

# Data Drive Revisions in PCI, STEMI Guidelines

BY ROBERT FINN  
San Francisco Bureau

The pace of research in cardiology is proceeding so rapidly that important changes have been issued to two guidelines initially promulgated in the not-so-distant past.

The "focused updates" involve the treatment of ST-elevation myocardial infarction (STEMI) and the technique of percutaneous coronary intervention (PCI). While the updates maintained many of the recommendations in the full guidelines, issued in 2004 for STEMI and 2005 for PCI, they each included significant recommendations for practice changes. (See boxes.)

The STEMI updates, for example, reiterate that the overarching goal of treatment remains rapid reperfusion. But they state that, with the exception of aspirin, NSAIDs and cyclooxygenase-2 inhibitors should be discontinued immediately. And  $\beta$ -blockers should not be administered to patients in certain high-risk groups.

The PCI updates emphasized the importance of ensuring that patients will be able to comply with dual antiplatelet therapy for a full year after receiving a drug-eluting stent. Bare-metal stents should be substituted when that compliance can't be ensured. This dual antiplatelet therapy is so important that physicians should take into account the possibility that the patient may later need medical procedures that would require that antiplatelet therapy be discontinued. Bare-metal stents or balloon angioplasty with provisional stent implantation should be considered for those patients.

The STEMI update was a joint effort of the American College of Cardiology and the American Heart Association and appeared in *Circulation* and the *Journal of the American College of Cardiology*. The PCI update was a joint effort of the ACC, the AHA, and the Society for Cardiovascular Angiography and Interventions (SCAI) and appeared in *Circulation*, the *Journal of the American College of Cardiology*, and *Catheterization and Cardiovascular Interventions*. The updates

are available online at [www.americanheart.org](http://www.americanheart.org) and [www.acc.org](http://www.acc.org).

The focused update strategy was developed by the ACC/AHA Task Force on Practice Guidelines as a way to speed up the often years-long process of developing comprehensive new guidelines on the basis of full literature reviews. Twice a year or more experts are polled, and if there is a consensus that data from late-breaking clinical trials warrant an update, one can be prepared relatively quickly.

According to Dr. Elliott M. Antman, cochair of the STEMI update committee and chair of the 2004 writing committee, new research suggests several important changes in the management of this most critical type of heart attack. Among at least 15 guideline modifications or additions, he highlighted several in an interview.

"We indicate that physicians should not routinely administer intravenous  $\beta$ -blockers acutely to patients with heart failure or shock, or who are at risk for heart failure

*Continued on following page*

## Highlights of the Percutaneous Coronary Intervention Updates

1. After implantation of a drug-eluting stent (DES), dual antiplatelet therapy comprising clopidogrel and aspirin is required for at least 1 year or longer.
2. If the patient is likely to face additional surgery requiring interruption of dual antiplatelet therapy, a bare-metal stent (BMS) or balloon angioplasty with provisional stent implantation should be considered instead of a DES.
3. Between 24 hours and 28 days after a heart attack, PCI is not recommended in patients with one- or two-vessel dis-

- ease and a totally occluded coronary artery if they are not hemodynamically and electrically stable and have no ongoing or easily provoked chest pain.
4. On the other hand, physicians might consider PCI for those patients or patients who respond favorably to initial fibrinolysis treatment if they don't continue to do well on drug therapy alone.
5. The balance of the evidence supports an early invasive strategy for PCI in patients with unstable angina or non-STEMI who are at moderate and higher risk.

6. In patients with STEMI, facilitated PCI with regimens other than full-dose fibrinolytic therapy may be considered in high-risk patients if PCI is not immediately available within 90 minutes and if the risk of bleeding is low.
7. In patients with STEMI, a planned reperfusion strategy using full-dose fibrinolytic therapy followed by immediate PCI may be harmful.
8. A strategy of coronary angiography with the intent to perform rescue PCI is reasonable for those patients in

- whom fibrinolytic therapy has failed.
9. The update includes specific guidelines for ancillary therapy in patients undergoing PCI for STEMI who received prior treatment with unfractionated heparin, enoxaparin, or fondaparinux.
10. Serum LDL cholesterol should be maintained below 100 mg/dL after PCI, and further reduction to less than 70 mg/dL is reasonable.

