

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BROVANA® (arformoterol tartrate) Inhalation Solution safely and effectively. See full prescribing information for BROVANA Inhalation Solution.

BROVANA® (arformoterol tartrate) Inhalation Solution
Initial U.S. Approval: 2006

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. (5.1)
- A placebo-controlled study with another long-acting beta₂-adrenergic agonist (salmeterol) showed an increase in asthma related deaths in patients receiving salmeterol. (5.1)
- The finding of an increase in the risk of asthma-related deaths with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA Inhalation Solution. The safety and efficacy of BROVANA Inhalation Solution in patients with asthma have not been established. All LABA, including BROVANA Inhalation Solution, are contraindicated in patients with asthma without use of a long-term asthma control medication. (4, 5.1)

INDICATIONS AND USAGE

BROVANA Inhalation Solution is a long-acting beta₂-adrenergic agonist (beta₂-agonist) indicated for:

- Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. (1.1)

Important limitations of use:

- BROVANA Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease. (1.2, 5.2)
- BROVANA Inhalation Solution is not indicated to treat asthma. (1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- A total daily dose of greater than 30 mcg is not recommended
- One 15 mcg/2mL vial every 12 hours (2)
- For use with a standard jet nebulizer (with a face mask or mouth piece) connected to an air compressor (2)

DOSAGE FORMS AND STRENGTHS

Inhalation Solution (unit dose vial for nebulization): 15 mcg/2mL solution (3)

CONTRAINDICATIONS

BROVANA Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product. (4)

All LABA, including BROVANA Inhalation Solution, are contraindicated in patients with asthma without use of a long-term asthma control medication. (4)

WARNINGS AND PRECAUTIONS

- Do not initiate BROVANA Inhalation Solution in acutely deteriorating patients. (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting beta₂-agonists can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use of BROVANA Inhalation Solution, or use in conjunction with other medications containing long acting beta₂-agonists, can result in clinically significant cardiovascular effects, and may be fatal. (5.3, 5.5)
- Life-threatening paradoxical bronchospasm can occur. Discontinue BROVANA Inhalation Solution immediately. (5.4)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or with sensitivity to sympathomimetic drugs. (5.6, 5.7)

ADVERSE REACTIONS

Most common adverse reactions (≥2% incidence and more common than placebo) are pain, chest pain, back pain, diarrhea, sinusitis, leg cramps, dyspnea, rash, flu syndrome, peripheral edema and lung disorder. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact (Sunovion Pharmaceuticals, Inc) at 1-877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Other adrenergic drugs may potentiate effect. Use with caution. (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (5.7, 7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants and drugs that prolong the QTc interval may potentiate effect on the cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness. May block bronchodilatory effects of beta-agonists. Use with caution and only when medically necessary. (7.5)

USE IN SPECIAL POPULATIONS

- Hepatic Impairment
Use with caution in patients with hepatic impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

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FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ASTHMA-RELATED DEATH

- 1 INDICATIONS AND USAGE**
 - 1.1 Maintenance Treatment of COPD
 - 1.2 Important Limitations of Use
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Asthma-Related Deaths
 - 5.2 Deterioration of Disease and Acute Episodes
 - 5.3 Excessive Use of Brovana Inhalation Solution and Use with Other Long-Acting Beta₂-Agonists
 - 5.4 Paradoxical Bronchospasm
 - 5.5 Cardiovascular Effects
 - 5.6 Coexisting Conditions
 - 5.7 Hypokalemia and Hyperglycemia
 - 5.8 Immediate Hypersensitivity Reactions
- 6 ADVERSE REACTIONS**
 - 6.1 Beta₂-Agonist Adverse Reaction Profile
 - 6.2 Clinical Trials Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Adrenergic Drugs
 - 7.2 Xanthine Derivatives, Steroids or Diuretics
 - 7.3 Non-potassium Sparing Diuretics
 - 7.4 MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs
 - 7.5 Beta-Blockers

- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Hepatic Impairment
 - 8.7 Renal Impairment
- 9 DRUG ABUSE AND DEPENDENCE**
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
 - 12.4 Pharmacogenetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES**
 - 14.1 Adult COPD Trials
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**
2

3 **WARNING: ASTHMA RELATED DEATH**

4 Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a
5 large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic
6 agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related
7 deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA,
8 including arformoterol, the active ingredient in BROVANA Inhalation Solution [see WARNINGS AND
9 PRECAUTIONS (5.1)]. The safety and efficacy of BROVANA Inhalation Solution in patients with
10 asthma have not been established. All LABA, including BROVANA Inhalation Solution, are
11 contraindicated in patients with asthma without use of a long-term asthma control medication [see
12 CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1)].

13
14 **1 INDICATIONS AND USAGE**

15 **1.1 Maintenance Treatment of COPD**

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

20 **1.2 Important Limitations of Use**

21 BROVANA Inhalation Solution is not indicated to treat acute deteriorations of
22 chronic obstructive pulmonary disease [see *WARNINGS AND PRECAUTIONS (5.2)*]

23 BROVANA Inhalation Solution is not indicated to treat asthma. The safety and
24 effectiveness of BROVANA Inhalation Solution in asthma have not been established.
25

26 **2 DOSAGE AND ADMINISTRATION**

27 The recommended dose of BROVANA (arformoterol tartrate) Inhalation Solution is
28 one 15 mcg unit-dose vial administered twice daily (morning and evening) by nebulization.
29 A total daily dose of greater than 30 mcg (15 mcg twice daily) is not recommended.

30 BROVANA Inhalation Solution should be administered by the orally inhaled route
31 via a standard jet nebulizer connected to an air compressor (see the accompanying
32 **Medication Guide**). BROVANA Inhalation Solution should not be swallowed.
33 BROVANA Inhalation Solution should be stored refrigerated in foil pouches. After opening
34 the pouch, unused unit-dose vials should be returned to, and stored in, the pouch. An opened
35 unit-dose vial should be used right away.

36 If the recommended maintenance treatment regimen fails to provide the usual
37 response, medical advice should be sought immediately, as this is often a sign of
38 destabilization of COPD. Under these circumstances, the therapeutic regimen should be
39 reevaluated and additional therapeutic options should be considered.

40 No dose adjustment is required for patients with renal or hepatic impairment.
41 However, since the clearance of BROVANA Inhalation Solution is prolonged in patients
42 with hepatic impairment, they should be monitored closely.

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

45 The safety and efficacy of BROVANA Inhalation Solution have been established in
46 clinical trials when administered using the PARI LC[®] Plus nebulizer (with a facemask or
47 mouth piece) and the PARI DURA NEB[™] 3000 compressor. The safety and efficacy of
48 BROVANA Inhalation Solution delivered from non-compressor based nebulizer systems
49 have not been established.

51 **3 DOSAGE FORMS AND STRENGTHS**

52 BROVANA (arformoterol tartrate) Inhalation Solution is supplied as a sterile solution
53 for nebulization in low-density polyethylene unit-dose vials. Each 2 mL vial contains 15 mcg
54 of arformoterol equivalent to 22 mcg of arformoterol tartrate.

