

1 **BROVANA[®]**
2 **(arformoterol tartrate) Inhalation Solution**
3 **15 mcg*/2 mL**

4 *potency expressed as arformoterol

5

6 **For oral inhalation only**

7

8 **WARNING: ASTHMA RELATED DEATH**

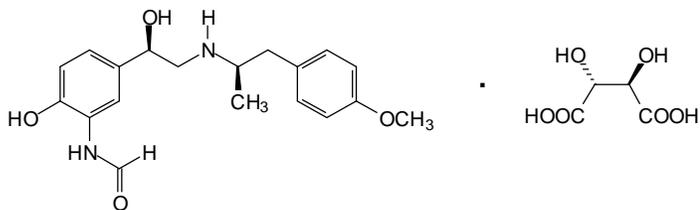
9 **Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related**
10 **death. Data from a large placebo-controlled US study that compared the safety of**
11 **another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual**
12 **asthma therapy showed an increase in asthma-related deaths in patients receiving**
13 **salmeterol. This finding with salmeterol is considered a class effect of LABA,**
14 **including arformoterol, the active ingredient in BROVANA (see [WARNINGS](#)). The**
15 **safety and efficacy of BROVANA in patients with asthma have not been established.**
16 **All LABA, including BROVANA, are contraindicated in patients with asthma**
17 **without use of a long-term asthma control medication (see**
18 **[CONTRAINDICATIONS](#)).**

19

20 **DESCRIPTION**

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

23 Arformoterol is a selective beta₂-adrenergic bronchodilator. The chemical name for
24 arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-
25 (4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-
26 dihydroxybutanedioate (1:1 salt), and its established structural formula is as follows:



27

28 The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula
29 is C₁₉H₂₄N₂O₄ · C₄H₆O₆ (1:1 salt). It is a white to off-white solid that is slightly soluble in
30 water.

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

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

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

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

48

49 **CLINICAL PHARMACOLOGY**

50 **Mechanism of Action**

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

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

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

72 **Animal Pharmacology**

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

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

83 **Pharmacokinetics**

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

88 **Absorption**

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

94 Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients
95 following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or
96 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks.

97 In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation
98 solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil[®]
99 Aerolizer[™]) was administered twice daily for 2 weeks, the accumulation index was
100 approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three
101 treatments. At steady state, geometric means of systemic exposure (AUC_{0-12h}) to
102 (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of
103 formoterol fumarate inhalation powder were 39.33 pg*hr/mL and 33.93 pg*hr/mL,
104 respectively (ratio 1.16; 90% CI 1.00, 1.35), while the geometric means of the C_{max} were
105 4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

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

111 **Distribution**

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

116 **Metabolism**

117 *In vitro* profiling studies in hepatocytes and liver microsomes have shown that
118 arformoterol is primarily metabolized by direct conjugation (glucuronidation) and
119 secondarily by O-demethylation. At least five human uridine
120 diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol
121 glucuronidation *in vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily
122 CYP2C19) catalyze the O-demethylation of arformoterol.

123 Arformoterol did not inhibit CYP1A2, CYP2A6, CYP2C9/10, CYP2C19, CYP2D6,
124 CYP2E1, CYP3A4/5, or CYP4A9/11 enzymes at >1,000-fold higher concentrations than
125 the expected peak plasma concentrations following a therapeutic dose.

126 Arformoterol was almost entirely metabolized following oral administration of 35 mcg of
127 radiolabeled arformoterol in eight healthy subjects. Direct conjugation of arformoterol
128 with glucuronic acid was the major metabolic pathway. Most of the drug-related material
129 in plasma and urine was in the form of glucuronide or sulfate conjugates of arformoterol.
130 O-Desmethylation and conjugates of the O-desmethyl metabolite were relatively minor
131 metabolites accounting for less than 17% of the dose recovered in urine and feces.

132 **Elimination**

133 After administration of a single oral dose of radiolabeled arformoterol to eight healthy
134 male subjects, 63% of the total radioactive dose was recovered in urine and 11% in feces
135 within 48 hours. A total of 89% of the total radioactive dose was recovered within
136 14 days, with 67% in urine and 22% in feces. Approximately 1% of the dose was
137 recovered as unchanged arformoterol in urine over 14 days. Renal clearance was 8.9 L/hr
138 for unchanged arformoterol in these subjects.

