FDA Panel Gives Nod to MRSA Antimicrobial

BY ELIZABETH MECHCATIE
Senior Writer

COLLEGE PARK, MD. — Clinical trial data indicate that the antibiotic telavancin is safe and effective for treating complicated skin and skin structure infections, including those caused by methicillin-resistant *Staphylococcus aureus*, the majority of a federal advisory panel agreed.

At a November meeting, the Food and Drug Administration's anti-infective drugs advisory committee voted 21-5 regarding the safety and efficacy of telavancin. Those voting in favor said that while they were concerned about nephrotoxicity, QT prolongation, and possible teratogenic effects associated with the drug, they believed these risks were manageable.

The panel voted 18-5, with 3 abstentions, that there could be clinical situations in which the benefits of telavancin in pregnant women would outweigh its risks. All but one panelist agreed that a risk management strategy was needed to prevent unintended use in pregnant women or in women of childbearing potential.

Theravance Inc., the drug's manufacturer, has developed a risk management plan designed to minimize pregnancy exposures, the risk of nephrotoxicity, and the risk related to QT prolongation, and has proposed that the drug not be used during pregnancy unless the benefit to the patient outweighs the potential risks to the fetus.

The plan also includes recommendations to adjust the dose based on creatinine clearance and avoid the drug in patients with conditions such as congenital long QT syndrome and uncompensated heart failure.

Those voting no on the safety and efficacy question cited concerns about the association of the drug with more than one toxicity, "Safety concerns in multiple systems, not just one, complicate risk management," said the acting panel chair, Dr. L. Barth Reller, professor of medicine and pathology at Duke University, Durham, N.C. He added that since the mechanism of action was not that different from vancomycin, it was not certain how much its use would affect the problem of increasing resistance.

The FDA usually follows the advice of its advisory panels, which are not binding. The proposed indication for telavancin is for the treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, the *Streptococcus anginosus* group, and *Enterococcus faecalis*.

Telavancin's mechanism of action is not that much different from vancomycin, so it is not certain how much it would address increasing resistance.

Telavancin, a bactericidal lipoglycopeptide antibiotic that has bactericidal activity against most gram-positive bacteria, is administered intravenously once daily. It has a dual mechanism of action: It inhibits cell wall synthesis like vancomycin, but also disrupts the function of the bacterial membrane, according to Theravance.

For approval, the company submitted the results of two double-blind, randomized phase III noninferiority studies of almost 1,800 adults with cSSSI caused by gram-positive bacteria, enrolled from 2005 to 2006. (Half of the 1,320 patients with microbiologic confirmation of pathogens at baseline had MRSA). Patients were treated with telavancin (10 mg/kg IV once daily) or vancomycin (1 g IV every 12 hours).

FDA and company analyses of different outcome measures indicated that in both studies treatment with telavancin for 7-14 days was as effective as treatment with vancomycin—the current standard of care. Efficacy against MRSA infections was slightly better among those treated with telavancin, but the difference was not significant. Cure rates were lower among patients with severe renal impairment.

Telavancin was associated with common adverse events that were mostly mild or moderate. The rate of renal adverse events among those on telavancin was 3.4%, compared with 1.2% among those on vancomycin; the rate of severe renal adverse events also was higher among those on telavancin (1.2% vs. 0.4%, respectively). The company is recommending that serum creatinine be monitored during treatment. ■

BROVANA® (arformoterol tartrate) Inhalation Solution 15 mcg*/2 mL *potency expressed as arformoterol **FOR ORAL INHALATION ONLY BRIEF SUMMARY**

WARNING: Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-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 may apply to arformoterol (a long-acting beta$_2$-adrenergic agonist), the active ingredient in BROVANA (see WARNINGS).

