

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BROVANA® safely and effectively. See full prescribing information for BROVANA.

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

### WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. (5.1)
- A placebo-controlled study with another long-acting beta<sub>2</sub>-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 beta<sub>2</sub>-adrenergic agonist (beta<sub>2</sub>-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. (2)
- One 15 mcg/2 mL vial every 12 hours. (2)
- For use with a standard jet nebulizer (with a face mask or mouthpiece) connected to an air compressor. (2)

### DOSAGE FORMS AND STRENGTHS

Inhalation Solution (unit-dose vial for nebulization): 15 mcg/2 mL 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 beta<sub>2</sub>-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 beta<sub>2</sub>-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](http://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 SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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## FULL PRESCRIBING INFORMATION

### **WARNING: ASTHMA RELATED DEATH**

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta<sub>2</sub>-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA Inhalation Solution [see *WARNINGS AND PRECAUTIONS (5.1)*]. 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 [see *CONTRAINDICATIONS (4)*, *WARNINGS AND PRECAUTIONS (5.1)*].

## **1 INDICATIONS AND USAGE**

### **1.1 Maintenance Treatment of COPD**

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

### **1.2 Important Limitations of Use**

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

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

## **2 DOSAGE AND ADMINISTRATION**

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

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

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

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

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

The safety and efficacy of BROVANA Inhalation Solution have been established in clinical trials when administered using the PARI LC<sup>®</sup> Plus nebulizer (with a face mask or mouthpiece) and the PARI DURA NEB<sup>™</sup> 3000 compressor. The safety and efficacy of BROVANA Inhalation Solution delivered from non-compressor based nebulizer systems have not been established.

### **3 DOSAGE FORMS AND STRENGTHS**

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

### **4 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.

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

## **5 WARNINGS AND PRECAUTIONS**

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

Data from a large placebo-controlled study in asthma patients showed that long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. This finding 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 [*see CONTRAINDICATIONS (4)*]. Data are not available to determine whether the rate of deaths in patients with COPD is increased by long-acting beta<sub>2</sub>-adrenergic agonists.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the long-acting beta<sub>2</sub>-adrenergic agonists, including BROVANA Inhalation Solution. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with BROVANA Inhalation Solution has been conducted.

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

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

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

BROVANA Inhalation Solution is not indicated for the treatment of acute episodes of bronchospasm, i.e., as rescue therapy and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta<sub>2</sub>-agonist.

When beginning BROVANA Inhalation Solution, patients who have been taking inhaled short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BROVANA Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting beta<sub>2</sub>-agonist and instruct the patient how it should be used. Increasing inhaled beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA Inhalation Solution no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective or the patient needs more inhalation of short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting, a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA Inhalation Solution beyond the recommended 15 mcg twice daily dose is not appropriate in this situation.

### **5.3 Excessive Use of BROVANA Inhalation Solution and Use with Other Long-Acting Beta<sub>2</sub>-Agonists**

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta<sub>2</sub>-adrenergic drugs, BROVANA Inhalation Solution should not be used more often, at higher doses than recommended, or in conjunction with other medications containing long-acting beta<sub>2</sub>-agonists.

### **5.4 Paradoxical Bronchospasm**

As with other inhaled beta<sub>2</sub>-agonists, BROVANA Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, BROVANA Inhalation Solution should be discontinued immediately and alternative therapy instituted.

### **5.5 Cardiovascular Effects**

BROVANA Inhalation Solution, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. BROVANA Inhalation Solution, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

### **5.6 Coexisting Conditions**

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

pulse rate the mean of maximal increases were 8.8-12.0 beats/min. Over the course of a one-year study measuring serial electrocardiograms while receiving a dose of 50 mcg daily of BROVANA Inhalation Solution resulted in an approximately 3.0 ms increase in QT<sub>C-F</sub> compared to the active comparator, salmeterol. Doses of the related beta<sub>2</sub>-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

