

Daptomycin Deemed Approvable for *S. aureus*

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Associate Editor

ROCKVILLE, MD. — The Food and Drug Administration's Anti-Infective Advisory Committee unanimously supported the approval of daptomycin (Cubicin) for *Staphylococcus aureus* bacteremia but was not as certain that the drug is safe and effective for infective endocarditis.

And despite the 9-0 vote on bacteremia, the panel had reservations. "I was shocked

at how low the overall cure rate was," said Dr. Jan Patterson, a committee member and professor of medicine at the University of Texas, San Antonio. "Nonetheless, it was as good as current therapy."

The panel voted 5-4 to approve daptomycin for infective endocarditis (IE). Those in favor said that since the drug was already being used off label—Cubist Pharmaceuticals estimated that 25% of off-label use is for *S. aureus* bacteremia—physicians should get better guidance. Panelists who voted against

approval for IE said there were too few patients in that arm to draw a conclusion.

Daptomycin was approved in 2003 for complicated skin and skin structure infections. Most physicians have been prescribing it at 4 mg/kg, but daptomycin was tested at 6 mg/kg for bacteremia and IE.

The FDA usually follows the advice of its advisory panels. In fact, within a few weeks of the meeting, the agency told Cubist that daptomycin was approvable, pending negotiations over the drug's label.

Cubist presented data from a 44-site, 236-patient trial, conducted during 2002-2005. Patients were randomized to daptomycin 6 mg/kg IV every 24 hours or vancomycin 1 g IV every 12 hours plus gentamicin 1 mg/kg every 8 hours for 4 days, or anti-staphylococcus penicillin 2 g every 4 hours, plus the gentamicin regimen. The intent-to-treat population was 120 patients in the daptomycin arm and 115 in the comparator arms. Patients had to have a positive blood culture within 2 days of enrollment.

The investigators judged success or failure after therapy. Success was defined as being clinically cured or improved; having a negative blood culture; and not receiving a potentially effective nonstudy antibiotic. Cure was assessed by a blinded independent panel 6 weeks post therapy.

The panel determined that the overall success rate, which included bacteremia and endocarditis, was 44% (53 of 120) for daptomycin and 42% (48 of 115) for the comparator group. The daptomycin and comparator success rates were higher for uncomplicated (56% and 55%) than for complicated bacteremia (43% for both).

The cure rate was not as high for IE, which was confirmed in a subset of the patients. For right-sided IE, 8 of 19 daptomycin patients were cured, vs. 7 of 16 in the comparator arm. For left-sided IE, 1 of 19 daptomycin patients were cured, vs. 2 of 9 in the comparator arm.

FDA reviewers and panel members were concerned about what they viewed as rising minimum inhibitory concentrations (MICs) of daptomycin. Peter Coderre, a microbiologist in the FDA's division of anti-infective and ophthalmology products, said breakpoints have not yet been established for intermediate and resistant isolates. According to the company, seven patients had high minimum inhibitory concentrations; only one was cured. He also noted that there have been eight reports of resistance to daptomycin since it was introduced last spring.

"The fact that you'll get resistance is no surprise," Dr. John Bradley, a panelist, and director of the infectious diseases division at Children's Hospital and Health Center in San Diego. "But in these seriously ill patients, the consequences are huge." Even so, he said he did not think a hint of resistance should prevent approval. Dr. Patterson said minimum inhibitory concentrations should be monitored closely, perhaps weekly, in treated patients.

Panel members were not as concerned about safety. Skeletal muscle is most often affected. Current labeling advises physicians to monitor creatine phosphokinase levels weekly and to consider discontinuing statins. In the trial, patients were monitored three times a week. Creatine phosphokinase elevations appear to be reversible, said Dr. Gloria Vigliani, Cubist's vice president of medical strategy.

