

New Drug Bulletin: Arformoterol tartrate (Brovana™ - Sepracor Inc.)

April 16, 2007

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Arformoterol is the first nebulized, long-acting beta-2 adrenergic bronchodilator on the market. It was approved by the FDA in October 2006 and is labeled for long-term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Arformoterol increases intracellular cyclic AMP levels leading to bronchial smooth muscle relaxation and also prevents mast cells from releasing inflammatory mediators. Arformoterol is the R-enantiomer of formoterol and is twice as potent as the racemic mixture.

Arformoterol is administered via nebulizer and is significantly absorbed through lung tissue. Onset of bronchodilation occurs within 7 minutes when defined as a 15% increase in forced expiratory volume in 1 second (FEV₁), and 20 minutes when defined as an increase in FEV₁ of 12% and 200 mL. Peak concentration occurs 30 minutes following administration, with maximum bronchodilation in 1 – 3 hours. At doses higher than the approved dosage, arformoterol is 52 – 65% bound to plasma protein. Arformoterol undergoes hepatic metabolism primarily through glucuronidation and also through O-demethylation by CYP2D6 and CYP2C19. The elimination half-life is 26 hours. Arformoterol is excreted in the urine (67%) and feces (22%) as metabolites.

Two 12-week, double-blind, randomized, controlled, multicenter, parallel group trials evaluated the efficacy of arformoterol 15 mcg twice daily (BID), 25 mcg BID, and 50 mcg daily compared with placebo. Salmeterol 42 mcg BID served as an active comparator in both trials although no results were reported. In both studies, FEV₁ increased significantly more with arformoterol 15 mcg BID than placebo. Improvement in FEV₁ lasted for 12 hours in most arformoterol patients. Higher doses did not demonstrate superior improvement in FEV₁.

Adverse effects of arformoterol are similar to those seen with other beta-2 agonists although specific frequencies are not available for these events, including angina, changes in blood pressure, tachycardia, arrhythmias or palpitation, nervousness, headache, and tremor. Adverse effects reported in arformoterol trials included pain (8%), chest pain (7%), back pain (6%), diarrhea (6%), sinusitis (5%), leg cramps (4%), dyspnea (4%), and rash (4%). Hypokalemia, hyperglycemia, and hypoglycemia were also reported, each occurring in less than 2% of patients. Hypokalemia is usually transient and does not require supplementation. In the clinical trials, the incidence of treatment-emergent arrhythmia was higher with arformoterol 25 mcg BID (37.6%) and 50 mcg daily (40.1%) compared to both other groups, although the rate of new-onset cardiac arrhythmias was similar for arformoterol 15 mcg BID and placebo (33 – 34%). Use arformoterol with caution in patients with baseline cardiovascular disease. Similar to other long-acting beta-2 agonists, arformoterol may increase the risk of asthma-related death and may cause paradoxical bronchospasm.

Pharmacodynamic interactions may occur with arformoterol. Concomitant administration with other drugs that alter potassium levels (eg, diuretics, corticosteroids, methylxanthines) may increase the risk of hypokalemia. Arformoterol's effects on the cardiovascular system may be potentiated by monoamine oxidase inhibitors, tricyclic antidepressants, and drugs that

prolong the QT interval. In one study, concurrent administration of theophylline and arformoterol increased heart rate 2 – 3 beats per minute and systolic blood pressure 6 – 8 mmHg compared with the general population. Paroxetine, a potent CYP2D6 inhibitor, does not affect the concentration of arformoterol.

The recommended dose is arformoterol 15 mcg via nebulizer BID in the morning and evening. Use of higher doses is not recommended due to increased adverse effects without additional benefits. Avoid using arformoterol as rescue therapy or in conjunction with other long-acting beta-2 agonists (ie, formoterol, salmeterol). Dosage adjustment is not necessary in renal or hepatic impairment.

Arformoterol is available as 15 mcg/2 mL nebulizer solution in unit dose vials. Refrigerate vials until use, then remove from foil pouch and use immediately after opening. There are no compatibility data for mixing arformoterol with other medications in the nebulizer. Sepracor plans to release arformoterol in the second quarter of 2007. Price information is not available.

In summary, the long-acting beta-2 agonist arformoterol may be an alternative for COPD patients unable to use formoterol (Foradil®) or salmeterol (Serevent®) powder inhalers. Arformoterol is not labeled for rescue therapy in patients with COPD.

References:

1. Brovana™ (arformoterol tartrate) package insert. Marlborough, MA: Sepracor Inc; October 2006.
2. FDA Approves Sepracor's Brovana™ (arformoterol tartrate) Inhalation Solution for Chronic Obstructive Pulmonary Disease. Available at: www.brovana.com. Accessed: February 14, 2007.

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