### **5.7 Hypokalemia and Hyperglycemia**

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

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

### **5.8 Immediate Hypersensitivity Reactions**

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

## **6 ADVERSE REACTIONS**

**Long-acting beta<sub>2</sub>-adrenergic agonists increase the risk of asthma-related death [see *BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)*].**

### **6.1 Beta<sub>2</sub>-Agonist Adverse Reaction Profile**

Adverse reactions to BROVANA Inhalation Solution are expected to be similar in nature to other beta<sub>2</sub>-adrenergic receptor agonists including: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

### **6.2 Clinical Trials Experience**

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

#### ***Adults with COPD in Short-Term Trials (12 weeks)***

The safety data described below for adults  $\geq 35$  years of age are based on 2 clinical trials of 12 weeks. In the 2 trials of 12 weeks duration, 1456 patients (860 males and 596 females, ages 34 to 89 years old) with COPD were treated with BROVANA Inhalation Solution 15 mcg twice daily, 25 mcg twice daily, 50 mcg once daily, salmeterol 42 mcg twice daily, or placebo. The racial/ethnic distribution in these two trials included 1383 Caucasians, 49 Blacks, 10 Asians, and 10 Hispanics, and 4 patients classified as Other. Among the 1,456 COPD patients in two 12-week, placebo-controlled trials, 288 were treated with BROVANA Inhalation Solution 15 mcg twice daily and 293 were treated with placebo. Doses of 25 mcg twice daily and 50 mcg once daily were also evaluated.

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

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

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

	BROVANA Inhalation Solution 15 mcg twice daily		Placebo	
	n	(%)	n	(%)
	Total Patients	288	(100)	293
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.

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

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

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

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

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

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

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

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

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

**Special Senses:** abnormal vision, glaucoma

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

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

#### *Adults with COPD in Long-Term (52-week) Safety Trial*

BROVANA Inhalation Solution was evaluated in one 52 week double-blind, randomized, placebo-controlled, safety trial conducted in patients with moderate to severe COPD. The primary endpoint was time to either respiratory death or first COPD exacerbation-related hospitalization, whichever occurred first. The event had to be a death or hospitalization for which the patient's respiratory status was predominant and/or inciting contributor, as determined by the clinical investigator. The objective of the trial was to demonstrate that the risk of respiratory death or COPD exacerbation-related hospitalization for patients treated with BROVANA Inhalation Solution was not greater than 40% more than the risk for patient treated with placebo. A total of 841 patients (479 males and 361 females, ages 41 to 94 years old) with COPD were randomized: 420 to BROVANA Inhalation Solution 15 mcg twice daily and 421 to placebo. Of the randomized patients, 255 (61%) in the BROVANA Inhalation Solution group and 211 (50%) in the placebo group, completed one year of treatment. The trial objective was met demonstrating that COPD patients treated with BROVANA Inhalation Solution are not at an increased risk of respiratory death or COPD exacerbation-related hospitalizations compared to placebo.

## **7 DRUG INTERACTIONS**

### **7.1 Adrenergic Drugs**

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

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

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

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

### **7.3 Non-potassium Sparing Diuretics**

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

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

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

#### **7.5 Beta-Blockers**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### ***Teratogenic Effects: Pregnancy Category C***

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

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

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses equal to and greater than approximately 8400 times adult exposure at the maximum recommended daily inhalation dose. Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at oral doses equal to and greater than approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis. Malformations including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were observed at

an oral dose approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis. Embryo lethality was observed at an oral dose approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis. Decreased pup body weights were observed at oral doses equal to and greater than approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis. There were no teratogenic findings in rabbits with oral doses equal to or less than approximately 4900 times adult exposure at the maximum recommended daily inhalation dose.