56 **4 CONTRAINDICATIONS**

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

60 All LABA, including BROVANA Inhalation Solution, are contraindicated in patients
61 with asthma without use of a long-term asthma control medication [see *WARNINGS AND*
62 *PRECAUTIONS (5)*].

64 **5 WARNINGS AND PRECAUTIONS**

65 **5.1 Asthma-Related Deaths** [see *BOXED WARNING*]

66 Data from a large placebo-controlled study in asthma patients showed that long-
67 acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. This
68 finding is considered a class effect of LABA, including arformoterol, the active ingredient in
69 BROVANA Inhalation Solution. The safety and efficacy of BROVANA Inhalation Solution
70 in patients with asthma have not been established. All LABA, including BROVANA
71 Inhalation Solution, are contraindicated in patients with asthma without use of a long-term
72 asthma control medication [see *CONTRAINDICATIONS (4)*]. Data are not available to
73 determine whether the rate of deaths in patients with COPD is increased by long-acting beta₂-
74 adrenergic agonists.

75 A 28-week, placebo-controlled US study comparing the safety of salmeterol with
76 placebo, each added to usual asthma therapy, showed an increases in asthma-related deaths in
77 patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in
78 patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-
79 related death is considered a class effect of the long-acting beta₂-adrenergic agonists,
80 including BROVANA Inhalation Solution. No study adequate to determine whether the rate
81 of asthma related death is increased in patients treated with BROVANA Inhalation Solution
82 has been conducted.

83 Clinical studies with racemic formoterol suggested a higher incidence of serious
84 asthma exacerbations in patients who received racemic formoterol than in those who received
85 placebo. The sizes of these studies were not adequate to precisely quantify the differences in
86 serious asthma exacerbation rates between treatment groups.

87 **5.2 Deterioration of Disease and Acute Episodes**

88 BROVANA Inhalation Solution should not be initiated in patients with acutely
89 deteriorating COPD, which may be a life-threatening condition. The use of BROVANA
90 Inhalation Solution in this setting is inappropriate.

91 BROVANA Inhalation Solution is not indicated for the treatment of acute episodes of
92 bronchospasm, i.e., as rescue therapy and extra doses should not be used for that purpose.
93 Acute symptoms should be treated with an inhaled short-acting beta₂-agonist.

94 When beginning BROVANA Inhalation Solution, patients who have been taking
95 inhaled short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be
96 instructed to discontinue the regular use of these drugs and use them only for symptomatic
97 relief of acute respiratory symptoms. When prescribing BROVANA Inhalation Solution, the
98 healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct
99 the patient how it should be used. Increasing inhaled beta₂-agonist use is a signal of
100 deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate
101 acutely over a period of hours or chronically over several days or longer. If BROVANA
102 Inhalation Solution no longer controls the symptoms of bronchoconstriction, or the patient's
103 inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more
104 inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of
105 disease. In this setting, a reevaluation of the patient and the COPD treatment regimen should
106 be undertaken at once. Increasing the daily dosage of BROVANA Inhalation Solution
107 beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

108 **5.3 Excessive Use of BROVANA Inhalation Solution and Use with Other Long- 109 Acting Beta₂-Agonists**

110 Fatalities have been reported in association with excessive use of inhaled
111 sympathomimetic drugs. As with other inhaled beta₂-adrenergic drugs, BROVANA
112 Inhalation Solution should not be used more often, at higher doses than recommended, or in
113 conjunction with other medications containing long-acting beta₂-agonists.

114 **5.4 Paradoxical Bronchospasm**

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

119 **5.5 Cardiovascular Effects**

120 BROVANA Inhalation Solution, like other beta₂-agonists, can produce a clinically
121 significant cardiovascular effect in some patients as measured by increases in pulse rate,
122 systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, the drug may
123 need to be discontinued. In addition, beta-agonists have been reported to produce ECG
124 changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment
125 depression. The clinical significance of these findings is unknown. BROVANA Inhalation
126 Solution, as with other sympathomimetic amines, should be used with caution in patients
127 with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and
128 hypertension.

129 **5.6 Coexisting Conditions**

130 BROVANA Inhalation Solution, like other sympathomimetic amines, should be used
131 with caution in patients with cardiovascular disorders, especially coronary insufficiency,
132 cardiac arrhythmias, and hypertension; in patients with convulsive disorders or
133 thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. In
134 two pooled 12 week placebo controlled trials investigating BROVANA Inhalation Solution
135 doses of 15 µg BID, 25 µg BID, and 50 µg QD, changes in mean predose and 2-hour post
136 dose systolic and/or diastolic blood pressure were seen as a general fall of 2 – 4 mm/Hg; for

137 pulse rate the mean of maximal increases were 8.8 – 12.0 beats/min Over the course of a one
138 year study measuring serial electrocardiograms while receiving a dose of 50 mcg daily of
139 BROVANA Inhalation Solution resulted in an approximately 3.0 ms increase in QTC_{C-F}
140 compared to the active comparator, salmeterol. Doses of the related beta₂-agonist albuterol,
141 when administered intravenously, have been reported to aggravate preexisting diabetes
142 mellitus and ketoacidosis.

143 **5.7 Hypokalemia and Hyperglycemia**

144 Beta-agonist medications may produce significant hypokalemia in some patients,
145 possibly through intracellular shunting, which has the potential to produce adverse
146 cardiovascular effects [see *CLINICAL PHARMACOLOGY (12.2)*]. The decrease in serum
147 potassium is usually transient, not requiring supplementation. Beta-agonist medications may
148 produce transient hyperglycemia in some patients.

149 Clinically significant and dose-related changes in serum potassium and blood glucose
150 were infrequent during clinical trials with long-term administration of BROVANA Inhalation
151 Solution at the recommended dose.

152 **5.8 Immediate Hypersensitivity Reactions**

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

156

157 **6 ADVERSE REACTIONS**

158 **Long acting beta₂-adrenergic agonists increase the risk of asthma-related death**
159 **[See *BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)*].**

160 **6.1 Beta₂-Agonist Adverse Reaction Profile**

161 Adverse reactions to BROVANA Inhalation Solution are expected to be similar in
162 nature to other beta₂-adrenergic receptor agonists including: angina, hypertension or
163 hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth,
164 palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia,
165 metabolic acidosis and insomnia.

166 **6.2 Clinical Trials Experience**

167 Because clinical trials are conducted under widely varying conditions, adverse
168 reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the
169 clinical trials of another drug and may not reflect the rates observed in clinical practice.

170 The safety data described below for adults ≥35 years of age are based on 2 clinical
171 trials of 12 weeks. In the 2 trials of 12 weeks duration, 1456 patients (860 males and 596
172 females, ages 34 to 89 years old) with COPD were treated with BROVANA Inhalation
173 Solution 15 mcg twice daily, 25 mcg twice daily, 50 mcg once daily, Salmeterol 42 mcg
174 twice daily, or placebo. The racial/ethnic distribution in these two trials included 1383
175 Caucasians, 49 Blacks, 10 Asians, and 10 Hispanics, and 4 patients classified as Other.

