Pharmacodynamics**

173 **Systemic Safety and Pharmacokinetic/ Pharmacodynamic Relationships**

174 The predominant adverse effects of inhaled $beta_2$-agonists occur as a result of excessive
175 activation of systemic beta-adrenergic receptors. The most common adverse effects may
176 include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma
177 potassium, and increases in plasma glucose.

178 <u>Effects on Serum Potassium and Serum Glucose Levels</u>

179 Changes in serum potassium and serum glucose were evaluated in a dose ranging study
180 of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily
181 (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA in COPD patients.
182 At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum
183 potassium ranging from 0 to –0.3 mEq/L were observed in the BROVANA groups with
184 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 Fridericia 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).

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

232 **Tachyphylaxis/ Tolerance**

233 In two placebo-controlled clinical trials in patients with COPD involving approximately
234 725 patients in each, the overall efficacy of BROVANA was maintained throughout the
235 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA
236 was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as
237 measured by FEV_1. FEV_1 improvement at the end of the 12-hour dosing interval
238 decreased by approximately one third (22.1% mean improvement after the first dose
239 compared to 14.6% at week 12). Tolerance to the FEV_1 bronchodilator effect of
240 BROVANA was not accompanied by other clinical manifestations of tolerance in these
241 trials.

242 **CLINICAL TRIALS**

243 **Adult COPD Trials**

244 BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical,
245 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel
246 group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A
247 total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD
248 who had a mean FEV_1 of 1.3 L (42% of predicted) were enrolled in the two clinical trials.
249 The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking
250 history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline
251 FEV1 $\leq$ 65% of predicted value and >0.70 L, and a FEV_1/ forced vital capacity (FVC)
252 ratio $\leq$70%). About 80% of patients in these studies had bronchodilator reversibility,
253 defined as a 10% or greater increase FEV_1 after inhalation of 2 actuations (180 mcg)
254 racemic albuterol from a metered dose inhaler). Both trials compared BROVANA
255 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily
256 (293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation
257 aerosol, 42 mcg twice daily as an active comparator (290 patients).

258 In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater
259 post-dose bronchodilation (as measured by percent change from study baseline FEV_1 at
260 the end of the dosing interval over the 12 weeks of treatment, the primary efficacy
261 endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily,
262 BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient
263 additional benefit on a variety of endpoints, including FEV_1, to support the use of higher
264 doses. Plots of the mean change in FEV_1 values obtained over the 12 hours after dosing
265 for the BROVANA 15 mcg twice daily dose group and for the placebo group are
266 provided in Figures 1 and 2 for Clinical Trial A, below. The plots include mean FEV_1
267 change observed after the first dose and after 12 weeks of treatment. The results from
268 Clinical Trial B were similar.

Figure 1 **Mean Change in FEV_1 Over Time for Clinical Trial A at Week 0 (Day 1)**