Source: J. Am. Coll. Cardiol. 2008;51:172-209.

## CLASSIFIEDS

[www.ehospitalistnews.com](http://www.ehospitalistnews.com)

### MICHIGAN

Medical Director needed for hospitalist program at 64-bed hospital in northern Michigan. BC/BP Internal Medicine or Med-Peds; 1-2 years experience in hospitalist or in-house setting preferred. Full-time experienced hospitalist also needed at 136-bed hospital in Livingston County, just north of Ann Arbor, Michigan. BC/BP IM. Hospitalists are responsible for covering general medical floors, ICU, ventilator management, coordination of codes, rounding, and more. 24/7 programs. Full-time HPMG employees enjoy competitive compensation, paid family medical benefits, Rx, dental, vision, life, LTD, 401(k), paid malpractice, CME, relocation, and much more. Please contact Tynia Arnold at 800-466-3764, x335 or [tarnold@hpmgpc.com](mailto:tarnold@hpmgpc.com). Visit HPMG at SHM Booth 511.

### Hospitalists

Campbell County Memorial Hospital in Gillette Wyoming is seeking two Hospitalists. We offer an exceptional staff and an excellent work environment. Earn market driven compensation, competitive benefits and live in a state with no state tax, excellent schools and abundant outdoor activities. Located an hour from the Big Horn Mountains and less than an hour from the Black Hills of South Dakota. For immediate consideration send your CV to [mindergrs@cmh.net](mailto:mindergrs@cmh.net) or call 1-307-688-1554. J1 and H1 candidates welcomed!

### OHIO HOSPITALIST OPPORTUNITIES

~ Cincinnati & Springfield locations  
~ Desirable schedule with minimal call  
~ Shareholder opportunity at one year with no buy-in!  
~ Benefits include pension, family medical plan, expense account & more  
**Premier Health Care Services** provides hospitalists the opportunity for a highly satisfying career with appealing equity ownership model. Contact Kim Avalos, (800) 726-3627, ext 3674.  
e-mail [kavalos@phcsday.com](mailto:kavalos@phcsday.com)  
fax (937) 312-3675.

### Beverly Hospital Beverly, Massachusetts

Private, well-respected and established, growing Hospitalist group 25 miles north of Boston is seeking full-time and part-time BC/BE internists with exemplary clinical and interpersonal skills to practice in a community hospital setting just north of Boston. Nocturnist coverage greatly minimizes night shifts and block scheduling allows for schedule predictability. For our full-time Hospitalists, we offer competitive salary, full benefits, and partnership opportunities. For immediate consideration, please send a cover letter and copy of your CV to Kathy Reed at [kreed@nhs-healthlink.org](mailto:kreed@nhs-healthlink.org). Tel. #978-922-3000, x3059.

Elite Hospitalist Opportunities in Dallas and El Paso, Texas and Las Vegas, Nevada with well respected MedicalEdge Healthcare. Flexible rounding schedules with production based high income potential! Full Benefit Package including health, life, dental and 401K with Match. Practice autonomy with the support of a \$300 million dollar a year company. Additional outpatient IM practice opportunities also available in the Dallas area. For more information please contact [kisenberg@med-edge.com](mailto:kisenberg@med-edge.com) 972 739 3721

### Moving?

Look to Classified Notices for practices available in your area.

### CLASSIFIED ADVERTISING DEADLINES

Absolute deadline for all advertising copy, cancellations, and changes is the 1st of the month prior to month of publication.

All copy, cancellations, and changes for issues must be received in the Classified Advertising office by 12 noon of the deadline date, whether via phone or mail.