176 Adults with COPD

177 Among 1,456 COPD patients in two 12-week, placebo-controlled trials, 288 were
178 treated with BROVANA Inhalation Solution 15 mcg twice daily and 293 were treated with
179 placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated.

180 Table 1 shows adverse reaction rates among patients from these two trials where the
181 frequency was greater than or equal to 2% in the BROVANA Inhalation Solution 15 mcg
182 twice daily group and where the rate in the BROVANA Inhalation Solution 15 mcg twice

183 daily group exceeded the rate in the placebo group. The total number and percent of patients
 184 who reported adverse events were 202 (70%) in the 15 mcg twice daily and 219 (75%) in the
 185 placebo groups. Ten adverse events demonstrated a dose relationship: asthenia, fever,
 186 bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor.
 187
 188
 189
 190

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.

191

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

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

196 **Cardiovascular:** arteriosclerosis, atrial flutter, AV block, congestive heart failure, heart
197 block, myocardial infarct, QT interval prolonged, supraventricular tachycardia, inverted T-
198 wave

199 **Digestive:** constipation, gastritis, melena, oral moniliasis, periodontal abscess, rectal
200 hemorrhage

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

203 **Musculoskeletal:** arthralgia, arthritis, bone disorder, rheumatoid arthritis, tendinous
204 contracture

205 **Nervous:** agitation, cerebral infarct, circumoral paresthesia, hypokinesia, paralysis,
206 somnolence, tremor

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

208 **Skin and Appendages:** dry skin, herpes simplex, herpes zoster, skin discoloration, skin
209 hypertrophy

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

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

213

214 In these trials the overall frequency of all cardiovascular adverse events was 6.9% in
215 BROVANA Inhalation Solution 15 mcg twice daily and 13.3% in the placebo group. There
216 were no frequently occurring specific cardiovascular adverse events for BROVANA
217 Inhalation Solution (frequency $\geq 1\%$ and greater than placebo). The rate of COPD
218 exacerbations was also comparable between the BROVANA Inhalation Solution 15 mcg
219 twice daily and placebo groups, 12.2% and 15.1%, respectively

220

221 **7 DRUG INTERACTIONS**

222 **7.1 Adrenergic Drugs**

223 If additional adrenergic drugs are to be administered by any route, they should be
224 used with caution because the sympathetic effects of arformoterol may be potentiated [see
225 *WARNINGS AND PRECAUTIONS* (5.3, 5.5, 5.6, 5.7)].

226 **7.2 Xanthine Derivatives, Steroids, or Diuretics**

227 Concomitant treatment with methylxanthine (aminophylline, theophylline), steroids,
228 or diuretics may potentiate any hypokalemic effect of adrenergic agonists including
229 BROVANA Inhalation Solution [see *WARNINGS AND PRECAUTIONS* (5.7)].

230 The concurrent use of intravenously or orally administered methylxanthines (e.g.,
231 aminophylline, theophylline) by patients receiving BROVANA Inhalation Solution has not
232 been completely evaluated. In two combined 12-week placebo controlled trials that included
233 BROVANA Inhalation Solution doses of 15 mcg twice daily, 25 mcg twice daily, and
234 50 mcg once daily, 54 of 873 BROVANA Inhalation Solution treated subjects received
235 concomitant theophylline at study entry. In a 12 month controlled trial that included a
236 50 mcg once daily BROVANA Inhalation Solution dose, 30 of the 528 BROVANA
237 Inhalation Solution treated subjects received concomitant theophylline at study entry. In
238 these trials, heart rate and systolic blood pressure were approximately 2-3 bpm and 6-8 mm

239 Hg higher, respectively, in subjects on concomitant theophylline compared with the overall
240 population.

241 **7.3 Non-potassium Sparing Diuretics**

242 The ECG changes and/or hypokalemia that may result from the administration of
243 non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened
244 by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.
245 Although the clinical significance of these effects is not known, caution is advised in the co-
246 administration of beta-agonists including BROVANA Inhalation Solution with non-
247 potassium sparing diuretics.

248 **7.4 MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs**

249 BROVANA Inhalation Solution, as with other beta-agonists, should be administered
250 with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic
251 antidepressants, or drugs known to prolong the QTc interval because of the effect of
252 adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs
253 that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

254 **7.5 Beta-Blockers**

255 Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA Inhalation
256 Solution may inhibit the effect of each other when administered concurrently. Beta-blockers
257 not only block the therapeutic effects of beta-agonists, but may produce severe
258 bronchospasm in COPD patients. Therefore, patients with COPD should not normally be
259 treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after
260 myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in
261 patients with COPD. In this setting, cardioselective beta-blockers could be considered,
262 although they should be administered with caution.

263

264 **8 USE IN SPECIFIC POPULATIONS**

265 **8.1 Pregnancy**

266 Teratogenic Effects: *Pregnancy Category C*

267 There are no adequate and well-controlled studies of BROVANA Inhalation Solution
268 in pregnant women. Arformoterol has been shown to be teratogenic in rats and rabbits.
269 Arformoterol also caused neonatal mortality and developmental delays in rats. Because
270 animal reproduction studies are not always predictive of human response, BROVANA
271 Inhalation Solution should be used during pregnancy, only if the potential benefit justifies the
272 potential risk to the fetus.

273 Arformoterol has been shown to be teratogenic in rats based upon findings of
274 omphalocele (umbilical hernia), a malformation, at oral doses equal to and greater than
275 approximately 370 times adult exposure at the maximum recommended daily inhalation
276 dose. Increased pup loss at birth and during lactation and decreased pup weights were
277 observed in rats at oral doses equal to and greater than approximately 1100 times adult
278 exposure at the maximum recommended daily inhalation dose. Delays in development were
279 evident with an oral dose approximately 2400 times adult exposure at the maximum
280 recommended daily inhalation dose.

281 Arformoterol has been shown to be teratogenic in rabbits based upon findings of
282 malpositioned right kidney, a malformation, at oral doses equal to and greater than
283 approximately 8400 times adult exposure at the maximum recommended daily inhalation
284 dose. Malformations including brachydactyly, bulbous aorta, and liver cysts were observed

285 at oral doses equal to and greater than approximately 22,000 times the maximum
286 recommended daily inhalation dose in adults on a mg/m² basis. Malformation including
287 adactyly, lobular dysgenesis of the lung, and interventricular septal defect were observed at
288 an oral dose approximately 43,000 times the maximum recommended daily inhalation dose
289 in adults on a mg/m² basis. Embryoletality was observed at an oral dose approximately
290 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis.
291 Decreased pup body weights were observed at oral doses equal to and greater than
292 approximately 22,000 times the maximum recommended daily inhalation dose in adults on a
293 mg/m² basis. There were no teratogenic findings in rabbits with oral doses equal to or less
294 than approximately 4900 times adult exposure at the maximum recommended daily
295 inhalation dose.