## **8.2 Labor and Delivery**

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

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

## **8.3 Nursing Mothers**

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

## **8.4 Pediatric Use**

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

## **8.5 Geriatric Use**

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

## **8.6 Hepatic Impairment**

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

## **8.7 Renal Impairment**

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

## 9 DRUG ABUSE AND DEPENDENCE

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

## 10 OVERDOSAGE

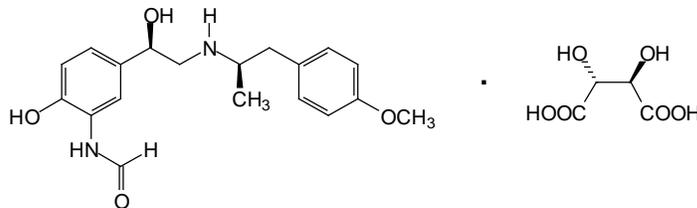
The expected signs and symptoms associated with overdose of BROVANA (arformoterol tartrate) Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under **ADVERSE REACTIONS**. Signs and symptoms may include angina,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

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

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

## 11 DESCRIPTION

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



The molecular weight of *arformoterol tartrate* is 494.5 g/mol, and its empirical formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>6</sub> (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

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

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

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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Arformoterol, the (R,R)-enantiomer of formoterol, is a selective long-acting beta<sub>2</sub>-adrenergic receptor agonist (beta<sub>2</sub>-agonist) that has two-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer is about 1,000-fold less potent as a beta<sub>2</sub>-agonist than the (R,R)-enantiomer. While it is recognized that beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, data indicate that there are also beta<sub>2</sub>-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may have cardiac effects.

The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including arformoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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

### 12.2 Pharmacodynamics

#### Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The predominant adverse effects of inhaled beta<sub>2</sub>-agonists occur as a result of excessive activation of systemic beta-adrenergic receptors. The most common adverse

effects may include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

#### Effects on Serum Potassium and Serum Glucose Levels

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

#### Electrophysiology

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

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

#### Electrocardiographic Monitoring in Patients with COPD

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

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

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

#### Tachyphylaxis/Tolerance

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

In two placebo-controlled clinical trials in patients with COPD involving approximately 725 patients in each, the overall efficacy of BROVANA Inhalation Solution was maintained throughout the 12-week trial duration. However, tolerance to the bronchodilator effect of BROVANA Inhalation Solution was observed after 6 weeks of dosing, as measured by a decrease in trough FEV<sub>1</sub>. FEV<sub>1</sub> improvement at the end of the 12-hour dosing interval decreased by approximately one-third (22.1% mean improvement after the first dose compared to 14.6% at week 12). Tolerance to the trough FEV<sub>1</sub> bronchodilator effect of BROVANA Inhalation Solution was not accompanied by other clinical manifestations of tolerance in these trials.

### **12.3 Pharmacokinetics**

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

#### Absorption

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

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

In a crossover study in patients with COPD, when arformoterol 15 mcg inhalation solution and 12 and 24 mcg formoterol fumarate inhalation powder (Foradil<sup>®</sup> Aerolizer<sup>®</sup>) was administered twice daily for 2 weeks, the accumulation index was approximately 2.5 based on the plasma (R,R)-formoterol concentrations in all three treatments. At steady-state, geometric means of systemic exposure (AUC<sub>0-12h</sub>) to (R,R)-formoterol following 15 mcg of arformoterol inhalation solution and 12 mcg of formoterol fumarate inhalation powder were 39.33 pg.hr/mL and 33.93 pg.hr/mL, respectively (ratio 1.16; 90% CI 1.00,

1.35), while the geometric means of the  $C_{max}$  were 4.30 pg/mL and 4.75 pg/mL, respectively (ratio 0.91; 90% CI 0.76, 1.09).

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

#### Distribution

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

#### Metabolism

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

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

#### Elimination

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

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

Special Populations:

#### Gender

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

#### Race

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

#### Geriatric

The pharmacokinetic profile of arformoterol in 24 elderly subjects (aged 65 years or older) was compared to a younger cohort of 24 subjects (18-45 years) that were matched for

body weight and gender. No significant differences in systemic exposure (AUC and  $C_{max}$ ) were observed when the two groups were compared.