For further information, contact John Baltazar, Hospitalist News, 360 Park Avenue South, New York, NY 10010. (212) 633-3829. FAX: (212) 633-3820.  
Email ad to: [j.baltazar@elsevier.com](mailto:j.baltazar@elsevier.com)

# Highlights of the ST-Elevation Myocardial Infarction Updates

1. As in the 2004 guidelines, the overarching goal for treatment of ST elevation myocardial infarction is that reperfusion therapy should begin within 2 hours, and ideally within 1 hour of the event.

2. The emphasis on percutaneous coronary intervention should not obscure the importance of fibrinolytic therapy.

3. With the exception of aspirin, all NSAIDs and cyclooxygenase-2 inhibitors should be discontinued immediately at the time of STEMI.

4. Early intravenous  $\beta$ -blocker therapy should not be given to STEMI patients who have signs of heart failure or other relative contraindications to  $\beta$ -blockade.

5. Long-term oral  $\beta$ -blockers should be used for secondary prevention in patients at high risk once they have stabilized.

6. The strategy of facilitated PCI (planned PCI immediately after administration of therapy to improve coronary patency) may be considered in subgroups of patients with a large MI

or hemodynamic or electrical instability who are at low risk of bleeding.

7. Rescue PCI is suitable for patients who have received fibrinolytic therapy and who have cardiogenic shock, ventricular arrhythmia, or severe heart failure and/or pulmonary edema.

8. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for at least 48 hours and preferably for the duration of the initial hospital stay up to 8 days.

9. Clopidogrel should be added to aspirin in patients with STEMI whether or not they receive reperfusion therapy, and the clopidogrel should be continued for at least 14 days.

10. Emergency medical systems that provide advanced life support should increase the use of prehospital 12-lead electrocardiography.

Sources: J. Am. Coll. Cardiol. 2008;51:210-47

Continued from previous page

or shock,” said Dr. Antman of Harvard Medical School, Boston. “There is information about facilitated PCI indicating that a strategy of a full-dose fibrinolytic followed by immediate routine PCI is not recommended anymore.”

On the other hand, “It’s not unreasonable to use a strategy of preparatory pharmacological regimen other than a full-dose fibrinolytic and routine immediate PCI in certain situations where the patient is at risk, PCI cannot be performed within 90 minutes, and bleeding risk is low.”

Dr. Antman said that he has not heard any significant criticisms of the new STEMI guidelines, and that most will not be difficult to implement. “Physicians understand the importance of responding to evidence,” he said. “These are strategies that are a matter of just organizing systems of care for patients with STEMI. We would hope that physicians would meet as a team in their local hospitals and local systems and consider how they are going to approach the STEMI patients in the future with this new information in mind.”

The recommendation for prehospital 12-lead ECG may be one of the most challenging to implement, since many emergency medical technicians are not trained in interpreting ECGs, and many ambulance systems don’t have prehospital ECG capability, he added.

In the PCI update, “We are reaching a point where we really have to look across time and also understand the impact of adjunctive therapies, and how we combine all of this I think is a real challenge,” said Dr. Sidney C. Smith Jr., cochair of the focused update writing committee, in an interview posted on the ACC’s Cardiosource Web site ([www.cardiosource.com/guidelinefocus](http://www.cardiosource.com/guidelinefocus)).

“My personal opinion is that comprehensive therapy really has a place in the management of patients,” continued Dr. Smith of the University of North Carolina, Chapel Hill. “I still think that the high-risk patients, the patients that are symptomatic, benefit from revascularization, but we definitely are getting to a point where I personally will be urging and being certain that my patients not only have revascularization when they need it, but that they adhere to the comprehensive medical therapies that are so important in terms of reducing future events.”

Each of the focused updates includes detailed information about potential conflicts of interest among members of the writing committees. Individual members who appeared to have a conflict recused themselves from voting on certain sections. ■

## Once-A-Day CUBICIN® (daptomycin for injection)

Brief summary of prescribing information.