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

141 **Special Populations**

142 ***Gender***

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

145 ***Race***

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

149 ***Geriatric***

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

154 ***Pediatric***

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

156 ***Hepatic Impairment***

157 The pharmacokinetic profile of arformoterol was assessed in 24 subjects with mild,
158 moderate, and severe hepatic impairment. The systemic exposure (C_{max} and AUC) to
159 arformoterol increased 1.3 to 2.4-fold in subjects with hepatic impairment compared to
160 16 demographically matched healthy control subjects. No clear relationship between
161 drug exposure and the severity of hepatic impairment was observed. BROVANA should
162 be used cautiously in patients with hepatic impairment.

163 ***Renal Impairment***

164 The impact of renal disease upon the pharmacokinetics of arformoterol was studied in
165 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure
166 (AUC and C_{max}) to arformoterol was similar in renally impaired patients compared with
167 demographically matched healthy control subjects.

168 **Pharmacogenetics**

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

176 **Pharmacodynamics**

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

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

182 Effects on Serum Potassium and Serum Glucose Levels

183 Changes in serum potassium and serum glucose were evaluated in a dose ranging study
184 of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily
185 (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA in COPD patients.
186 At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in serum
187 potassium ranging from 0 to -0.3 mEq/L were observed in the BROVANA groups with
188 similar changes observed after 2 weeks of treatment. Changes in mean serum glucose

189 levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL were observed
190 for BROVANA dose groups at both 2 and 6 hours post dose, both after the first dose and
191 14 days of daily treatment.

192 Electrophysiology

193 The effect of BROVANA on QT interval was evaluated in a dose ranging study
194 following multiple doses of BROVANA 5 mcg, 15 mcg, or 25 mcg twice daily or
195 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with COPD. ECG
196 assessments were performed at baseline, time of peak plasma concentration and
197 throughout the dosing interval. Different methods of correcting for heart rate were
198 employed, including a subject-specific method and the Fridericia method.

199 Relative to placebo, the mean change in subject-specific QT_c averaged over the dosing
200 interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA on cardiac
201 repolarization after 2 weeks of treatment. The maximum mean change in subject-specific
202 QT_c for the BROVANA 15 mcg twice daily dose was 17.3 msec, compared with
203 15.4 msec in the placebo group. No apparent correlation of QT_c with arformoterol
204 plasma concentration was observed.

205 **Electrocardiographic Monitoring in Patients with COPD**

206 The effect of different doses of BROVANA on cardiac rhythm was assessed using
207 24-hour Holter monitoring in two 12-week double-blind, placebo-controlled studies of
208 1,456 patients with COPD (873 received BROVANA at 15 or 25 mcg twice daily or
209 50 mcg once daily doses; 293 received placebo; 290 received salmeterol). The 24-hour
210 Holter monitoring occurred once at baseline, and up to 3 times during the 12-week
211 treatment period. The rates of new-onset cardiac arrhythmias not present at baseline over
212 the double-blind 12-week treatment period were similar (approximately 33-34%) for
213 patients who received BROVANA 15 mcg twice daily to those who received placebo.
214 There was a dose-related increase in new, treatment emergent arrhythmias seen in
215 patients who received BROVANA 25 mcg twice daily and 50 mcg once daily, 37.6% and
216 40.1 %, respectively. The frequencies of new treatment emergent events of non-
217 sustained (3-10 beat run) and sustained (>10 beat run) ventricular tachycardia were 7.4%
218 and 1.1% in BROVANA 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients
219 who received BROVANA 25 mcg twice daily and 50 mcg once daily the frequencies of
220 non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0%
221 and 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported
222 as adverse events (1 in BROVANA 15 mcg twice daily and 4 in placebo), with two of
223 these events leading to discontinuation of treatment (2 in placebo).