INDICATIONS AND USAGE 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 is for use by nebulization only. **CONTRAINDICATIONS** BROVANA (arformoterol tartrate) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to arformoterol, racemic formoterol or to any other components of this product. **WARNINGS Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death**. 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 may represent a class effect of the long-acting beta$_2$-adrenergic agonists, including BROVANA. No study adequate to determine whether the rate of asthma-related death is increased in patients treated with BROVANA has been conducted. Clinical studies with racemic formoterol (Foradil® Aerolizer™) 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. **The studies described above enrolled patients with asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta$_2$-adrenergic agonists. BROVANA is indicated for the long term, twice daily (morning and evening) maintenance treatment for bronchoconstriction in chronic obstructive pulmonary disease (COPD), and is not indicated for the treatment of acute episodes of bronchospasm, ie, rescue therapy. BROVANA should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of BROVANA in this setting is inappropriate. BROVANA should not be used in children as the safety and efficacy of BROVANA have not been established in pediatric patients. BROVANA should not be used in conjunction with other inhaled, long-acting beta$_2$-agonists. BROVANA should not be used with other medications containing long-acting beta$_2$-agonists. When beginning treatment with BROVANA, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (eg, 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. Paradoxical Bronchospasm** As with other inhaled beta$_2$-agonists, BROVANA can produce paradoxical bronchospasm that may be life-theatening. If paradoxical bronchospasm occurs, BROVANA should be discontinued immediately and alternative therapy instituted. **Deterioration of Disease** COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BROVANA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta$_2$-agonist becomes less effective or the patient needs more inhalation of short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BROVANA beyond the recommended 15 mcg twice daily dose is not appropriate in this situation. **Cardiovascular Effects** BROVANA, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of BROVANA at the recommended dose, if they 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, as with other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension (see **PRECAUTIONS, General**). **Immediate Hypersensitivity Reactions** Immediate hypersensitivity reactions may occur after administration of BROVANA as demonstrated by cases of anaphylactic reaction, urticaria, angioedema, rash and bronchospasm. **Do Not Exceed Recommended Dose** Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. As with other inhaled beta$_2$-adrenergic drugs, BROVANA should not be used more often, at higher doses than recommended, or with other long acting beta-agonists. **PRECAUTIONS, General** BROVANA (arformoterol tartrate) Inhalation Solution should not be used to treat acute symptoms of COPD. BROVANA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. When prescribing BROVANA, the physician should also provide the patient with an inhaled, short-acting beta$_2$-agonist for treatment of COPD symptoms that occur acutely, despite regular twice-daily (morning and evening) use of BROVANA. Patients should also be cautioned that increasing inhaled beta$_2$-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. BROVANA, 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. Clinically significant changes in systolic and/or diastolic blood pressure, pulse rate and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with arformoterol tartrate. Doses of the related beta$_2$-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Beta-agonist medications may produce significant hypokalemia in some patients, possibly though intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were infrequent during clinical studies with long-term administration of BROVANA at the recommended dose. **Information for Patients Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill.** Patients should be given the following information: Patients should be informed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. BROVANA 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$_2$-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, if BROVANA treatment becomes less effective, or if they need more inhalations of a short-acting beta$_2$-agonist than usual. Patients should not inhale more than one dose at any one time. The daily dosage of BROVANA should not exceed one vial (15 mcg) by inhalation twice daily (30 mcg total daily dose). Patients should be informed that treatment with beta$_2$-agonists may lead to adverse events which include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Patients should be instructed to use BROVANA by nebulizer only and not to inject or swallow this inhalation solution. Patients should protect BROVANA single-use low-density polyethylene (LDPE) vials from light and excessive heat. The protective foil pouches should be stored under refrigeration between 2°C and 8°C (36°–46°F). They should not be used after the expiration date stamped on the container. Patients should be instructed that once the foil pouch is opened, the contents of the vial should be used immediately and to discard any vial if the solution is not colorless. The drug compatibility (physical and chemical), efficacy and safety of BROVANA when mixed with other drugs in a nebulizer have not been established. Women should be advised to contact their physician if they become pregnant or if they are nursing. It is important that patients understand how to use BROVANA appropriately and how it should be used in relation to other medications to treat COPD they are taking. **Drug Interactions** If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of BROVANA may be potentiated. When paroxetine, a potent inhibitor of CYP2D6, was co-administered with BROVANA at steady-state, exposure to either drug was not altered. Dosage adjustments of BROVANA are not necessary when the drug is given concomitantly with potent CYP2D6 inhibitors. Concomitant treatment with methylxanthines (aminophylline, theophylline), steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists. 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 with non-potassium sparing diuretics. BROVANA, as with other beta$_2$-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 the action 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. The concurrent use of intravenously or orally administered methylxanthines (eg, aminophylline, theophylline) by patients receiving BROVANA has not been completely evaluated. In two combined 12-week placebo controlled trials that included BROVANA doses of 15 mcg twice daily, 25 mcg twice daily, and 50 mcg once daily, 54 of 873 BROVANA-treated subjects received concomitant theophylline at study entry. In a 12-month controlled trial that included a 50 mcg once daily BROVANA dose, 30 of the 528 BROVANA-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. Beta-adrenergic receptor antagonists (beta-blockers) and BROVANA may interfere with 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. **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^2 basis). **Teratogenic Effects. Pregnancy Category C** 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). 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). There are no adequate and well-controlled studies in pregnant women. BROVANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Use in Labor and Delivery** There are no human studies that have investigated the effects of BROVANA on preterm labor or labor at term. Because beta-agonists may potentially interfere with uterine contractility, BROVANA should be used during labor and delivery only if the potential benefit justifies the potential risk. **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 is administered to a nursing woman. **Pediatric** BROVANA 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 effectiveness of BROVANA in pediatric patients have not been established. **Geriatric** Of the 873 patients who received BROVANA 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 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 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. **ADVERSE REACTIONS Experience in Adult Patients with COPD** Of the 1,456 COPD patients in the two 12-week, placebo-controlled trials, 288 were treated with BROVANA (arformoterol tartrate) inhalation solution 15 mcg twice daily and 293 were treated with placebo. The numbers and percent of patients who reported adverse events were comparable in the 15 mcg twice daily and placebo groups. Adverse events for which the rates in the BROVANA 15-mcg twice-daily group was equal to or greater than 2% and greater than that for the placebo group were (BROVANA and placebo rates, respectively) pain (8%, 5%), chest pain (7%, 6%), back pain (6%, 2%), diarrhea (6%, 4%), sinusitis (5%, 4%), leg cramps (4%, 2%), dyspnea (4%, 2%), rash (4%, 2%), flu syndrome (3%, 1%), peripheral edema (3%, 2%), lung disorder (2%, 1%). Ten adverse events demonstrated a dose relationship: asthenia, fever, bronchitis, COPD, headache, vomiting, hyperkalemia, leukocytosis, nervousness, and tremor. Overall, the frequency of all cardiovascular adverse events for BROVANA in the two placebo-controlled trials was low and comparable to placebo (6.9% in BROVANA 15-mcg twice-daily and 13.3% in the placebo group). There were no frequently occurring specific cardiovascular adverse events for BROVANA (frequency ≥1% and greater than placebo). The rate of COPD exacerbations was also comparable between the BROVANA 15-mcg twice-daily and placebo groups, 12.2% and 15.1%, respectively. Other adverse reactions that may occur with selective beta$_2$-adrenoceptor agonists, such as BROVANA, include angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis, and insomnia. **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**, e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 bpm, 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. Treatment of overdosage consists of discontinuation of BROVANA 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. 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/m^2 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^2 basis).

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