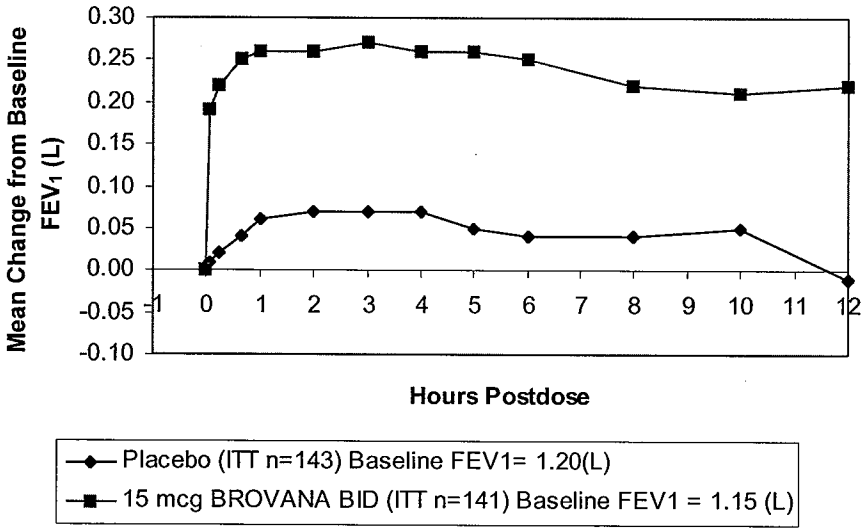


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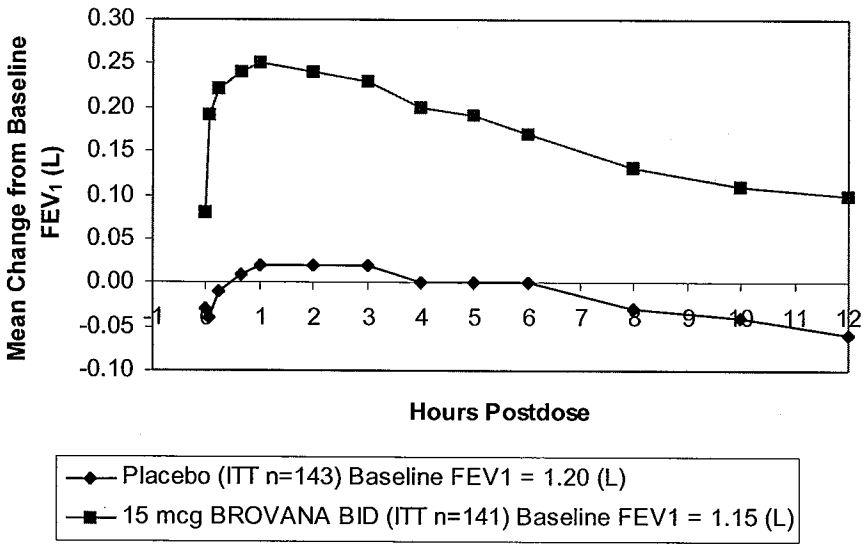
Figure 2 **Mean Change in FEV_1 Over Time for Clinical Trial A at Week 12**



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271 BROVANA 15 mcg twice daily significantly improved bronchodilation compared to
272 placebo over the 12 hours after dosing (FEV_1 $AUC_{0\text{-}12h}$). This improvement was
273 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 FEV_1 increase of 15%, occurred at 6.7 min. When defined as an increase in FEV_1 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 beta$_2$-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 beta$_2$-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 beta$_2$-adrenergic agonists.**
- **BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive**

313 **pulmonary disease (COPD), and is not indicated for the treatment of acute**
314 **episodes of bronchospasm, i.e., rescue therapy.**

315 • **BROVANA should not be initiated in patients with acutely deteriorating COPD,**
316 **which may be a life-threatening condition. The use of BROVANA in this setting**
317 **is inappropriate.**

318 • **BROVANA should not be used in children as the safety and efficacy of**
319 **BROVANA have not been established in pediatric patients.**

320 • **BROVANA should not be used in conjunction with other inhaled, long-acting**
321 **beta$_2$-agonists. BROVANA should not be used with other medications**
322 **containing long-acting beta$_2$-agonists.**

323 • **When beginning treatment with BROVANA, patients who have been taking**
324 **inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day)**
325 **should be instructed to discontinue the regular use of these drugs and use them**
326 **only for symptomatic relief of acute respiratory symptoms.**

327 • **See PRECAUTIONS, Information for Patients and the accompanying**
328 **Medication Guide.**

329 ### Paradoxical Bronchospasm

330 As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm
331 that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA should be
332 discontinued immediately and alternative therapy instituted.

333 ### Deterioration of Disease

334 COPD may deteriorate acutely over a period of hours or chronically over several days or
335 longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the
336 patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs
337 more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of
338 deterioration of disease. In this setting, a re-evaluation of the patient and the COPD
339 treatment regimen should be undertaken at once. Increasing the daily dosage of
340 BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this
341 situation.

342 ### Cardiovascular Effects

343 BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular
344 effect in some patients as measured by increases in pulse rate, blood pressure, and/or
345 symptoms. Although such effects are uncommon after administration of BROVANA at
346 the recommended dose, if they occur, the drug may need to be discontinued. In addition,
347 beta-agonists have been reported to produce ECG changes, such as flattening of the
348 T wave, prolongation of the QTc interval, and ST segment depression. The clinical
349 significance of these findings is unknown. BROVANA, as with other sympathomimetic
350 amines, should be used with caution in patients with cardiovascular disorders, especially
351 coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS,**
352 **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

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-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 beta$_2$-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$_2$-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 beta$_2$-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 though 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 beta$_2$-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, beta$_2$-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 beta$_2$-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 beta$_2$-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 the 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 concomitantly with potent CYP2D6 inhibitors.

Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The 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

433 by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.
434 Although the clinical significance of these effects is not known, caution is advised in the
435 co-administration of beta-agonists with non-potassium sparing diuretics.

436 BROVANA, as with other $beta_2$-agonists, should be administered with extreme caution to
437 patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or
438 drugs known to prolong the QT_c interval because the action of adrenergic agonists on the
439 cardiovascular system may be potentiated by these agents. Drugs that are known to
440 prolong the QT_c interval have an increased risk of ventricular arrhythmias. The
441 concurrent use of intravenously or orally administered methylxanthines (e.g.,
442 aminophylline, theophylline) by patients receiving BROVANA has not been completely
443 evaluated. In two combined 12-week placebo controlled trials that included BROVANA
444 doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873
445 BROVANA -treated subjects received concomitant theophylline at study entry. In a
446 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the
447 528 BROVANA -treated subjects received concomitant theophylline at study entry. In
448 these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and
449 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with
450 the overall population.

451 Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with
452 the effect of each other when administered concurrently. Beta-blockers not only block
453 the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD
454 patients. Therefore, patients with COPD should not normally be treated with beta-
455 blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial
456 infarction, there may be no acceptable alternatives to the use of beta-blockers in patients
457 with COPD. In this setting, cardioselective beta-blockers could be considered, although
458 they should be administered with caution.

459 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

460 Long-term studies were conducted in mice using oral administration and rats using
461 inhalation administration to evaluate the carcinogenic potential of arformoterol.

462 In a 24-month carcinogenicity study in CD-1 mice, arformoterol caused a dose-related
463 increase in the incidence of uterine and cervical endometrial stromal polyps and stromal
464 cell sarcoma in female mice at oral doses of 1 mg/kg and above (AUC exposure
465 approximately 70 times adult exposure at the maximum recommended daily inhalation
466 dose).

467 In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a
468 statistically significant increase in the incidence of thyroid gland c-cell adenoma and
469 carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure
470 approximately 130 times adult exposure at the maximum recommended daily inhalation
471 dose). There were no tumor findings with an inhalation dose of 40 mcg/kg (AUC
472 exposure approximately 55 times adult exposure at the maximum recommended daily
473 inhalation dose).

474 Arformoterol was not mutagenic or clastogenic in the following tests: mutagenicity tests
475 in bacteria, chromosome aberration analyses in mammalian cells, and micronucleus test
476 in mice.

477 Arformoterol had no effects on fertility and reproductive performance in rats at oral doses
478 up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation
479 dose in adults on a mg/m^2 basis).

480 **Pregnancy: Teratogenic Effects**

481 **Pregnancy Category C**

482 Arformoterol has been shown to be teratogenic in rats based upon findings of
483 omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above
484 (AUC exposure approximately 370 times adult exposure at the maximum recommended
485 daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup
486 weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure
487 approximately 1100 times adult exposure at the maximum recommended daily inhalation
488 dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC
489 exposure approximately 2400 times adult exposure at the maximum recommended daily
490 inhalation dose).

491 Arformoterol has been shown to be teratogenic in rabbits based upon findings of
492 malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC
493 exposure approximately 8400 times adult exposure at the maximum recommended daily
494 inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts
495 were observed at doses of 40 mg/kg and above (approximately 22,000 times the
496 maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Malformation
497 including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were
498 observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily
499 inhalation dose in adults on a mg/m^2 basis). Embryolethality was observed at
500 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation
501 dose in adults on a mg/m^2 basis). Decreased pup body weights were observed at doses of
502 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily
503 inhalation dose in adults on a mg/m^2 basis). There were no teratogenic findings in rabbits
504 with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult
505 exposure at the maximum recommended daily inhalation dose).

506 There are no adequate and well-controlled studies in pregnant women. BROVANA
507 should be used during pregnancy only if the potential benefit justifies the potential risk to
508 the fetus.