224 There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour
225 Holter monitoring in patients treated with BROVANA 15 mcg twice daily or placebo.
226 New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of patients who
227 received BROVANA 15 mcg twice daily and 0.3% of patients who received placebo.
228 There was a dose-related increase in the frequency of atrial fibrillation/ flutter reported in
229 the BROVANA 25 mcg twice daily and 50 mcg once daily dose groups of 0.7% and
230 1.4%, respectively. Two cases of atrial fibrillation/ flutter were reported as adverse
231 events (1 in BROVANA 15 mcg twice daily and 1 in placebo).

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

236 **Tachyphylaxis/ Tolerance**

237 In two placebo-controlled clinical trials in patients with COPD involving approximately
238 725 patients in each, the overall efficacy of BROVANA was maintained throughout the
239 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA
240 was observed after 6 weeks of dosing, evidenced by a decrease in bronchodilator effect as
241 measured by FEV₁. FEV₁ improvement at the end of the 12-hour dosing interval
242 decreased by approximately one third (22.1% mean improvement after the first dose
243 compared to 14.6% at week 12). Tolerance to the FEV₁ bronchodilator effect of
244 BROVANA was not accompanied by other clinical manifestations of tolerance in these
245 trials.

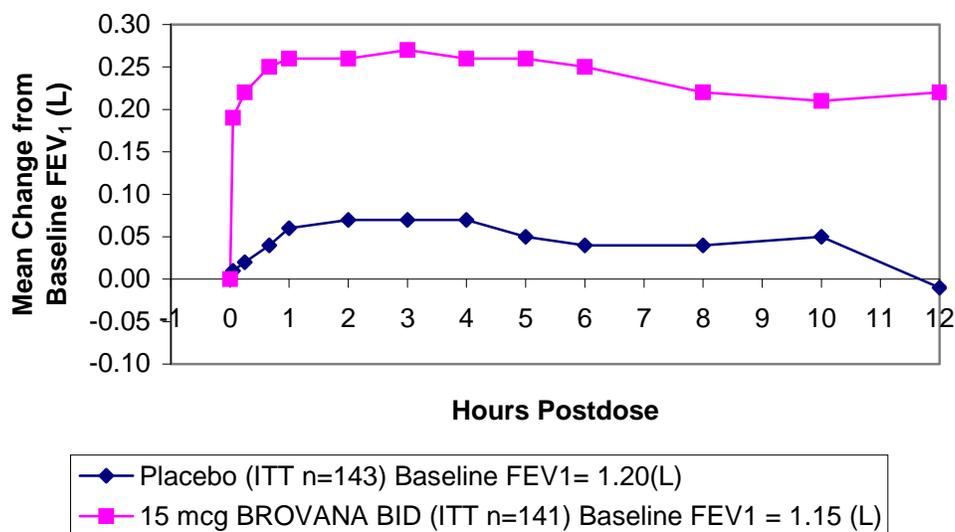
246 **CLINICAL TRIALS**

247 **Adult COPD Trials**

248 BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical,
249 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel
250 group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A
251 total of 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years) with COPD
252 who had a mean FEV₁ of 1.3 L (42% of predicted) were enrolled in the two clinical trials.
253 The diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking
254 history (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline
255 FEV₁ ≤ 65% of predicted value and >0.70 L, and a FEV₁/ forced vital capacity (FVC)
256 ratio ≤70%). About 80% of patients in these studies had bronchodilator reversibility,
257 defined as a 10% or greater increase FEV₁ after inhalation of 2 actuations (180 mcg
258 racemic albuterol from a metered dose inhaler). Both trials compared BROVANA
259 15 mcg twice daily (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily
260 (293 patients) with placebo (293 subjects). Both trials included salmeterol inhalation
261 aerosol, 42 mcg twice daily as an active comparator (290 patients).