#### Pediatric

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

#### Hepatic Impairment

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

#### Renal Impairment

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

#### Drug-Drug Interaction

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

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

### **12.5 Pharmacogenomics**

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

## **13 NONCLINICAL TOXICOLOGY**

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

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

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

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

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

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

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

#### Animal Pharmacology

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

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

#### Reproductive Toxicology Studies

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

Arformoterol has been shown to be teratogenic in rabbits based upon findings of malpositioned right kidney, a malformation, at oral doses of 20 mg/kg and above (AUC exposure approximately 8400 times adult exposure at the maximum recommended daily inhalation dose). Malformations including brachydactyly, bulbous aorta, and liver cysts were observed at doses of 40 mg/kg and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Malformations including adactyly, lobular dysgenesis of the lung, and interventricular septal defect were observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Embryoletality was observed at 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). Decreased pup body weights were observed at doses of 40 mg/kg/day and above (approximately 22,000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis). There were no teratogenic findings in rabbits with oral dose of 10 mg/kg and lower (AUC exposure approximately 4900 times adult exposure at the maximum recommended daily inhalation dose).

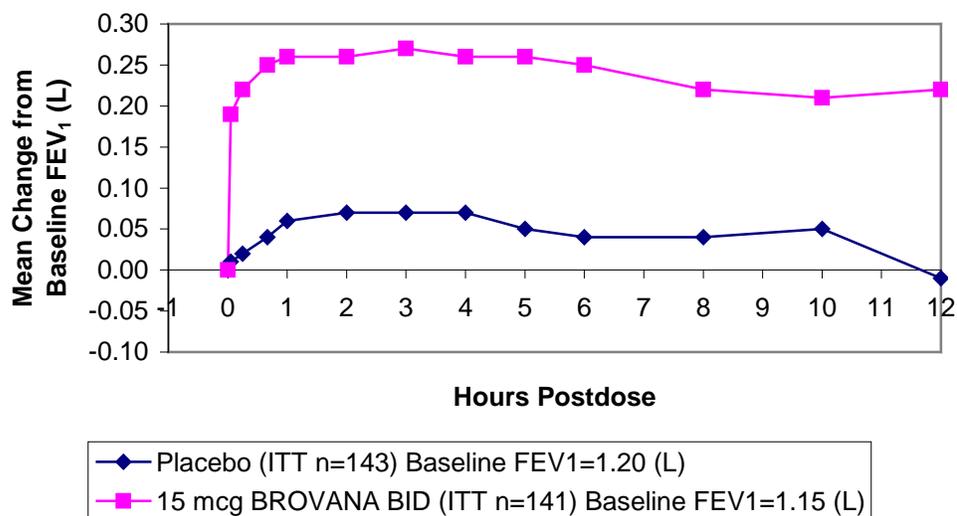
## 14 CLINICAL STUDIES

### 14.1 Adult COPD Trials

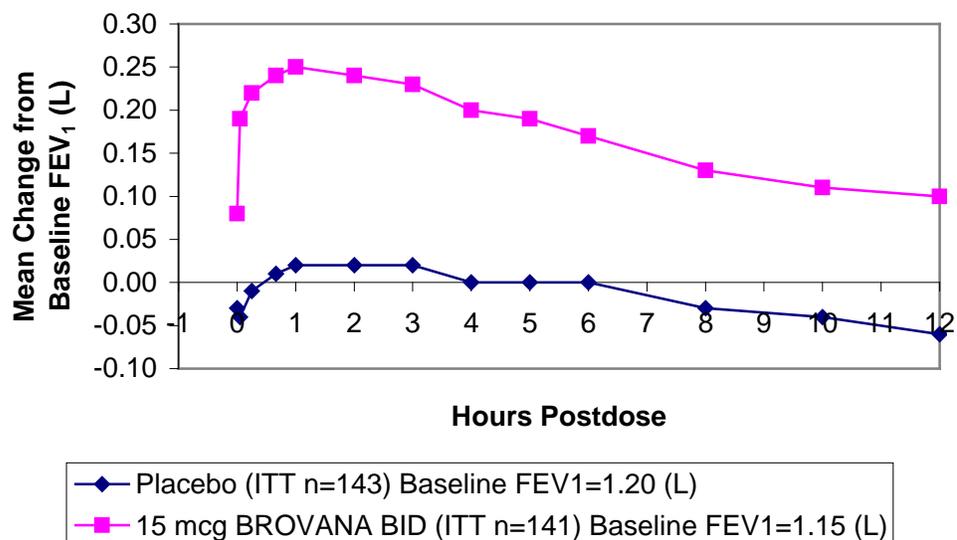
BROVANA (arformoterol tartrate) Inhalation Solution was studied in two identical, 12-week, double-blind, placebo- and active-controlled, randomized, multi-center, parallel group trials conducted in the United States (Clinical Trial A and Clinical Trial B). A total of 1,456 adult patients (age range: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