BONIVA® (ibandronate sodium) INJECTION

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

- Known hypersensitivity to BONIVA Injection or to any of its excipients
- Uncorrected hypocalcemia (see **PRECAUTIONS: General**)

WARNINGS

BONIVA Injection, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values (see **PRECAUTIONS**). BONIVA Injection must only be administered intravenously. Care must be taken not to administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue damage. Do not administer BONIVA Injection by any other route of administration. The safety and efficacy of BONIVA Injection following non-intravenous routes of administration have not been established.

PRECAUTIONS: General

Mineral Metabolism: Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism must be effectively treated before starting BONIVA Injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

Renal Impairment: Treatment with intravenous bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (ie, increased serum creatinine) and in rare cases, acute renal failure. No cases of acute renal failure were observed in controlled clinical trials in which intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears to be inversely related to the rate of drug administration. Patients who receive BONIVA Injection should have serum creatinine measured prior to each dosage administration. Patients with concomitant diseases that have the potential for adverse effects on the kidney or patients who are taking concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate. Treatment should be withheld for renal deterioration. BONIVA Injection should not be administered to patients with severe renal impairment (ie, patients with serum creatinine >200 µmol/L [2.3 mg/dL] or creatinine clearance [measured or estimated] <30 mL/min).

Jaw Osteonecrosis: Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain: In postmarketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs includes BONIVA (ibandronate sodium) Injection. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Information for Patients: BONIVA Injection must be administered intravenously only by a health care professional. Patients should be instructed to read the Patient Information Leaflet carefully before BONIVA Injection is administered and to re-read it each time the prescription is renewed. BONIVA Injection should be administered once every 3 months. If the dose is missed, the injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer BONIVA Injection more frequently than once every 3 months. Patients must receive supplemental calcium and vitamin D.

Drug Interactions

See **FULL PRESCRIBING INFORMATION, CLINICAL PHARMACOLOGY: Drug Interactions**

Drug/Laboratory Test Interactions: Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 96 and 14 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increase in incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (32 to 51 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these findings to humans is unknown.

Mutagenesis: There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

Impairment of Fertility: In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea and implantation sites, and increased preimplantation loss were observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In male rats treated for 28 days prior to mating, a decrease in sperm production and altered sperm morphology were observed at intravenous doses ≥0.3 mg/kg/day (≥40 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Pregnancy: Pregnancy Category C. In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17 post-coitum until Day 20 postpartum, ibandronate treatment resulted in dystocia, maternal mortality, and early postnatal pup loss in all dose groups (≥2 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Reduced body weight at birth was observed at 0.15 and 0.5 mg/kg/day (≥4 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal odontology that decreased food consumption and body weight gain at 0.15 and 0.5 mg/kg/day (≥18 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia. Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at an intravenous dose of 1 mg/kg/day (≥47 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In this spontaneous delivery study, dystocia was counteracted by perinatal calcium supplementation. In rat studies with intravenous dosing during gestation, fetal weight and pup growth were reduced at doses ≥0.1 mg/kg/day (≥5 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the period of organogenesis, maternal mortality, reduced maternal body weight gain, decreased litter size due to increased resorption rate, and decreased fetal weight were observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg every 3 months, based on cumulative body surface area comparison, mg/m²). Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established. There are no adequate and well-controlled studies in pregnant women. BONIVA Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers: In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the patients receiving BONIVA Injection 3 mg every 3 months for 1 year (DIVA study), 51% were over 65 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity in some older individuals cannot be ruled out.

ADVERSE REACTIONS

Daily Oral Tablet: Treatment with BONIVA 2.5 mg daily oral tablet was studied, in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily tablet in these studies was similar to that of placebo.

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily oral tablet group and the placebo group. Overall, and according to body system, there was no difference between BONIVA daily oral tablet and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

Table 1 lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated with BONIVA 2.5 mg daily oral tablet than patients treated with placebo. Adverse events are shown without attribution of causality.