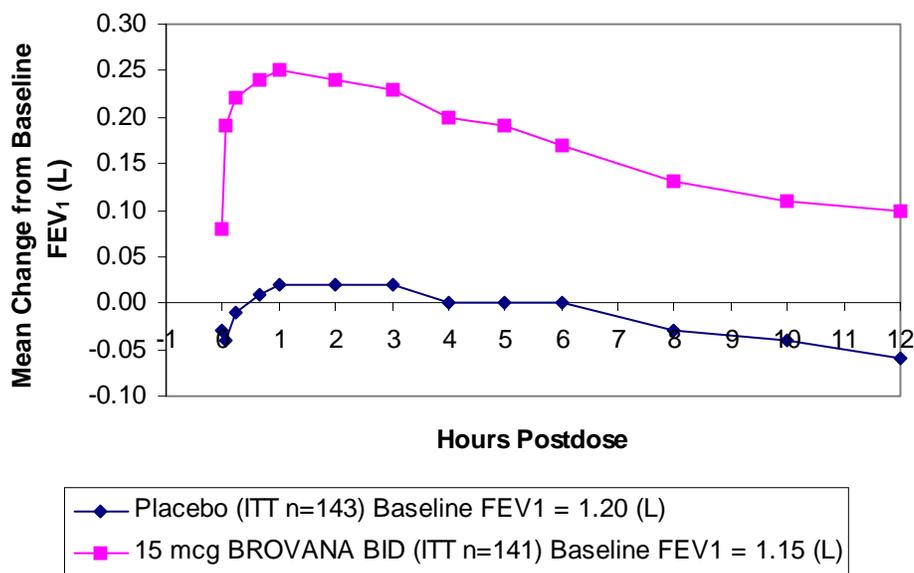
262 In both 12-week trials, BROVANA 15 mcg twice daily resulted in significantly greater
263 post-dose bronchodilation (as measured by percent change from study baseline FEV₁ at
264 the end of the dosing interval over the 12 weeks of treatment, the primary efficacy
265 endpoint) compared to placebo. Compared to BROVANA 15 mcg twice daily,
266 BROVANA 25 mcg twice daily and 50 mcg once daily did not provide sufficient
267 additional benefit on a variety of endpoints, including FEV₁, to support the use of higher
268 doses. Plots of the mean change in FEV₁ values obtained over the 12 hours after dosing
269 for the BROVANA 15 mcg twice daily dose group and for the placebo group are
270 provided in [Figures 1](#) and [2](#) for Clinical Trial A, below. The plots include mean FEV₁
271 change observed after the first dose and after 12 weeks of treatment. The results from
272 Clinical Trial B were similar.

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



273

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



274

275 BROVANA 15 mcg twice daily significantly improved bronchodilation compared to
 276 placebo over the 12 hours after dosing (FEV₁ AUC_{0-12h}). This improvement was
 277 maintained over the 12 week study period.

278 Following the first dose of BROVANA 15 mcg, the median time to onset of
279 bronchodilation, defined by an FEV₁ increase of 15%, occurred at 6.7 min. When
280 defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation
281 was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours
282 of dosing.

283 In both clinical trials, compared to placebo, patients treated with BROVANA
284 demonstrated improvements in peak expiratory flow rates, supplemental ipratropium and
285 rescue albuterol use.

286 **INDICATIONS AND USAGE**

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

291 **CONTRAINDICATIONS**

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

295 All LABA, including BROVANA, are contraindicated in patients with asthma without
296 use of a long-term asthma control medication (see WARNINGS).

297 **WARNINGS**

298 • **ASTHMA RELATED DEATH**

299 **Long-acting beta₂-adrenergic agonists increase the risk of asthma-related death.**
300 **The safety and efficacy of BROVANA in patients with asthma have not been**
301 **established. All LABA, including BROVANA, are contraindicated in patients**
302 **with asthma without use of a long-term asthma control medication (see**
303 **CONTRAINDICATIONS).**

304 ○ A 28-week, placebo-controlled US study comparing the safety of salmeterol
305 with placebo, each added to usual asthma therapy, showed an increase in
306 asthma-related deaths in patients receiving salmeterol (13/13,176 in patients
307 treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37,
308 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered
309 a class effect of the long-acting beta₂-adrenergic agonists, including
310 BROVANA. No study adequate to determine whether the rate of asthma
311 related death is increased in patients treated with BROVANA has been
312 conducted.

313 Clinical studies with racemic formoterol (Foradil[®] Aerolizer[™]) suggested a
314 higher incidence of serious asthma exacerbations in patients who received
315 racemic formoterol than in those who received placebo. The sizes of these studies
316 were not adequate to precisely quantify the differences in serious asthma
317 exacerbation rates between treatment groups.