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

**Figure 1 Mean Change in FEV<sub>1</sub> Over Time for Clinical Trial A at Week 0 (Day 1)**



**Figure 2 Mean Change in FEV<sub>1</sub> Over Time for Clinical Trial A at Week 12**



BROVANA Inhalation Solution 15 mcg twice daily significantly improved bronchodilation compared to placebo over the 12 hours after dosing (FEV<sub>1</sub> AUC<sub>0-12h</sub>). This improvement was maintained over the 12-week study period.

Following the first dose of BROVANA Inhalation Solution 15 mcg, the median time to onset of bronchodilation, defined by an FEV<sub>1</sub> increase of 15%, occurred at 6.7 min. When defined as an increase in FEV<sub>1</sub> of 12% and 200 mL, the time to onset of bronchodilation was

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

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

### Storage and Handling

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) with each new prescription and refill.

**The complete text of the Medication Guide is reprinted at the end of this document.** Patients should be given the following information:

### Asthma-Related Deaths, Acute Exacerbations or Deteriorations

Patients should be informed that long-acting beta<sub>2</sub>-adrenergic agonists, such as BROVANA Inhalation Solution, increase risk of asthma-related death in patients with asthma.

BROVANA Inhalation Solution is not indicated to relieve acute respiratory symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist (the healthcare provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen despite recommended doses of BROVANA Inhalation Solution, if BROVANA Inhalation Solution treatment becomes less effective, or if they need more inhalations of a short-acting beta<sub>2</sub>-agonist than usual.

### Appropriate Dosing

Patients should not stop using BROVANA Inhalation Solution unless told to do so by a healthcare provider because symptoms may get worse. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA Inhalation Solution should

not exceed one unit-dose vial (15 mcg) by inhalation twice daily (30 mcg total daily dose). Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

#### Concomitant Therapy

Patients who have been taking inhaled, short-acting beta<sub>2</sub>-agonists (e.g., levalbuterol) on a regular basis should be instructed to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

BROVANA Inhalation Solution should not be used in conjunction with other inhaled medications containing long-acting beta<sub>2</sub>-agonists. Patients should be warned not to stop or change the dose of other concomitant COPD therapy without medical advice, even if symptoms improve after initiating treatment with BROVANA Inhalation Solution.

#### Common Adverse Reactions with Beta<sub>2</sub>-agonists

Patients should be informed that treatment with beta<sub>2</sub>-agonists may lead to adverse reactions that include palpitations, chest pain, rapid heart rate, increased or decreased blood pressure, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, dizziness, fatigue, malaise, low blood potassium, high blood sugar, high blood acid, or trouble sleeping [see *ADVERSE REACTIONS (6.1)*].

#### Instructions for Administration

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

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

#### FDA-Approved Medication Guide

See the accompanying **Medication Guide**.



**SUNOVION**

Manufactured for:

**Sunovion Pharmaceuticals Inc.**

Marlborough, MA 01752 USA

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

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

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

901552R02

MEDICATION GUIDE  
**BROVANA<sup>®</sup> [*Brō vā'-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.