Table 1: Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated with BONIVA 2.5 mg Daily Oral Tablet than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies

Body System	Placebo (n=1134)	BONIVA 2.5 mg daily (n=1140)
Body as a Whole		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
Digestive System		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
Metabolic and Nutritional Disorders		
Hypercholesterolemia	4.2	4.8
Musculoskeletal System		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
Nervous System		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
Respiratory System		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
Urogenital System		
Urinary Tract Infection	4.2	5.5

Quarterly IV Injection: In a 1-year, double-blind, multicenter study comparing BONIVA Injection administered intravenously as 3 mg every 3 months to BONIVA 2.5 mg daily oral tablet in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two dosing regimens were similar. The incidence of serious adverse events was 8.0% in the BONIVA 2.5 mg daily group and 7.5% in the BONIVA Injection 3 mg once every 3 months group. The percentage of patients who withdrew from treatment due to adverse events was approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the BONIVA Injection 3 mg every 3 months group.

Table 2 lists the adverse events reported in >2% of patients without attribution of causality.

Table 2: Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA Injection (3 mg once every 3 months) or BONIVA Daily Oral Tablet (2.5 mg)

Body System/Adverse Event	BONIVA 2.5 mg Daily (Oral) % (n=465)	BONIVA 3 mg q 3 mo (IV) % (n=469)
Infections and Infestations		
Influenza	8.0	4.7
Nasopharyngitis	6.0	3.4
Cystitis	3.4	1.9
Gastroenteritis	3.4	1.5
Urinary Tract Infection	3.2	2.6
Bronchitis	2.8	2.1
Upper Respiratory Tract Infection	2.8	1.1
Gastrointestinal Disorders		
Abdominal Pain*	5.6	5.1
Dyspepsia	4.3	3.6
Nausea	4.3	2.1
Constipation	4.1	3.4
Diarrhea	2.4	2.8
Gastritis	2.2	1.9
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	8.6	9.6
Back Pain	7.5	7.0
Localized Osteoarthritis	2.4	1.5
Pain in Extremity	2.2	2.8
Myalgia	0.9	2.8
Nervous System Disorders		
Dizziness	2.8	1.9
Headache	2.6	3.6
Vascular Disorders		
Hypertension	7.1	5.3
Psychiatric Disorders		
Insomnia	2.6	1.1
Depression	2.2	1.3
General Disorders and Administration Site Conditions		
Influenza-like illness†	1.1	4.9
Fatigue	1.1	2.8
Skin and Subcutaneous Tissue Disorders		
Rash‡	2.8	2.3
Metabolism and Nutrition		
Hypercholesterolemia	4.3	1.5

*Is a combination of abdominal pain and abdominal pain upper.

†Combination of influenza-like illness and acute phase reaction.

‡Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash papular, rash generalized, dermatitis medicamentosa, rash erythematous.

Acute Phase Reaction-like Events: Symptoms consistent with acute phase reaction (APR) have been reported with intravenous bisphosphonate use. The overall incidence of patients with APR-like events was higher in the intravenous treatment group (4% in the BONIVA 2.5 mg daily oral tablet group vs. 10% in the BONIVA Injection 3 mg once every 3 months group). These incidence rates are based on reporting of any of 33 potential APR-like symptoms within 3 days of an IV dose and for a duration of 7 days or less. In most cases, no specific treatment was required and the symptoms subsided within 24 to 48 hours.

Injection Site Reactions: Local reactions at the injection site, such as redness or swelling, were observed infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%; 1/465). In most cases, the reaction was of mild to moderate severity.

Ocular Adverse Events: Bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

Laboratory Test Findings: There were no clinically significant changes from baseline values or shifts in any laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3 months induced clinically significant laboratory abnormalities indicative of hepatic or renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

OVERDOSAGE: No cases of overdose were reported in premarketing studies with BONIVA Injection. Intravenous overdose may result in hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. Dialysis would not be beneficial unless it is administered within 2 hours following the overdose.

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