296 **8.2 Labor and Delivery**

297 There are no human studies that have investigated the effects of BROVANA
298 Inhalation Solution on preterm labor or labor at term.

299 Because beta-agonists may potentially interfere with uterine contractility,
300 BROVANA Inhalation Solution should be used during labor and delivery only if the
301 potential benefit justifies the potential risk.

302 **8.3 Nursing Mothers**

303 In reproductive studies in rats, arformoterol was excreted in the milk. It is not known
304 whether arformoterol is excreted in human milk. Because many drugs are excreted in human
305 milk, caution should be exercised when BROVANA Inhalation Solution is administered to a
306 nursing woman.

307 **8.4 Pediatric Use**

308 BROVANA Inhalation Solution is approved for use in the long term maintenance
309 treatment of bronchoconstriction associated with chronic obstructive pulmonary disease,
310 including chronic bronchitis and emphysema. This disease does not occur in children. The
311 safety and efficacy of BROVANA Inhalation Solution in pediatric patients have not been
312 established.

313 **8.5 Geriatric Use**

314 Of the 873 patients who received BROVANA Inhalation Solution in two placebo-
315 controlled clinical studies in adults with COPD, 391 (45%) were 65 years of age or older
316 while 96 (11%) were 75 years of age or older. No overall differences in safety or
317 effectiveness were observed between these subjects and younger subjects. Among subjects
318 age 65 years and older, 129 (33%) received BROVANA Inhalation Solution at the
319 recommended dose of 15 mcg twice daily, while the remainder received higher doses. ECG
320 alerts for ventricular ectopy in patients 65 to ≤75 years of age were comparable among
321 patients receiving 15 mcg twice daily, 25 mcg twice daily, and placebo (3.9%, 5.2%, and
322 7.1%, respectively). A higher frequency (12.4%) was observed when BROVANA Inhalation
323 Solution was dosed at 50 mcg once daily. The clinical significance of this finding is not
324 known. Other reported clinical experience has not identified differences in responses
325 between the elderly and younger patients, but greater sensitivity of some older individuals
326 cannot be ruled out.

327 **8.6 Hepatic Impairment**

328 BROVANA Inhalation Solution should be used cautiously in patients with hepatic
329 impairment due to increased systemic exposure in these patients [see *Pharmacokinetics*
330 (12.3)].

331 **8.7 Renal Impairment**

332 The systemic exposure to arformoterol was similar to renally impaired patients
333 compared with demographically matched healthy control subjects [see *Pharmacokinetics*
334 (12.3)].

335
336 **9 DRUG ABUSE AND DEPENDENCE**

337 There were no reported cases of abuse or evidence of drug dependence with the use
338 of BROVANA Inhalation Solution in the clinical trials.

339
340 **10 OVERDOSAGE**

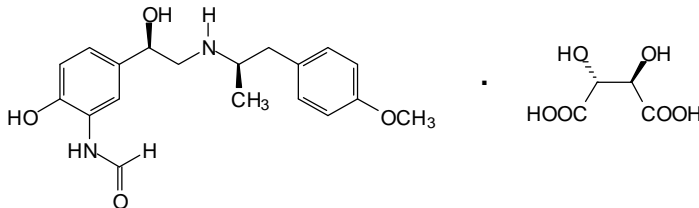
341 The expected signs and symptoms associated with overdosage of BROVANA
342 (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic stimulation
343 and/or occurrence or exaggeration of any of the signs and symptoms listed under **ADVERSE**
344 **REACTIONS**. Signs and symptoms may include angina, hypertension or hypotension,
345 tachycardia, with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, dry
346 mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia,
347 hyperglycemia, metabolic acidosis and insomnia. As with all inhaled sympathomimetic
348 medications, cardiac arrest and even death may be associated with an overdose of
349 BROVANA Inhalation Solution.

350 Treatment of overdosage consists of discontinuation of BROVANA Inhalation
351 Solution together with institution of appropriate symptomatic and/or supportive therapy. The
352 judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind
353 that such medication can produce bronchospasm. There is insufficient evidence to determine
354 if dialysis is beneficial for overdosage of BROVANA Inhalation Solution. Cardiac
355 monitoring is recommended in cases of overdosage.

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

362
363 **11 DESCRIPTION**

364 BROVANA (arformoterol tartrate) Inhalation Solution is a sterile, clear, colorless,
365 aqueous solution of the tartrate salt of arformoterol, the (R,R)-enantiomer of formoterol.
366 Arformoterol is a selective beta₂-adrenergic bronchodilator. The chemical name for
367 arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-
368 (4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate
369 (1:1 salt), and its established structural formula is as follows:



370

371 The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula is
372 $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (1:1 salt). It is a white to off-white solid that is slightly soluble in
373 water.

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

376 BROVANA (arformoterol tartrate) Inhalation Solution is supplied as 2 mL of
377 arformoterol tartrate solution packaged in 2.1 mL unit-dose, low-density polyethylene
378 (LDPE) unit-dose vials. Each unit-dose vial contains 15 mcg of arformoterol (equivalent to
379 22 mcg of arformoterol tartrate) in a sterile, isotonic saline solution, pH-adjusted to 5.0 with
380 citric acid and sodium citrate.

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

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

392

393 **12 CLINICAL PHARMACOLOGY**

394 **12.1 Mechanism of Action**

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

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

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

415 **12.2 Pharmacodynamics**

416 Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

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

421 Effects on Serum Potassium and Serum Glucose Levels

422 Changes in serum potassium and serum glucose were evaluated in a dose ranging
423 study of twice daily (5 mcg, 15 mcg, or 25 mcg; 215 patients with COPD) and once daily
424 (15 mcg, 25 mcg, or 50 mcg; 191 patients with COPD) BROVANA Inhalation Solution in
425 COPD patients. At 2 and 6 hours post dose at week 0 (after the first dose), mean changes in
426 serum potassium ranging from 0 to -0.3 mEq/L were observed in the BROVANA Inhalation
427 Solution groups with similar changes observed after 2 weeks of treatment. Changes in mean
428 serum glucose levels, ranging from a decrease of 1.2 mg/dL to an increase of 32.8 mg/dL
429 were observed for BROVANA Inhalation Solution dose groups at both 2 and 6 hours post
430 dose, both after the first dose and 14 days of daily treatment.

431 Electrophysiology

432 The effect of BROVANA Inhalation Solution on QT interval was evaluated in a dose
433 ranging study following multiple doses of BROVANA Inhalation Solution 5 mcg, 15 mcg, or
434 25 mcg twice daily or 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks in patients with
435 COPD. ECG assessments were performed at baseline, time of peak plasma concentration
436 and throughout the dosing interval. Different methods of correcting for heart rate were
437 employed, including a subject-specific method and the Fridericia method.