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

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

- **People with asthma, who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines, such as BROVANA, have an increased risk of death from asthma problems.**
- **It is not known if LABA medicines, such as BROVANA, increase the risk of death in people with chronic obstructive pulmonary disease (COPD).**
- **Get emergency medical care if:**
  - **breathing problems worsen quickly**
  - **you use your rescue inhaler medicine, but it does not relieve your breathing problems**

**What is BROVANA?**

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

BROVANA is only for use with a nebulizer.

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

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

**Who should not use BROVANA?**

**Do not use BROVANA if you:**

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

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

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

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems

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

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

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

### **How should I use BROVANA?**

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

- Use BROVANA exactly as prescribed. One ready-to-use vial of BROVANA is one dose. The usual dose of BROVANA is 1 ready-to-use vial, twice a day (morning and evening) breathed in through your nebulizer machine. The 2 doses should be about 12 hours apart. **Do not use more than 2 ready-to-use vials of BROVANA a day.**
- Do not swallow or inject BROVANA.
- BROVANA is for use with a standard jet nebulizer machine connected to an air compressor. Read the complete instructions for use at the end of this Medication Guide before starting BROVANA.
- Do not mix other medicines with BROVANA in your nebulizer machine.
- If you miss a dose of BROVANA, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- While you are using BROVANA 2 times each day:
  - **do not use** other medicines that contain a long-acting beta<sub>2</sub>-agonist (LABA) for any reason.
  - **do not use** your short-acting beta<sub>2</sub>-agonist medicine on a regular basis (four times a day).
- **BROVANA does not relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider to have one prescribed for you.
- Do not stop using BROVANA or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **Do not use BROVANA:**
  - **more often than prescribed**
  - **more medicine than prescribed to you**
  - **with other LABA medicines**

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

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

## What are the possible side effects with BROVANA?

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

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

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

- **chest or back pain**
- **diarrhea**
- **sinus congestion**
- **headache**
- **tremor**
- **nervousness**
- **leg cramps**
- **high blood potassium**
- **shortness of breath**
- **rash**
- **fever**
- **increased white blood cells**
- **vomiting**
- **tiredness**
- **leg swelling**
- **chest congestion or bronchitis**

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

### **How should I store BROVANA?**

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

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

- BROVANA may also be stored at room temperature between 68° to 77°F (20° to 25°C) for up to 6 weeks (42 days). If stored at room temperature, discard BROVANA if it is not used after 6 weeks or if past the expiration date, whichever is sooner. Space is provided on the packaging to record room temperature storage times.
- Do not use BROVANA after the expiration date provided on the foil pouch and ready-to-use vial.
- BROVANA should be colorless. Discard BROVANA if it is not colorless.
- **Keep BROVANA and all medicines out of the reach of children.**

#### **General Information about BROVANA**

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

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

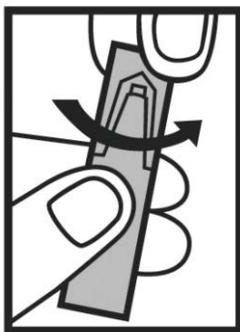
## Instructions for Using BROVANA (arformoterol tartrate) Inhalation Solution

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

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

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

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



**Figure 1**

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



**Figure 2**

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



Figure 3



Figure 4

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

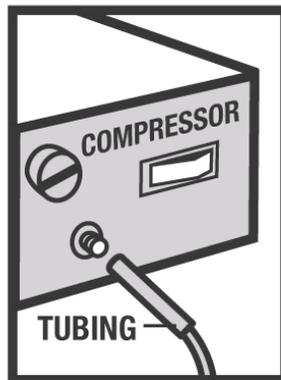
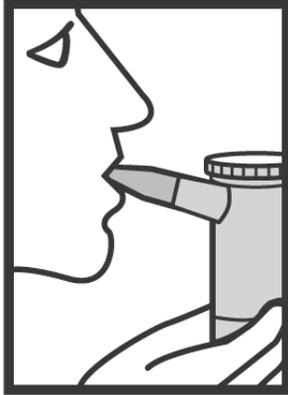


Figure 5

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



**Figure 6**

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

Rx Only

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

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