**INDICATIONS AND USAGE** CUBICIN (daptomycin for injection) is indicated for the following infections (see also **DOSE AND ADMINISTRATION** and **CLINICAL STUDIES** in full prescribing information): **Complicated skin and skin structure infections (cSSSI)** caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. ***Staphylococcus aureus* bloodstream infections** (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see **CLINICAL STUDIES** in full prescribing information). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis. Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection (see **PRECAUTIONS**). CUBICIN is not indicated for the treatment of pneumonia. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin. Empiric therapy may be initiated while awaiting test results. Antimicrobial therapy should be adjusted as needed based upon test results. To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS** CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

**WARNINGS** *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CUBICIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

**PRECAUTIONS** **General** The use of antibiotics may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Persisting or Relapsing *S. aureus* Infection** Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection. Appropriate surgical intervention (eg, debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required. Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8%) CUBICIN-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 CUBICIN-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see **CLINICAL STUDIES** in full prescribing information).

**Skeletal Muscle** In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no skeletal muscle effects or CPK elevations were observed. In Phase 3 cSSSI trials of CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients. In the *S. aureus* bacteremia/endocarditis trial, at a dose of 6 mg/kg, elevations in CPK were reported as clinical adverse events in 8/120 (6.7%) CUBICIN-treated patients compared with 1/116 (<1%) comparator-treated patients. There were a total of 11 patients who experienced CPK elevations to above 500 U/L. Of these 11 patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Skeletal muscle effects associated with CUBICIN were observed in animals (see **ANIMAL PHARMACOLOGY** in full prescribing information). Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor. In patients with renal insufficiency, both renal function and CPK should be monitored more frequently. Patients who develop unexplained elevations in CPK while receiving CUBICIN should be monitored more frequently. In the cSSSI studies, among patients with abnormal CPK (>500 U/L) at baseline, 2/19 (10.5%) treated with CUBICIN and 4/24 (16.7%) treated with comparator developed further increases in CPK while on therapy. In this same population, no patients developed myopathy. CUBICIN-treated patients with baseline CPK >500 U/L (N=19) did not experience an increased incidence of CPK elevations or myopathy relative to those treated with comparator (N=24). In the *S. aureus* bacteremia/endocarditis study, 3 (2.6%) CUBICIN-treated patients, including 1 with trauma

associated with a heroin overdose and 1 with spinal cord compression, had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. None of the patients in the comparator group had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1,000 U/L (~5x ULN), or in patients without reported symptoms who have marked elevations in CPK >2,000 U/L ( $\geq 10\times$  ULN). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN. In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no evidence of nerve conduction deficits or symptoms of peripheral neuropathy was observed. In a small number of patients in Phase 1 and Phase 2 studies at doses up to 6 mg/kg, administration of CUBICIN was associated with decreases in nerve conduction velocity and with adverse events (eg, paresthesias, Bell’s palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In Phase 3 cSSSI and community-acquired pneumonia (CAP) studies, 7/989 (0.7%) CUBICIN-treated patients and 7/1,018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In the *S. aureus* bacteremia/endocarditis trial, a total of 11/120 (9.2%) CUBICIN-treated patients had treatment-emergent adverse events related to the peripheral nervous system. All of the events were classified as mild to moderate in severity; most were of short duration and resolved during continued treatment with CUBICIN or were likely due to an alternative etiology. In animals, effects of CUBICIN on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY** in full prescribing information). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving CUBICIN. **Drug Interactions**