509 **Use in Labor and Delivery**

510 There are no human studies that have investigated the effects of BROVANA on preterm
511 labor or labor at term.

512 Because beta-agonists may potentially interfere with uterine contractility, BROVANA
513 should be used during labor and delivery only if the potential benefit justifies the
514 potential risk.

515 **Nursing Mothers**

516 In reproductive studies in rats, arformoterol was excreted in the milk. It is not known
517 whether arformoterol is excreted in human milk. Because many drugs are excreted in
518 human milk, caution should be exercised when BROVANA is administered to a nursing
519 woman.

520 **Pediatric**

521 BROVANA is approved for use in the long term maintenance treatment of
522 bronchoconstriction associated with chronic obstructive pulmonary disease, including
523 chronic bronchitis and emphysema. This disease does not occur in children. The safety
524 and effectiveness of BROVANA in pediatric patients have not been established.

525 **Geriatric**

526 Of the 873 patients who received BROVANA in two placebo-controlled clinical studies
527 in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were
528 75 years of age or older. No overall differences in safety or effectiveness were observed
529 between these subjects and younger subjects. Among subjects age 65 years and older,
530 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while
531 the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to
532 $\leq$ 75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg
533 twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively). A higher frequency
534 (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical
535 significance of this finding is not known. Other reported clinical experience has not
536 identified differences in responses between the elderly and younger patients, but greater
537 sensitivity of some older individuals cannot be ruled out.

538 **ADVERSE REACTIONS**

539 **Experience in Adult Patients with COPD**

540 Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were
541 treated with BROVANA (arformoterol tartrate) inhalation solution 15 mcg twice daily
542 and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily
543 were also evaluated. The numbers and percent of patients who reported adverse events
544 were comparable in the 15 mcg twice daily and placebo groups.

545 The following table shows adverse events where the frequency was greater than or equal
546 to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events
547 in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events
548 demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting,
549 hyperkalemia, leukocytosis, nervousness, and tremor.

Table 1: Number of Patients Experiencing Adverse Events from Two 12 Week, Double-Blind, Placebo Controlled Clinical Trials

	BROVANA 15 mcg twice daily		Placebo	
	n	(%)	n	(%)
Total Patients	288	(100)	293	(100)
Pain	23	(8)	16	(5)
Chest Pain	19	(7)	19	(6)
Back Pain	16	(6)	6	(2)
Diarrhea	16	(6)	13	(4)
Sinusitis	13	(5)	11	(4)
Leg Cramps	12	(4)	6	(2)
Dyspnea	11	(4)	7	(2)
Rash	11	(4)	5	(2)
Flu Syndrome	10	(3)	4	(1)
Peripheral Edema	8	(3)	7	(2)
Lung Disorder*	7	(2)	2	(1)

* Reported terms coded to "Lung Disorder" were predominantly pulmonary or chest congestion.

551 Adverse events occurring in patients treated with BROVANA 15 mcg twice daily with a
552 frequency of <2%, but greater than placebo were as follows:

553 **Body as a Whole:** abscess, allergic reaction, digitalis intoxication, fever, hernia, injection
554 site pain, neck rigidity, neoplasm, pelvic pain, retroperitoneal hemorrhage

555 **Cardiovascular**: arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart
556 block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted
557 T-wave

558 **Digestive:** constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal
559 hemorrhage

560 **Metabolic and Nutritional Disorders:** dehydration, edema, glucose tolerance decreased,
561 gout, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia

562 **Musculoskeletal:** arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous
563 contracture

564 **Nervous:** agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis,
565 somnolence, tremor

566 **Respiratory:** carcinoma of the lung, respiratory disorder, voice alteration

567 **Skin and Appendages:** dry skin, herpes simplex, herpes zoster, skin discoloration, skin
568 hypertrophy

569 **Special Senses:** abnormal vision, glaucoma

570 **Urogenital:** breast neoplasm, calcium crystalluria, cystitis, glycosuria, hematuria, kidney
571 calculus, nocturia, PSA increase, pyuria, urinary tract disorder, urine abnormality.

572 Overall, the frequency of all cardiovascular adverse events for BROVANA in the two,
573 placebo controlled trials was low and comparable to placebo (6.9% in BROVANA
574 15 mcg twice daily and 13.3% in the placebo group). There were no frequently occurring
575 specific cardiovascular adverse events for BROVANA (frequency ≥1% and greater than
576 placebo). The rate of COPD exacerbations was also comparable between the
577 BROVANA 15 mcg twice daily and placebo groups, 12.2% and 15.1%, respectively.