438 Relative to placebo, the mean change in subject-specific QT_c averaged over the
439 dosing interval ranged from -1.8 to 2.7 msec, indicating little effect of BROVANA Inhalation
440 Solution on cardiac repolarization after 2 weeks of treatment. The maximum mean change in
441 subject-specific QT_c for the BROVANA Inhalation Solution 15 mcg twice daily dose was
442 17.3 msec, compared with 15.4 msec in the placebo group. No apparent correlation of QT_c
443 with arformoterol plasma concentration was observed.

444 Electrocardiographic Monitoring in Patients with COPD

445 The effect of different doses of BROVANA Inhalation Solution on cardiac rhythm
446 was assessed using 24-hour Holter monitoring in two 12-week double-blind, placebo-
447 controlled studies of 1,456 patients with COPD (873 received BROVANA Inhalation
448 Solution at 15 or 25 mcg twice daily or 50 mcg once daily doses; 293 received placebo; 290
449 received salmeterol). The 24-hour Holter monitoring occurred once at baseline, and up to
450 3 times during the 12-week treatment period. The rates of new-onset cardiac arrhythmias not
451 present at baseline over the double-blind 12-week treatment period were similar
452 (approximately 33-34%) for patients who received BROVANA Inhalation Solution 15 mcg
453 twice daily to those who received placebo. There was a dose-related increase in new,
454 treatment emergent arrhythmias seen in patients who received BROVANA Inhalation
455 Solution 25 mcg twice daily and 50 mcg once daily, 37.6% and 40.1 %, respectively. The
456 frequencies of new treatment emergent events of non-sustained (3-10 beat run) and sustained
457 (>10 beat run) ventricular tachycardia were 7.4% and 1.1% in BROVANA Inhalation
458 Solution 15 mcg twice daily and 6.9% and 1.0% in placebo. In patients who received
459 BROVANA Inhalation Solution 25 mcg twice daily and 50 mcg once daily the frequencies of
460 non-sustained (6.2% and 8.2%, respectively) and sustained ventricular tachycardia (1.0% and

461 1.0%, respectively) were similar. Five cases of ventricular tachycardia were reported as
462 adverse events (1 in BROVANA Inhalation Solution 15 mcg twice daily and 4 in placebo),
463 with two of these events leading to discontinuation of treatment (2 in placebo).

464 There were no baseline occurrences of atrial fibrillation/ flutter observed on 24-hour
465 Holter monitoring in patients treated with BROVANA Inhalation Solution 15 mcg twice
466 daily or placebo. New, treatment emergent atrial fibrillation/ flutter occurred in 0.4% of
467 patients who received BROVANA Inhalation Solution 15 mcg twice daily and 0.3% of
468 patients who received placebo. There was a dose-related increase in the frequency of atrial
469 fibrillation/ flutter reported in the BROVANA Inhalation Solution 25 mcg twice daily and
470 50 mcg once daily dose groups of 0.7% and 1.4%, respectively. Two cases of atrial
471 fibrillation/ flutter were reported as adverse events (1 in BROVANA Inhalation Solution
472 15 mcg twice daily and 1 in placebo).

473 Dose-related increases in mean maximum change in heart rate in the 12 hours after
474 dosing were also observed following 12 weeks of dosing with BROVANA Inhalation
475 Solution 15 mcg twice daily (8.8 bpm), 25 mcg twice daily (9.9 bpm) and 50 mcg once daily
476 (12 bpm) versus placebo (8.5 bpm).

477 Tachyphylaxis/ Tolerance

478 Tolerance to the effects of inhaled beta-agonists can occur with regularly-scheduled,
479 chronic use.

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

489 **12.3 Pharmacokinetics**

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

493 Absorption

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

499 Systemic exposure to (R,R)-formoterol increased linearly with dose in COPD patients
500 following arformoterol doses of 5 mcg, 15 mcg, or 25 mcg twice daily for 2 weeks or
501 15 mcg, 25 mcg, or 50 mcg once daily for 2 weeks.

502 In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation
503 solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil[®] Aerolizer[®])
504 was administered twice daily for 2 weeks, the accumulation index was approximately
505 2.5 based on the plasma (R,R)-formoterol concentrations in all three treatments. At steady
506 state, geometric means of systemic exposure (AUC_{0-12h}) to (R,R)-formoterol following

507 15 mcg of arformoterol inhalation solution and 12 mcg of formoterol fumarate inhalation
508 powder were 39.33 pg*hr/mL and 33.93 pg*hr/mL, respectively (ratio 1.16; 90% CI 1.00,
509 1.35), while the geometric means of the C_{max} were 4.30 pg/mL and 4.75 pg/mL, respectively
510 (ratio 0.91; 90% CI 0.76, 1.09).

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

516 Distribution

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

521 Metabolism

522 *In vitro* profiling studies in hepatocytes and liver microsomes have shown that
523 arformoterol is primarily metabolized by direct conjugation (glucuronidation) and
524 secondarily by O-demethylation. At least five human uridine
525 diphosphoglucuronosyltransferase (UGT) isozymes catalyze arformoterol glucuronidation *in*
526 *vitro*. Two cytochrome P450 isozymes (CYP2D6 and secondarily CYP2C19) catalyze the
527 O-demethylation of arformoterol.

528 Arformoterol was almost entirely metabolized following oral administration of
529 35 mcg of radiolabeled arformoterol in eight healthy subjects. Direct conjugation of
530 arformoterol with glucuronic acid was the major metabolic pathway. Most of the drug-
531 related material in plasma and urine was in the form of glucuronide or sulfate conjugates of
532 arformoterol. O-Desmethylation and conjugates of the O-desmethyl metabolite were
533 relatively minor metabolites accounting for less than 17% of the dose recovered in urine and
534 feces.

535 Elimination

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

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

544 Special Populations

545 Gender

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

548 Race

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

552 Geriatric

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

557 Pediatric

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

559 Hepatic Impairment

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

566 Renal Impairment

567 The impact of renal disease upon the pharmacokinetics of arformoterol was studied in
568 24 subjects with mild, moderate, or severe renal impairment. Systemic exposure (AUC and
569 C_{max}) to arformoterol was similar in renally impaired patients compared with
570 demographically matched healthy control subjects.

571 Drug-Drug Interaction

572 When paroxetine, a potent inhibitor of CYP2D6, was co-administered with
573 BROVANA Inhalation Solution at steady-state, exposure to either drug was not altered.
574 Dosage adjustments of BROVANA Inhalation Solution are not necessary when the drug is
575 given concomitantly with potent CYP2D6 inhibitors.

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

579 **12.4 Pharmacogenetics**

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

586

587 **13 NONCLINICAL TOXICOLOGY**

588 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

595 In a 24-month carcinogenicity study in Sprague-Dawley rats, arformoterol caused a
596 statistically significant increase in the incidence of thyroid gland c-cell adenoma and
597 carcinoma in female rats at an inhalation dose of 200 mcg/kg (AUC exposure approximately

598 130 times adult exposure at the maximum recommended daily inhalation dose). There were
599 no tumor findings with an inhalation dose of 40 mcg/kg (AUC exposure approximately
600 55 times adult exposure at the maximum recommended daily inhalation dose).

