

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 (Sepracor 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.

Revised: Month Year

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

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.

FULL PRESCRIBING INFORMATION

WARNING: ASTHMA RELATED DEATH

Long-acting beta₂-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 beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol 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[®] Plus nebulizer (with a facemask or mouth piece) and the PARI DURA NEB[™] 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 beta₂-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 beta₂-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 beta₂-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 beta₂-agonist.

When beginning BROVANA Inhalation Solution, patients who have been taking inhaled short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BROVANA Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient how it should be used. Increasing inhaled beta₂-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 beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-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 Beta₂-Agonists

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta₂-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 beta₂-agonists.

5.4 Paradoxical Bronchospasm

As with other inhaled beta₂-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 beta₂-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 QTc_{C-F} compared to the active comparator, salmeterol. Doses of the related beta₂-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 beta₂-adrenergic agonists increase the risk of asthma-related death [See **BOXED WARNING and **WARNINGS AND PRECAUTIONS (5.1)**].**

6.1 Beta₂-Agonist Adverse Reaction Profile

Adverse reactions to BROVANA Inhalation Solution are expected to be similar in nature to other beta₂-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.

The safety data described below for adults ≥ 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.

Adults with COPD

Among 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	Placebo
--	---------	---------

	15 mcg twice daily			
	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.

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

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/m² basis. Malformation 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/m² basis. Embryo lethality was observed at an oral dose approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² 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/m² 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 \leq 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 *Pharmacokinetics* (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 overdosage 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.

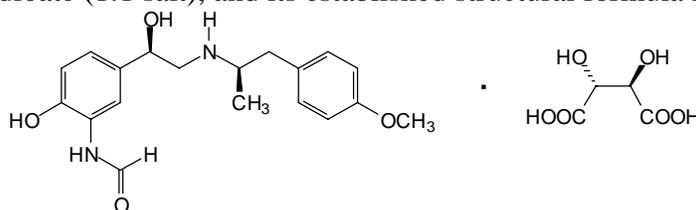
Treatment of overdosage consists of discontinuation of BROVANA Inhalation Solution together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.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

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/m² 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/m² 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 beta₂-adrenergic bronchodilator. The chemical name for arformoterol tartrate is formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-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 C₁₉H₂₄N₂O₄ · C₄H₆O₆ (1:1 salt). It is a white to off-white solid that is slightly soluble in water.

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

BROVANA (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[®] PLUS nebulizer (with mouthpiece) connected to a PARI DURA NEB[™] 3000 compressor under *in vitro* conditions, the mean delivered dose from the mouthpiece (% nominal) was approximately 4.1 mcg (27.6%) at a mean flow rate of 3.3 L/min. The mean nebulization time was 6 minutes or less. BROVANA 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 beta₂-adrenergic receptor agonist (beta₂-agonist) that has two-fold greater potency than racemic formoterol (which contains both the (S,S) and (R,R)-enantiomers). The (S,S)-enantiomer is about 1,000-fold less potent as a beta₂-agonist than the (R,R)-enantiomer. While it is recognized that beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, data

indicate that there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

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

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

12.2 Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The predominant adverse effects of inhaled beta₂-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 QT_c 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 QT_c 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 QT_c 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 FEV₁. FEV₁ 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 FEV₁ 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_{max}) and systemic exposure (AUC_{0-12h}) were 4.3 pg/mL and 34.5 pg*hr/mL, respectively. The median steady-state peak (R,R)-formoterol plasma concentration time (t_{max}) was observed approximately one half hour after drug administration.

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

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

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

Distribution

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

Metabolism

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

Arformoterol 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.

12.4 Pharmacogenetics

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

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/m² 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 on 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/m² basis). Malformation including adactyly, lobular dysgenesis of the lung, interventricular septal defect were observed at 80 mg/kg (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² basis). Embryo lethality was observed at 80 mg/kg/day (approximately 43,000 times the maximum recommended daily inhalation dose in adults on a mg/m² 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/m² 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 FEV₁ 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 FEV₁ ≤65% of predicted value and >0.70 L, and a FEV₁/ forced vital capacity (FVC) ratio ≤70%). About 80% of patients in these studies had bronchodilator reversibility, defined as a 10% or greater increase FEV₁ after inhalation of 2 actuations (180 mcg racemic albuterol from a metered dose inhaler). Both trials compared BROVANA 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 FEV₁ (as measured by percent change from study baseline FEV₁ at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo.