578 Other adverse reactions which may occur with selective $beta_2$-adrenoceptor agonists such
579 as BROVANA; include angina, hypertension or hypotension, tachycardia, arrhythmias,
580 nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness,
581 fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

582 **Drug Abuse and Dependence**

583 There were no reported cases of abuse or evidence of drug dependence with the use of
584 BROVANA in the clinical trials.

585 **OVERDOSAGE**

586 The expected signs and symptoms associated with overdosage of BROVANA
587 (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic
588 stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed
589 under **ADVERSE REACTIONS**, e.g., angina, hypertension or hypotension, tachycardia,

590 with rates up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth,
591 palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia,
592 hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic
593 medications, cardiac arrest and even death may be associated with an overdose of
594 BROVANA.

595 Treatment of overdosage consists of discontinuation of BROVANA together with
596 institution of appropriate symptomatic and/or supportive therapy. The judicious use of a
597 cardioselective beta-receptor blocker may be considered, bearing in mind that such
598 medication can produce bronchospasm. There is insufficient evidence to determine if
599 dialysis is beneficial for overdosage of BROVANA. Cardiac monitoring is
600 recommended in cases of overdosage.

601 Clinical signs in dogs included flushing of the body surface and facial area, reddening of
602 the ears and gums, tremor, and increased heart rate. A death was reported in dogs after a
603 single oral dose of 5 mg/kg (approximately 4500 times the maximum recommended daily
604 inhalation dose in adults on a mg/m^2 basis). Death occurred for a rat that received
605 arformoterol at a single inhalation dose of 1600 mcg/kg (approximately 430 times the
606 maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

607 **DOSAGE AND ADMINISTRATION**

608 The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution for
609 COPD patients is 15 mcg administered twice a day (morning and evening) by
610 nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not
611 recommended. BROVANA should be administered by the inhaled route via a standard
612 jet nebulizer connected to an air compressor (see the accompanying **Medication Guide).**
613 BROVANA should not be swallowed. BROVANA should be stored refrigerated in
614 individual unit dose, low-density polyethylene (LDPE) vials sealed in single foil pouches.
615 Vials should be removed from the foil pouches and used immediately after opening.

616 If the recommended maintenance treatment regimen fails to provide the usual response,
617 medical advice should be sought immediately, as this is often a sign of destabilization of
618 COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and
619 additional therapeutic options should be considered.

620 No dose adjustment is required for patients with renal or hepatic impairment. However,
621 since the clearance of BROVANA is prolonged in patients with hepatic impairment, they
622 should be monitored closely.

623 The drug compatibility (physical and chemical), efficacy, and safety of BROVANA
624 when mixed with other drugs in a nebulizer have not been established.

625 The safety and efficacy of BROVANA have been established in clinical trials when
626 administered using the PARI LC PLUS® nebulizers and PARI DURA-NEB® 3000
627 compressors. The safety and efficacy of BROVANA when administered using other
628 nebulizer systems has not been established.

629

HOW SUPPLIED

BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a sterile solution in unit-dose, low-density polyethylene (LDPE) vials individually overwrapped in foil. BROVANA is available in a shelf-carton containing 30 or 60 individually pouched vials.

NDC 63402-911-30: carton of 30 unit-dose individually pouched vials.

NDC 63402-911-60: carton of 60 unit-dose individually pouched vials.

CAUTION: Federal law (U.S.) prohibits dispensing without prescription.

Storage

Store BROVANA in the protective foil pouch under refrigeration at 36°-46°F (2°-8°C). Protect from light and excessive heat. Once the foil pouch is opened, the contents of the vial should be used immediately. Discard any vial if the solution is not colorless. Unopened foil pouches of BROVANA can also be stored at room temperature 68°-77°F, (20°-25°C) for up to 6 weeks. If stored at room temperature, discard if not used after 6 weeks or if past the expiration date, whichever is sooner.

SEPRACOR

Manufactured for:
Sepracor Inc.
Marlborough, MA 01752 USA
For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

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