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

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

607 **13.2 Animal Toxicology and/or Pharmacology**

608 Animal Pharmacology

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

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

619 Reproductive Toxicology Studies

620 Arformoterol has been shown to be teratogenic in rats based upon findings of
621 omphalocele (umbilical hernia), a malformation, at oral doses of 1 mg/kg and above (AUC
622 exposure approximately 370 times adult exposure at the maximum recommended daily
623 inhalation dose). Increased pup loss at birth and during lactation and decreased pup weights
624 were observed in rats at oral doses of 5 mg/kg and above (AUC exposure approximately
625 1100 times adult exposure at the maximum recommended daily inhalation dose). Delays in
626 development were evident with an oral dose of 10 mg/kg (AUC exposure approximately
627 2400 times adult exposure at the maximum recommended daily inhalation dose).

628 Arformoterol has been shown to be teratogenic in rabbits based on upon findings of
629 malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC
630 exposure approximately 8400 times adult exposure at the maximum recommended daily
631 inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were
632 observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum
633 recommended daily inhalation dose in adults on a mg/m² basis). Malformation including
634 adactyly, lobular dysgenesis of the lung, interventricular septal defect were observed at 80
635 mg/kg (approximately 43,000 times the maximum recommended daily inhalation dose in
636 adults on a mg/m² basis). Embryoletality was observed at 80 mg/kg/day (approximately
637 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis).
638 Decreased pup body weights were observed at doses of 40 mg/kg/day and above
639 (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a
640 mg/m² basis). There were no teratogenic findings in rabbits with oral dose of 10 mg/kg and
641 lower (AUC exposure approximately 4900 times adult exposure at the maximum
642 recommended daily inhalation dose).

643

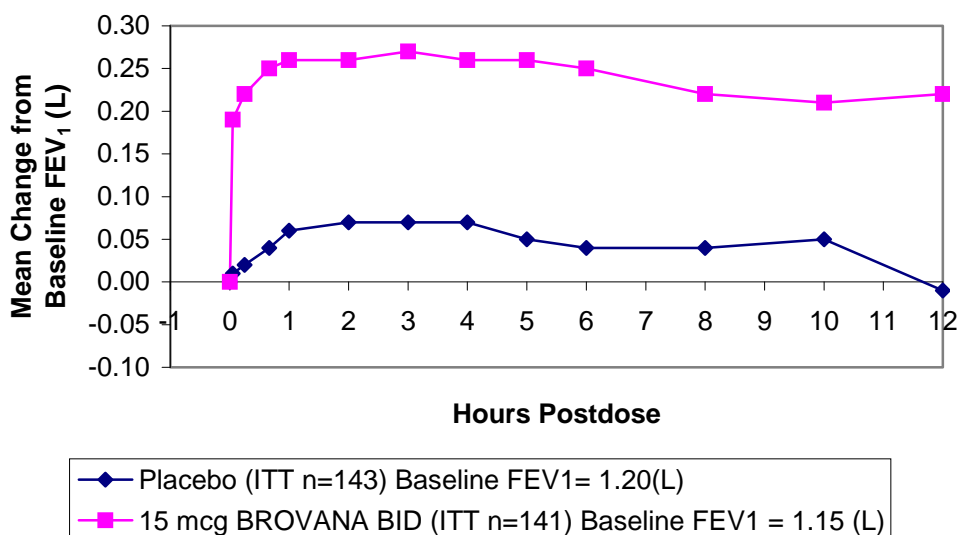
644 **14 CLINICAL STUDIES**

645 **14.1 Adult COPD Trials**

646 BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical,
647 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel
648 group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A total of
649 1,456 adult patients (age range: 34 to 89 years; mean age: 63 years; gender: 860 males and
650 596 females) with COPD who had a mean FEV₁ of 1.3 L (42% of predicted) were enrolled in
651 the two clinical trials. The racial/ethnic distribution in these two trials included 1383
652 Caucasians, 49 Blacks, 10 Asians, and 10 Hispanics, and 4 patients classified as Other. The
653 diagnosis of COPD was based on a prior clinical diagnosis of COPD, a smoking history
654 (greater than 15 pack-years), age (at least 35 years), spirometry results (baseline FEV₁ ≤65%
655 of predicted value and >0.70 L, and a FEV₁/ forced vital capacity (FVC) ratio ≤70%). About
656 80% of patients in these studies had bronchodilator reversibility, defined as a 10% or greater
657 increase FEV₁ after inhalation of 2 actuations (180 mcg racemic albuterol from a metered
658 dose inhaler). Both trials compared BROVANA Inhalation Solution 15 mcg twice daily
659 (288 patients), 25 mcg twice daily (292 patients), 50 mcg once daily (293 patients) with
660 placebo (293 subjects). Both trials included salmeterol inhalation aerosol, 42 mcg twice
661 daily as an active comparator (290 patients).

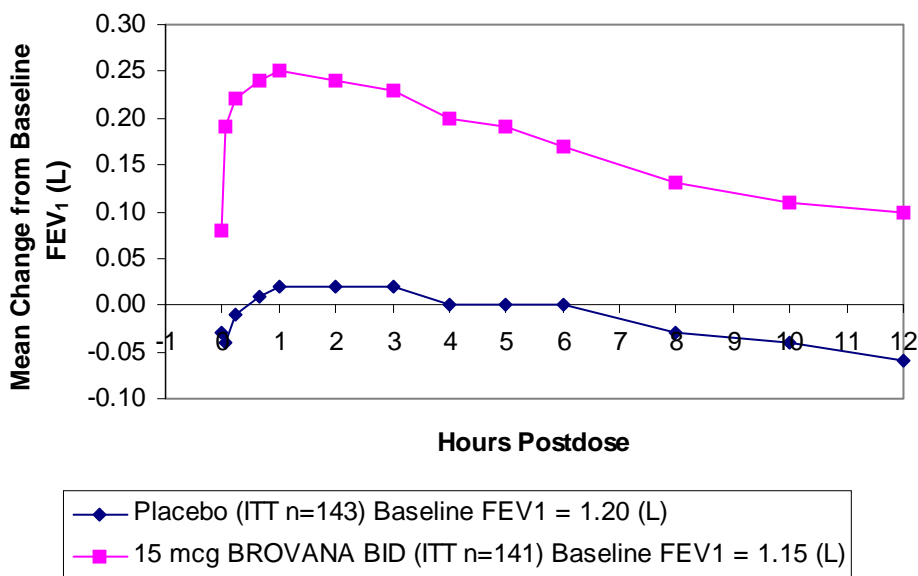
662 In both 12-week trials, BROVANA Inhalation Solution 15 mcg twice daily resulted
663 in a statistically significant change of approximately 11% in mean FEV₁ (as measured by
664 percent change from study baseline FEV₁ at the end of the dosing interval over the 12 weeks
665 of treatment, the primary efficacy endpoint) compared to placebo. Compared to BROVANA
666 Inhalation Solution 15 mcg twice daily, BROVANA Inhalation Solution 25 mcg twice daily
667 and 50 mcg once daily did not provide sufficient additional benefit on a variety of endpoints,
668 including FEV₁, to support the use of higher doses. Plots of the mean change in FEV₁ values
669 obtained over the 12 hours after dosing for the BROVANA Inhalation Solution 15 mcg twice
670 daily dose group and for the placebo group are provided in Figures 1 and 2 for Clinical Trial
671 A, below. The plots include mean FEV₁ change observed after the first dose and after 12
672 weeks of treatment. The results from Clinical Trial B were similar.