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

339 **Paradoxical Bronchospasm**

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

343 **Deterioration of Disease**

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

352 **Cardiovascular Effects**

353 BROVANA, like other beta₂-agonists, can produce a clinically significant cardiovascular
354 effect in some patients as measured by increases in pulse rate, blood pressure, and/or
355 symptoms. Although such effects are uncommon after administration of BROVANA at
356 the recommended dose, if they occur, the drug may need to be discontinued. In addition,
357 beta-agonists have been reported to produce ECG changes, such as flattening of the

358 T wave, prolongation of the QT_c interval, and ST segment depression. The clinical
359 significance of these findings is unknown. BROVANA, as with other sympathomimetic
360 amines, should be used with caution in patients with cardiovascular disorders, especially
361 coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS,**
362 **General**).

363 **Immediate Hypersensitivity Reactions**

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

367 **Do Not Exceed Recommended Dose**

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

372 **PRECAUTIONS**

373 **General**

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

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

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

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

398 **Information for Patients**

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

- 402 1. Patients should be informed that long-acting beta₂-adrenergic agonists, such as
403 BROVANA, increase the risk of asthma-related death. All LABA, including
404 BROVANA, should not be used in patients with asthma without use of a long-
405 term asthma control medication (see [CONTRAINDICATIONS](#)).
- 406 2. BROVANA is not indicated to relieve acute respiratory symptoms and extra
407 doses should not be used for that purpose. Acute symptoms should be treated
408 with an inhaled, short-acting, beta₂-agonist (the health-care provider should
409 prescribe the patient with such medication and instruct the patient in how it
410 should be used). Patients should be instructed to seek medical attention if their
411 symptoms worsen, if BROVANA treatment becomes less effective, or if they
412 need more inhalations of a short-acting beta₂-agonist than usual. Patients should
413 not inhale more than one dose at any one time. The daily dosage of BROVANA
414 should not exceed one ready-to-use vial (15 mcg) by inhalation twice daily
415 (30 mcg total daily dose).
- 416 3. Patients should be informed that treatment with beta₂-agonists may lead to
417 adverse events which include palpitations, chest pain, rapid heart rate, tremor, or
418 nervousness.
- 419 4. Patients should be instructed to use BROVANA by nebulizer only and not to
420 inject or swallow this inhalation solution.
- 421 5. Patients should protect BROVANA ready-to-use vials from light and excessive
422 heat. The protective foil pouches should be stored under refrigeration between
423 2°C and 8°C (36°–46°F). They should not be used after the expiration date
424 stamped on the container. After opening the pouch, unused ready-to-use vials
425 should be returned to, and stored in, the pouch. An opened ready-to-use vial
426 should be used right away. Discard any ready-to-use vial if the solution is not
427 colorless.
- 428 6. The drug compatibility (physical and chemical), efficacy and safety of
429 BROVANA when mixed with other drugs in a nebulizer have not been
430 established.
- 431 7. Women should be advised to contact their physician if they become pregnant or if
432 they are nursing.
- 433 8. It is important that patients understand how to use BROVANA appropriately and
434 how it should be used in relation to other medications to treat COPD they are
435 taking (see the accompanying [Medication Guide](#) and the [Instructions for Using](#)
436 [BROVANA](#)).

437 **Drug Interactions**

438 If additional adrenergic drugs are to be administered by any route, they should be used
439 with caution because the pharmacologically predictable sympathetic effects of
440 BROVANA may be potentiated.

441 When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA
442 at steady-state, exposure to either drug was not altered. Dosage adjustments of
443 BROVANA are not necessary when the drug is given concomitantly with potent
444 CYP2D6 inhibitors.

