

External Counterpulsation Reduces Mortality

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CHICAGO — Enhanced external counterpulsation therapy results in significantly increased left ventricular ejection fraction and improved 1-year survival in patients with advanced ischemic heart disease, according to two studies presented by Dr. William E. Lawson at the annual meeting of the American College of Cardiology.

Enhanced external counterpulsation

(EECP) already is covered by Medicare and other third-party payers for relief of refractory symptoms of angina pectoris or heart failure. Prior studies have documented that the noninvasive outpatient therapy results in improvements in myocardial perfusion, endovascular function, exercise capacity, and quality of life.

These two new studies provide the first evidence of additional benefits in the key areas of mortality and ventricular function, noted Dr. Lawson, professor of med-

icine and director of preventive cardiology and heart center outcomes research at Stony Brook (N.Y.) University.

In one study, he analyzed the records of 4,597 patients with end-stage coronary disease enrolled in the prospective observational International EECP Patient Registry. He compared 1-year outcomes in the 3,962 patients who completed the standard course of 35 hours of EECP over 7 weeks with the 14% who completed fewer than 30 hours (a mean of 13 hours).

After censoring deaths within 60 days of starting EECP as a potential confounding variable, researchers report the 1-year mortality in EECP completers as 4.1%, vs. 14.1% in noncompleters. There were significant differences in other 1-year outcomes as well: 85% of EECP completers had improved by at least one Canadian Cardiovascular Society angina functional class, compared with 25% of noncompleters; and 4.1% in the completer group had an MI, vs. 7.7% of noncompleters.

Baseline characteristics of the two groups were similar: 89% had previously undergone a revascularization procedure, 70% had a prior MI, 92% had class III or IV

angina, and only 15% were candidates for coronary revascularization.

In a separate study conducted by Dr. Lawson and cardiologists at the People's College of Medical Sciences and Research Center, Jamnagar, India, 505 patients

with ischemic heart disease underwent 2-D echocardiography 1 week before starting a 35-hour, 7-week course of EECP and again within 1 week after completing therapy.

Among the 145 patients who had a baseline left ventricular (LV) ejection fraction (EF) of 35% or less, EF increased from a mean baseline of 29% to 45%, while stroke volume improved from 68 mL to 75 mL with no change in heart rate.

In the 360 patients with a baseline EF greater than 35%, EECP was associated with an increase from a mean baseline of 48% to 56% post therapy, while stroke volume rose from 78 mL to 86 mL.

These beneficial changes in cardiac function resulted chiefly from a significant reduction in LV end systolic volume from 59 mL to 53 mL in the group with a baseline EF of 35% or less, and from 55 mL to 50 mL in patients with a baseline EF above 35%. There was no significant change in LV end diastolic volume, he continued.

Dr. Lawson is on the speakers bureau for Vasomedical Inc., which markets a proprietary EECP system.



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 (≥10x 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 ≥65 years of age compared with those <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥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 infection, 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 ≥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 2.2% 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%. *Comparator included vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (ie, nafcillin, oxacillin, cloxacillin, fluclloxacillin; 4 to 12 g/day IV in divided doses). The incidence (%) of adverse events that occurred in ≥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%); bacteraemia 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, fluclloxacillin; 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%), thrombocythaemia (<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*: candidal 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, fluclloxacillin; 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, tracheal 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}) ≥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).



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