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



673

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



674

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

678

679

680

Following the first dose of BROVANA Inhalation Solution 15 mcg, the median time to onset of bronchodilation, defined by an FEV₁ increase of 15%, occurred at 6.7 min. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was

681 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours of
682 dosing.

683 In both clinical trials, compared to placebo, patients treated with BROVANA
684 Inhalation Solution demonstrated improvements in peak expiratory flow rates, supplemental
685 ipratropium and rescue albuterol use.

686

687 **16 HOW SUPPLIED/STORAGE AND HANDLING**

688 BROVANA (arformoterol tartrate) Inhalation Solution is supplied in a single strength
689 (15 mcg of arformoterol, equivalent to 22 mcg of arformoterol tartrate) as 2 mL of a sterile
690 solution in low-density polyethylene (LDPE) unit-dose vials overwrapped in foil.

691 BROVANA Inhalation Solution is available in a shelf-carton containing 30 or 60 unit-dose
692 vials.

693

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

695 NDC 63402-911-64: carton of 60 unit-dose vials (15×4 unit-dose vial pouches).

696

697 Storage and Handling:

698 Store BROVANA Inhalation Solution in the protective foil pouch under refrigeration
699 at 36°-46°F (2°-8°C). Protect from light and excessive heat. After opening the pouch,
700 unused unit-dose vials should be returned to, and stored in, the pouch. An opened unit-dose
701 vial should be used right away. Discard any unit-dose vial if the solution is not colorless.

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

705

706 **17 PATIENT COUNSELING INFORMATION**

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

710 Asthma-Related Deaths, Acute Exacerbations or Deteriorations

711 Patients should be informed that long-acting beta₂-adrenergic agonists, such as
712 BROVANA Inhalation Solution, increase risk of asthma-related death in patients with
713 asthma.

714 BROVANA Inhalation Solution is not indicated to relieve acute respiratory
715 symptoms and extra doses should not be used for that purpose. Acute symptoms should be
716 treated with an inhaled, short-acting, beta₂-agonist (the health-care provider should prescribe
717 the patient with such medication and instruct the patient in how it should be used). Patients
718 should be instructed to seek medical attention if their symptoms worsen despite
719 recommended doses of BROVANA Inhalation Solution, if BROVANA Inhalation Solution
720 treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-
721 agonist than usual.

722 Appropriate Dosing

723 Patients should not stop using BROVANA Inhalation Solution unless told to do so by
724 a healthcare provider because symptoms may get worse. Patients should not inhale more
725 than one dose at any one time. The daily dosage of BROVANA Inhalation Solution should
726 not exceed one unit-dose vial (15 mcg) by inhalation twice daily (30 mcg total daily dose).

727 Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be
728 fatal.

729 Concomitant Therapy

730 Patients who have been taking inhaled, short-acting beta₂-agonists (e.g., levalbuterol)
731 on a regular basis should be instructed to discontinue the regular use of these products and
732 use them only for the symptomatic relief of acute symptoms.

733 BROVANA Inhalation Solution should not be used in conjunction with other inhaled
734 medications containing long-acting beta₂-agonists. Patients should be warned not to stop or
735 change the dose of other concomitant COPD therapy without medical advice, even if
736 symptoms improve after initiating treatment with BROVANA Inhalation Solution.

737 Common Adverse Reactions with Beta₂-agonists

738 Patients should be informed that treatment with beta₂-agonists may lead to adverse
739 reactions that include palpitations, chest pain, rapid heart rate, increased or decreased blood
740 pressure, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, dizziness,
741 fatigue, malaise, low blood potassium, high blood sugar, high blood acid, or trouble sleeping
742 [see *ADVERSE REACTIONS (6.1)*].

743 Instructions for Administration

744 It is important that patients understand how to use BROVANA Inhalation Solution
745 with a nebulizer appropriately and how it should be used in relation to other medications to
746 treat COPD they are taking [see the *accompanying Medication Guide*]. Patients should be
747 instructed not to mix other medications with BROVANA Inhalation Solution and not to
748 inject or swallow BROVANA Inhalation Solution. Patients should throw the plastic
749 dispensing vials away immediately after use. Due to their small size, the vials pose a danger
750 of choking to young children.

751 Women should be advised to contact their physician if they become pregnant or if
752 they are nursing.

753 FDA-Approved Medication Guide

754 See the accompanying **Medication Guide**.

755



756 **SUNOVION**

757 Manufactured for:

758 **Sunovion Pharmaceuticals Inc.**

759 Marlborough, MA 01752 USA

760 BROVANA is a registered trademark of Sunovion Pharmaceuticals Inc.

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

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

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

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MEDICATION GUIDE
BROVANA® /*Brō vǎ'-nah*/
(arformoterol tartrate) Inhalation Solution

BROVANA is only for use with a nebulizer.

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

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

11 **BROVANA can cause serious side effects, including:**

- 12 • **People with asthma, who take long-acting beta₂ adrenergic agonist (LABA) medicines, such as**
13 **BROVANA, have an increased risk of death from asthma problems.**
- 14 • It is not known if LABA medicines, such as BROVANA, increase the risk of death in people with chronic
15 obstructive pulmonary disease (COPD).
- 16 • **Get emergency medical care if:**
- 17 • **breathing problems worsen quickly**
- 18 • **you use your rescue inhaler medicine, but it does not relieve your breathing problems**

19 **What is BROVANA?**

20 **BROVANA is used long term, 2 times each day (morning and evening), in controlling symptoms of**
21 **chronic obstructive pulmonary disease (COPD) in adults with COPD.**

22
23 BROVANA is only for use with a nebulizer.

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

26 BROVANA should not be used in children. **It is not known if BROVANA is safe and effective in children.**
27 **It is not known if BROVANA is safe and effective in people with asthma.**

28
29 **Who should not use BROVANA?**

30 **Do not use BROVANA if you:**

- 31 • have had a serious allergic reaction to arformoterol, formoterol, or any of the ingredients in
32 BROVANA. Ask your healthcare provider if you are not sure. See the end of this Medication Guide
33 for a complete list of ingredients in BROVANA.
- 34 • have asthma without using a long-term asthma control medicine.

35 **What should I tell my healthcare provider before using BROVANA?**

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

- 37 • have heart problems
- 38 • have high blood pressure
- 39 • have seizures
- 40 • have thyroid problems

- 41 • have diabetes
- 42 • have liver problems
- 43 • are pregnant or planning to become pregnant. It is not known if BROVANA can harm your unborn
- 44 baby.
- 45 • are breastfeeding. It is not known if BROVANA passes into your milk and if it can harm your baby.