Compared to BROVANA 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 FEV₁, to support the use of higher doses. Plots of the mean change in FEV₁ values obtained over the 12 hours after dosing for the BROVANA 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 FEV₁ change observed after the first dose and after 12 weeks of treatment. The results from Clinical Trial B were similar.

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

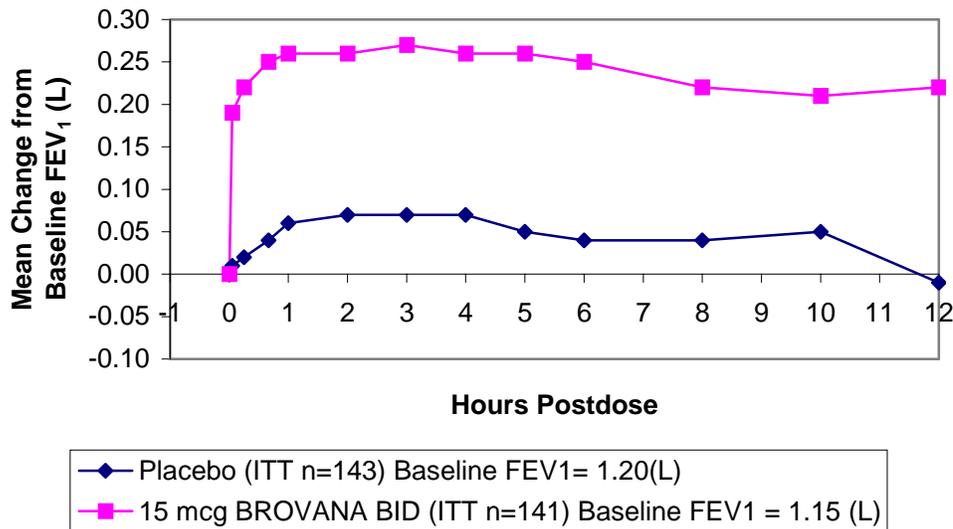
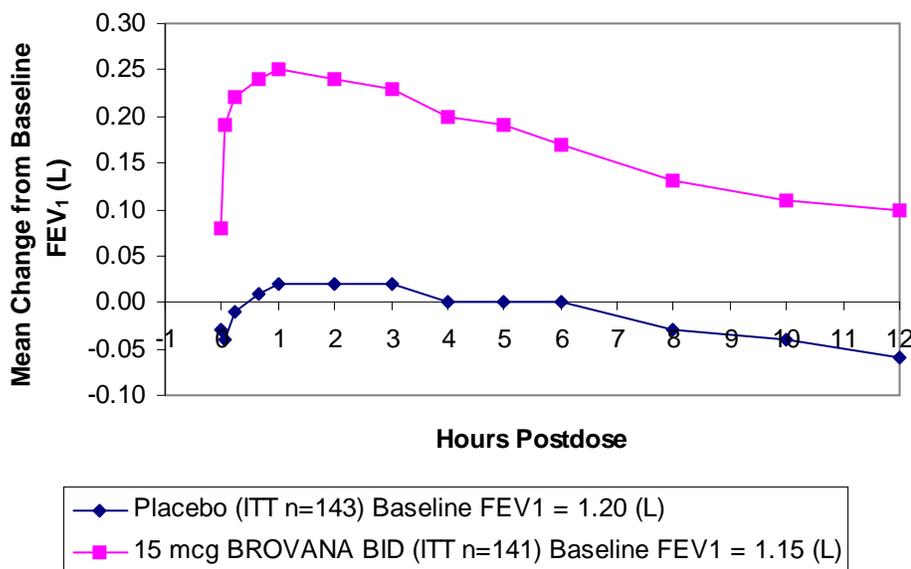


Figure 2 Mean Change in FEV₁ Over Time for Clinical Trial A at Week 12



BROVANA Inhalation Solution 15 mcg twice daily significantly improved bronchodilation compared to placebo over the 12 hours after dosing (FEV₁ AUC_{0-12h}). 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 FEV₁ increase of 15%, occurred at 6.7 min. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was 20 min after dosing. Peak bronchodilator effect was generally seen within 1-3 hours of dosing.

In both clinical trials, compared to placebo, patients treated with BROVANA 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

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

Asthma-Related Deaths, Acute Exacerbations or Deteriorations

Patients should be informed that long-acting beta₂-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, beta₂-agonist (the health-care provider should prescribe the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen 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 beta₂-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 beta₂-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 beta₂-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 Beta₂-agonists

Patients should be informed that treatment with beta₂-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

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.

Month Year

901005RXX