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

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

452 BROVANA, as with other beta₂-agonists, should be administered with extreme caution to
453 patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or
454 drugs known to prolong the QT_c interval because the action of adrenergic agonists on the
455 cardiovascular system may be potentiated by these agents. Drugs that are known to
456 prolong the QT_c interval have an increased risk of ventricular arrhythmias. The
457 concurrent use of intravenously or orally administered methylxanthines (e.g.,
458 aminophylline, theophylline) by patients receiving BROVANA has not been completely
459 evaluated. In two combined 12-week placebo controlled trials that included BROVANA
460 doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873
461 BROVANA -treated subjects received concomitant theophylline at study entry. In a
462 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the
463 528 BROVANA -treated subjects received concomitant theophylline at study entry. In
464 these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and
465 6-8 mm Hg higher, respectively, in subjects on concomitant theophylline compared with
466 the overall population.

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

475 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

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

493 Arformoterol had no effects on fertility and reproductive performance in rats at oral doses
494 up to 10 mg/kg (approximately 2700 times the maximum recommended daily inhalation
495 dose in adults on a mg/m² basis).

496 **Pregnancy: Teratogenic Effects**

497 *Pregnancy Category C*

498 Arformoterol has been shown to be teratogenic in rats based upon findings of
499 omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above
500 (AUC exposure approximately 370 times adult exposure at the maximum recommended
501 daily inhalation dose). Increased pup loss at birth and during lactation and decreased pup
502 weights were observed in rats at oral doses of 5 mg/kg and above (AUC exposure
503 approximately 1100 times adult exposure at the maximum recommended daily inhalation
504 dose). Delays in development were evident with an oral dose of 10 mg/kg (AUC
505 exposure approximately 2400 times adult exposure at the maximum recommended daily
506 inhalation dose).

507 Arformoterol has been shown to be teratogenic in rabbits based upon findings of
508 malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC
509 exposure approximately 8400 times adult exposure at the maximum recommended daily
510 inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts
511 were observed at doses of 40 mg/kg and above (approximately 22,000 times the
512 maximum recommended daily inhalation dose in adults on a mg/m² basis). Malformation
513 including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were
514 observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily
515 inhalation dose in adults on a mg/m² basis). Embryoletality was observed at
516 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation
517 dose in adults on a mg/m² basis). Decreased pup body weights were observed at doses of
518 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily
519 inhalation dose in adults on a mg/m² basis). There were no teratogenic findings in rabbits

520 with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult
521 exposure at the maximum recommended daily inhalation dose).

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

525 **Use in Labor and Delivery**

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

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

531 **Nursing Mothers**

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

536 **Pediatric**

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

541 **Geriatric**

542 Of the 873 patients who received BROVANA in two placebo-controlled clinical studies
543 in adults with COPD, 391 (45%) were 65 years of age or older while 96 (11%) were
544 75 years of age or older. No overall differences in safety or effectiveness were observed
545 between these subjects and younger subjects. Among subjects age 65 years and older,
546 129 (33%) received BROVANA at the recommended dose of 15 mcg twice daily, while
547 the remainder received higher doses. ECG alerts for ventricular ectopy in patients 65 to
548 \leq 75 years of age were comparable among patients receiving 15 mcg twice daily, 25 mcg
549 twice daily, and placebo (3.9%, 5.2%, and 7.1%, respectively). A higher frequency
550 (12.4%) was observed when BROVANA was dosed at 50 mcg once daily. The clinical
551 significance of this finding is not known. Other reported clinical experience has not
552 identified differences in responses between the elderly and younger patients, but greater
553 sensitivity of some older individuals cannot be ruled out.

554 **ADVERSE REACTIONS**

555 **Experience in Adult Patients with COPD**

556 Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were
557 treated with BROVANA (arformoterol tartrate) Inhalation Solution 15 mcg twice daily
558 and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily

559 were also evaluated. The numbers and percent of patients who reported adverse events
560 were comparable in the 15 mcg twice daily and placebo groups.

561 The following table shows adverse events where the frequency was greater than or equal
562 to 2% in the BROVANA 15 mcg twice daily group and where the rates of adverse events
563 in the BROVANA 15 mcg twice daily group exceeded placebo. Ten adverse events
564 demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting,
565 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.