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

49 Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time
50 you get a new medicine.

51 **How should I use BROVANA?**

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

- 53 • Use BROVANA exactly as prescribed. One ready-to-use vial of BROVANA is one dose. The usual dose
54 of BROVANA is 1 ready-to-use vial, twice a day (morning and evening) breathed in through your
55 nebulizer machine. The 2 doses should be about 12 hours apart. **Do not use more than 2 ready-to-use**
56 **vials of BROVANA a day.**
- 57 • Do not swallow or inject BROVANA.
- 58 • BROVANA is for use with a standard jet nebulizer machine connected to an air compressor. Read the
59 complete instructions for use at the end of this Medication Guide before starting BROVANA.
- 60 • Do not mix other medicines with BROVANA in your nebulizer machine.
- 61 • If you miss a dose of BROVANA. Just skip that dose. Take your next dose at your usual time. Do not
62 take 2 doses at one time.
- 63 • While you are using BROVANA 2 times each day:
 - 64 • **do not use** other medicines that contain a long-acting beta₂-agonist (LABA) for any reason.
 - 65 • **do not use** your short-acting beta₂-agonist medicine on a regular basis (four times a day).
- 66 • **BROVANA does not relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with
67 you to treat sudden symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider
68 to have one prescribed for you.
- 69 • Do not stop using BROVANA or other medicines to control or treat your COPD unless told to do so by
70 your healthcare provider because your symptoms might get worse. Your healthcare provider will change
71 your medicines as needed.
- 72 • **Do not use BROVANA:**
 - 73 ○ **more often than prescribed**
 - 74 ○ **more medicine than prescribed to you**
 - 75 ○ **with other LABA medicines**

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

- 77 • your breathing problems worsen with BROVANA
- 78 • you need to use your rescue inhaler medicine more often than usual
- 79 • your rescue inhaler medicine does not work as well for you at relieving symptoms

80 **What are the possible side effects with BROVANA?**

81 **BROVANA can cause serious side effects, including:**

- 82 • See “**What is the most important information I should know about BROVANA?**”
- 83 • Sudden shortness of breath immediately after use of BROVANA
- 84 • If your COPD symptoms worsen over time do not increase your dose of BROVANA, instead call your
85 healthcare provider.
- 86 • Increased blood pressure
- 87 • Fast or irregular heartbeat
- 88 • **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and**
89 **breathing problems.** Call your healthcare provider or get emergency medical care if you get any
90 symptoms of a serious allergic reaction.

91 **Common side effects of BROVANA include:**

- 92 • **chest or back pain**
- 93 • **diarrhea**
- 94 • **sinus congestion**
- 95 • **headache**
- 96 • **tremor**
- 97 • **nervousness**
- 98 • **leg cramps**
- 99 • **high blood potassium**
- 100 • **shortness of breath**
- 101 • **rash**
- 102 • **fever**
- 103 • **increased white blood cells**
- 104 • **vomiting**
- 105 • **tiredness**
- 106 • **leg swelling**
- 107 • **chest congestion or bronchitis**

108 Tell your healthcare provider if you get any side effect that bothers you or that does not go away.
109 These are not all the side effects with BROVANA. Ask your healthcare provider or pharmacist for more
110 information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
111 800-FDA-1088.

112 **How should I store BROVANA?**

- 113 • Store BROVANA in a refrigerator between 36° to 46°F (2° to 8°C) in the protective foil pouch. Protect
114 from light and excessive heat. **Do not open a sealed pouch until you are ready to use a dose of**
115 **BROVANA. After opening the pouch, unused ready-to-use vials should be returned to, and stored**

116 **in, the pouch. An opened ready-to-use vial should be used right away.** BROVANA may be used
117 directly from the refrigerator.

118 • BROVANA may also be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to
119 6 weeks (42 days). If stored at room temperature, discard BROVANA if it is not used after 6 weeks or if
120 past the expiration date, whichever is sooner. Space is provided on the packaging to record room
121 temperature storage times.

122 • Do not use BROVANA after the expiration date provided on the foil pouch and ready-to-use vial.

123 • BROVANA should be colorless. Discard BROVANA if it is not colorless.

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

125 **General Information about BROVANA**

126 Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do
127 not use BROVANA for a condition for which it was not prescribed. Do not give
128 BROVANA to other people, even if they have the same condition. It may harm them.
129 This Medication Guide summarizes the most important information about BROVANA. If you would like more
130 information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for
131 information about BROVANA that was written for healthcare professionals.

132 • For customer service, call 1-888-394-7377.

133 • To report side effects, call 1-877-737-7226.

134 • For medical information, call 1-800-739-0565.

135 Instructions for Using BROVANA (arformoterol tartrate) Inhalation Solution

136

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

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

141 BROVANA comes sealed in a foil pouch. Do not open a sealed pouch until you are ready to use a dose of
142 BROVANA. After opening the pouch, unused ready-to-use vials should be returned to, and stored in, the
143 pouch. An opened ready-to-use vial should be used right away.

144 1. Open the foil pouch by tearing on the rough edge along the seam of the pouch.

145 Remove a ready-to-use vial of BROVANA.

146 2. Carefully twist open the top of the ready-to-use vial and use it right away (**Figure 1**).

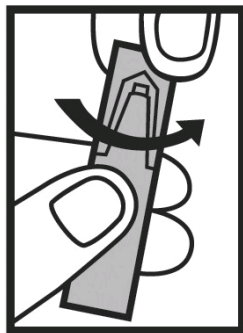


Figure 1

147

148 3. Squeeze all of the medicine from the ready-to-use vial into the nebulizer medicine
149 cup (reservoir) (**Figure 2**).



Figure 2

150

151 4. Connect the nebulizer reservoir to the mouthpiece (**Figure 3**) or face mask (**Figure**
152 **4**).



Figure 3



Figure 4

153

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

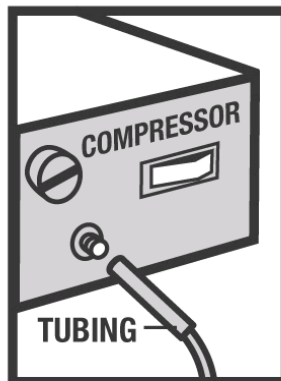


Figure 5

155

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

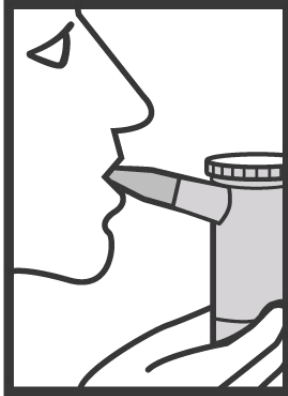


Figure 6

- 158
159 7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the
160 nebulizer reservoir. It takes about 5 to 10 minutes for each treatment.
- 161 8. Clean the nebulizer (see manufacturer's instructions).

162

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166 Rx Only

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



SUNOVION

Manufactured for:

Sunovion Pharmaceuticals Inc.

Marlborough, MA 01752 USA

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