**Warfarin** Concomitant administration of CUBICIN (6 mg/kg q24h for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the INR was not significantly altered. As experience with the concomitant administration of CUBICIN and warfarin is limited, anticoagulant activity in patients receiving CUBICIN and warfarin should be monitored for the first several days after initiating therapy with CUBICIN (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information). **HMG-CoA Reductase Inhibitors** Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in a placebo-controlled Phase 1 trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with CUBICIN (4 mg/kg q24h) for 14 days. In the Phase 3 *S. aureus* bacteremia/endocarditis trial, 5/22 CUBICIN-treated patients who received prior or concomitant therapy with an HMG-CoA reductase inhibitor developed CPK elevations >500 U/L. Experience with co-administration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving CUBICIN (see **ADVERSE REACTIONS, Post-Marketing Experience**). **Drug-Laboratory Test Interactions** There are no reported drug-laboratory test interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an in vivo micronucleus assay, an in vitro DNA repair assay, and an in vivo sister chromatid exchange assay in Chinese hamsters. Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the estimated human exposure level based upon AUCs. **Pregnancy Teratogenic Effects: Pregnancy Category B** Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 2 and 4 times the 6 mg/kg human dose, respectively, on a body surface area basis, have revealed no evidence of harm to the fetus due to daptomycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** It is not known if daptomycin is excreted in human milk. Caution should be exercised when CUBICIN is administered to nursing women. **Pediatric Use** Safety and efficacy of CUBICIN in patients under the age of 18 have not been established. **Geriatric Use** Of the 534 patients treated with CUBICIN in Phase 3 controlled clinical trials of cSSSI, 27.0% were 65 years of age or older and 12.4% were 75 years of age or older. Of the 120 patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25.0% were 65 years of age or older and 15.8% were 75 years of age or older. In Phase 3 clinical studies of cSSSI and *S. aureus* bacteremia/endocarditis, lower clinical success rates were seen in patients  $\geq 65$  years of age compared with those <65 years of age. In addition, treatment-emergent adverse events were more common in patients  $\geq 65$  years old than in patients <65 years of age.

**ADVERSE REACTIONS** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Clinical studies sponsored by Cubist enrolled 1,667 patients treated with CUBICIN and 1,319 treated with comparator. Most adverse events reported in Cubist-sponsored Phase 1, 2, and 3 clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse event, while comparator was discontinued in 17/558 (3.0%) patients. In the *S. aureus* bacteremia/endocarditis trial, CUBICIN was discontinued in 20/120 (16.7%) patients due to an adverse event, while comparator was discontinued in 21/116 (18.1%) patients. **Gram-Negative Infections** In the *S. aureus* bacteremia/endocarditis trial, serious Gram-negative infections and nonserious Gram-negative bloodstream infections were reported in 10/120 (8.3%) CUBICIN-treated and 0/115 comparator-treated patients. Comparator patients received dual therapy that included initial gentamicin for 4 days. Events were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn’s disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative organisms. One patient with sternal osteomyelitis following mitral valve repair developed *S. aureus* endocarditis with a 2 cm mitral vegetation and had a course complicated with bowel infarction, polymicrobial bacteremia, and death. **Other Adverse Reactions** The incidence (%) of adverse events that occurred in  $\geq 2\%$  of patients in either CUBICIN 4 mg/kg (N=534) or comparator (N=558) treatment groups in Phase 3 cSSSI studies were as follows: *Gastrointestinal Disorders*: constipation 6.2% and 6.8%; nausea 5.8% and 9.5%; diarrhea 5.2% and 4.3%; vomiting 3.2% and 3.8%; dys-

