# Daptomycin Deemed Approvable for *S. aureus*

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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 antistaphylococcus 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).

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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. with 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. ■