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

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

571 **Cardiovascular:** arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart
572 block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted
573 T-wave

574 **Digestive:** constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal
575 hemorrhage

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

578 **Musculoskeletal:** arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous
579 contracture

580 **Nervous:** agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis,
581 somnolence, tremor

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

583 **Skin and Appendages:** dry skin, herpes simplex, herpes zoster, skin discoloration, skin
584 hypertrophy

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

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

588 Overall, the frequency of all cardiovascular adverse events for BROVANA in the two
589 placebo controlled trials was low and comparable to placebo (6.9% in BROVANA
590 15 mcg twice daily and 13.3% in the placebo group). There were no frequently occurring
591 specific cardiovascular adverse events for BROVANA (frequency $\geq 1\%$ and greater than
592 placebo). The rate of COPD exacerbations was also comparable between the
593 BROVANA 15 mcg twice daily and placebo groups, 12.2% and 15.1%, respectively.

594 Other adverse reactions which may occur with selective beta₂-adrenoceptor agonists such
595 as BROVANA include: angina, hypertension or hypotension, tachycardia, arrhythmias,
596 nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness,
597 fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

598 **Drug Abuse and Dependence**

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

601 **OVERDOSAGE**

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

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

611 Treatment of overdose consists of discontinuation of BROVANA together with
612 institution of appropriate symptomatic and/or supportive therapy. The judicious use of a
613 cardioselective beta-receptor blocker may be considered, bearing in mind that such
614 medication can produce bronchospasm. There is insufficient evidence to determine if
615 dialysis is beneficial for overdose of BROVANA. Cardiac monitoring is
616 recommended in cases of overdose.

617 Clinical signs in dogs included flushing of the body surface and facial area, reddening of
618 the ears and gums, tremor, and increased heart rate. A death was reported in dogs after a
619 single oral dose of 5 mg/kg (approximately 4500 times the maximum recommended daily
620 inhalation dose in adults on a mg/m² basis). Death occurred for a rat that received
621 arformoterol at a single inhalation dose of 1600 mcg/kg (approximately 430 times the
622 maximum recommended daily inhalation dose in adults on a mg/m² basis).

623 **DOSAGE AND ADMINISTRATION**

624 The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution for
625 COPD patients is 15 mcg administered twice a day (morning and evening) by
626 nebulization. A total daily dose greater than 30 mcg (15 mcg twice daily) is not
627 recommended. BROVANA should be administered by the inhaled route via a standard
628 jet nebulizer connected to an air compressor (see the accompanying **Medication Guide**).
629 BROVANA should not be swallowed. BROVANA[®] should be stored refrigerated in foil
630 pouches. After opening the pouch, unused ready-to-use vials should be returned to, and
631 stored in, the pouch. An opened ready-to-use vial should be used right away.

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

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

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

641 The safety and efficacy of BROVANA have been established in clinical trials when
642 administered using the PARI LC PLUS[®] nebulizers and PARI DURA-NEB[®] 3000
643 compressors. The safety and efficacy of BROVANA when administered using other
644 nebulizer systems has not been established.

645

646 **HOW SUPPLIED**

647 BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength
648 (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a
649 sterile solution in low-density polyethylene (LDPE) ready-to-use vials overwrapped in
650 foil. BROVANA is available in a shelf-carton containing 30 or 60 ready-to-use vials.

651 NDC 63402-911-30: carton of 30 individually pouched ready-to-use vials.

652 NDC 63402-911-64: carton of 60 ready-to-use vials (15×4 ready-to-use vial pouches).

653

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

655 **Storage**

656 Store BROVANA in the protective foil pouch under refrigeration at 36°-46°F (2°-8°C).

657 Protect from light and excessive heat. After opening the pouch, unused ready-to-use
658 vials should be returned to, and stored in, the pouch. An opened ready-to-use vial should
659 be used right away. Discard any ready-to-use vial if the solution is not colorless.

660 Unopened foil pouches of BROVANA can also be stored at room temperature 68°-77°F,
661 (20°-25°C) for up to 6 weeks. If stored at room temperature, discard if not used after
662 6 weeks or if past the expiration date, whichever is sooner.

663



664

665 Manufactured for:

666 **Sepracor Inc.**

667 Marlborough, MA 01752 USA

668 For customer service, call 1-888-394-7377.

669 To report adverse events, call 1-877-737-7226.

670 For medical information, call 1-800-739-0565.

671

672 Month Year

673 901005R0X