pepsia 0.9% and 2.5%; *General Disorders*: injection site reactions 5.8% and 7.7%; fever 1.9% and 2.5%; *Nervous system disorders*: headache 5.4% and 5.4%; insomnia 4.5% and 5.4%; dizziness 2.2% and 2.0%; *Skin/subcutaneous disorders*: rash 4.3% and 3.8%; pruritus 2.8% and 3.8%; *Diagnostic investigations*: abnormal liver function tests 3.0% and 1.6%; elevated CPK 2.8% and 1.8%; *Infections*: fungal infections 2.6% and 3.2%; urinary tract infection 2.4% and 0.5%; *Vascular disorders*: hypotension 2.4% and 1.4%; hypertension 1.1% and 2.0%; *Renal/urinary disorders*: renal failure 2.8% and 2.7%; *Blood/lymphatic disorders*: anemia 2.1% and 2.3%; *Respiratory disorders*: dyspnea 2.1% and 1.6%; *Musculoskeletal disorders*: limb pain 1.5% and 2.0%; arthralgia 0.9% and 2.2%. \*Comparators included vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (ie, nafcillin, oxacillin, cloxacillin, flucloxacillin; 4 to 12 g/day IV in divided doses). The incidence (%) of adverse events that occurred in  $\geq 5\%$  of patients organized by system organ class (SOC), in either CUBICIN 6 mg/kg (N=120) or comparator (N=116) treatment groups in the *S. aureus* bacteremia/endocarditis study were as follows: *Infections and Infestations*: 65 (54.2%) and 56 (48.3%); urinary tract infection NOS 8 (6.7%) and 11 (9.5%); osteomyelitis NOS 7 (5.8%) and 7 (6.0%); sepsis NOS 6 (5.0%) and 3 (2.6%); bacteremia 6 (5.0%) and 0 (0%); pneumonia NOS 4 (3.3%) and 9 (7.8%); *Gastrointestinal Disorders*: 60 (50.0%) and 68 (58.6%); diarrhoea NOS 14 (11.7%) and 21 (18.1%); vomiting NOS 14 (11.7%) and 15 (12.9%); constipation 13 (10.8%) and 14 (12.1%); nausea 12 (10.0%) and 23 (19.8%); abdominal pain NOS 7 (5.8%) and 4 (3.4%); dyspepsia 5 (4.2%) and 8 (6.9%); loose stools 5 (4.2%) and 6 (5.2%); gastrointestinal haemorrhage NOS 2 (1.7%) and 6 (5.2%); *General Disorders and administration site conditions*: 53 (44.2%) and 69 (59.5%); oedema peripheral 8 (6.7%) and 16 (13.8%); pyrexia 8 (6.7%) and 10 (8.6%); chest pain 8 (6.7%) and 7 (6.0%); oedema NOS 8 (6.7%) and 5 (4.3%); asthenia 6 (5.0%) and 6 (5.2%); injection site erythema 3 (2.5%) and 7 (6.0%); *Respiratory, thoracic, and mediastinal disorders*: 38 (31.7%) and 43 (37.1%); pharyngolaryngeal pain 10 (8.3%) and 2 (1.7%); pleural effusion 7 (5.8%) and 8 (6.9%); cough 4 (3.3%) and 7 (6.0%); dyspnoea 4 (3.3%) and 6 (5.2%); *Skin and subcutaneous tissue disorders*: 36 (30.0%) and 40 (34.5%); rash NOS 8 (6.7%) and 10 (8.6%); pruritus 7 (5.8%) and 6 (5.2%); erythema 6 (5.0%) and 6 (5.2%); sweating increased 6 (5.0%) and 0 (0%); *Musculoskeletal and connective tissue disorders*: 35 (29.2%) and 42 (36.2%); pain in extremity 11 (9.2%) and 11 (9.5%); back pain 8 (6.7%) and 10 (8.6%); arthralgia 4 (3.3%) and 13 (11.2%); *Psychiatric Disorders*: 35 (29.2%) and 28 (24.1%); insomnia 11 (9.2%) and 8 (6.9%); anxiety 6 (5.0%) and 6 (5.2%); *Nervous system disorders*: 32 (26.7%) and 32 (27.6%); headache 8 (6.7%) and 12 (10.3%); dizziness 7 (5.8%) and 7 (6.0%); *Investigations*: 30 (25.0%) and 33 (28.4%); blood creatine phosphokinase increased 8 (6.7%) and 1 (<1%); *Blood and lymphatic system disorders*: 29 (24.2%) and 24 (20.7%); anaemia NOS 15 (12.5%) and 18 (15.5%); *Metabolism and nutrition disorders*: 26 (21.7%) and 38 (32.8%); hypokalaemia 11 (9.2%) and 15 (12.9%); hyperkalaemia 6 (5.0%) and 10 (8.6%); *Vascular disorders*: 21 (17.5%) and 20 (17.2%); hypertension NOS 7 (5.8%) and 3 (2.6%); hypotension NOS 6 (5.0%) and 9 (7.8%); *Renal and urinary disorders*: 18 (15.0%) and 26 (22.4%); renal failure NOS 4 (3.3%) and 11 (9.5%); renal failure acute 4 (3.3%) and 7 (6.0%); \*Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (ie, nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin. The following events, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group: *Blood and Lymphatic System Disorders*: eosinophilia (1.7%), lymphadenopathy (<1%), thrombocytopenia (<1%), thrombocytopenia (<1%); *Cardiac Disorders*: atrial fibrillation (<1%), atrial flutter (<1%), cardiac arrest (<1%); *Ear and Labyrinth Disorders*: tinnitus (<1%); *Eye Disorders*: vision blurred (<1%); *Gastrointestinal Disorders*: dry mouth (<1%), epigastric discomfort (<1%), gingival pain (<1%), hypoaesthesia oral (<1%); *Infections and Infestations*: candidial infection NOS (1.7%), vaginal candidiasis (1.7%), fungaemia (<1%), oral candidiasis (<1%), urinary tract infection fungal (<1%); *Investigations*: blood phosphorous increased (2.5%), blood alkaline phosphatase increased (1.7%), INR ratio increased (1.7%), liver function test abnormal (1.7%), alanine aminotransferase increased (<1%), aspartate aminotransferase increased (<1%), prothrombin time prolonged (<1%); *Metabolism and Nutrition Disorders*: appetite decreased NOS (<1%); *Musculoskeletal and Connective Tissue Disorders*: myalgia (<1%); *Nervous System Disorders*: dyskinesia (<1%), paraesthesia (<1%); *Psychiatric Disorders*: hallucination NOS (<1%); *Renal and Urinary Disorders*: proteinuria (<1%), renal impairment NOS (<1%); *Skin and Subcutaneous Tissue Disorders*: heat rash (<1%), pruritus generalized (<1%), rash vesicular (<1%). In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**). The incidence of decreased renal function based on creatinine clearance levels in CUBICIN 6 mg/kg (N=120) and comparator (N=116) was as follows: Days 2 to 4, 2/96 (2.1%) and 6/90 (6.7%); Days 2 to 7, 6/115 (5.2%) and 16/113 (14.2%); Day 2 to End of Therapy, 13/118 (11.0%) and 30/114 (26.3%). \*Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (ie, nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin. **Post-Marketing Experience** The following adverse reactions have been reported with CUBICIN in worldwide post-marketing experience. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. *Immune System Disorders*: anaphylaxis; hypersensitivity reactions, including pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia. *Musculoskeletal System*: rhabdomyolysis; some reports involved patients treated concurrently with CUBICIN and HMG-CoA reductase inhibitors.

**OVERDOSAGE** In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered over 4 hours) or peritoneal dialysis (approximately 11% recovered over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with low-flux membranes.

**DOSE** The recommended dosage of CUBICIN (daptomycin for injection) in adult patients is as follows: *Creatinine clearance ( $CL_{CR}$ )  $\geq 30$  mL/min*: 4 mg/kg once every 24 hours (cSSSI) or 6 mg/kg once every 24 hours (*S. aureus* bloodstream infections); *Creatinine clearance ( $CL_{CR}$ ) <30 mL/min, including hemodialysis or CAPD*: 4 mg/kg once every 48 hours (cSSSI) or 6 mg/kg once every 48 hours (*S. aureus* bloodstream infections).



3985072607  
CUBIST is a registered trademark of Cubist Pharmaceuticals, Inc.  
©2003–2007 Cubist Pharmaceuticals, Inc.