DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Mr. Michael W. Bonney
President & CEO
Cubist Pharmaceuticals
65 Hayden Avenue
Lexington, MA 02421

Re: NDA # 21-572
Cubicin™ (daptomycin for injection)
MACMIS # 12433

WARNING LETTER

Dear Mr. Bonney:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) for Cubicin™ (daptomycin for injection), submitted by Cubist Pharmaceuticals (Cubist) under cover of Form FDA 2253. The ad fails to reveal important risk information associated with the use of Cubicin and, therefore, misbrands the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. See 21 U.S.C. 321(n), 352(n); 21 C.F.R. 202.1(e)(3)(i). Additionally, DDMAC has reviewed promotional statements for this drug that appear on a website (URL: http://www.cubicin.com) maintained by Cubist, and also submitted on Form FDA 2253. The website is misleading because it broadens the indication for Cubicin, fails to reveal important risk information associated with the use of Cubicin, and makes an unsubstantiated comparative claim. Therefore, the website misbrands Cubicin. See 21 U.S.C. 321(n), 352(a), (n). Your broadening of the indication for Cubicin and failure to reveal important risk information associated with the use of Cubicin poses serious public health and safety concerns because the inappropriate use of Cubicin can result in therapeutic failure, and increases in morbidity and mortality in infections for which Cubicin has not been proven safe and effective.

Background

The Indications and Usage section of the approved product labeling (PI) for Cubicin states:

> "CUBICIN (daptomycin for injection) is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms (see also **DOSAGE AND ADMINISTRATION**): *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimillis* and *Enterococcus faecalis* (vancomycin-susceptible strains only). Combination therapy may be clinically indicated if

the documented or presumed pathogens include Gram-negative or anaerobic organisms (see **CLINICAL STUDIES**).

Daptomycin is not indicated for the treatment of pneumonia.

Cubicin is associated with several important contraindications, warnings, precautions, and adverse events. For example, the Precautions section of the PI for Cubicin contains the following important risk information:

> "***Skeletal Muscle:*** In Phase 3 complicated skin and skin structure infection (cSSSI) trials, elevations in serum creatine phosphokinase (CPK) were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/558 (1.8%) comparator-treated patients. Skeletal muscle effects associated with daptomycin were observed in animals (see **ANIMAL PHARMACOLOGY**).
>
> Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. CPK levels should be monitored weekly in patients who receive CUBICIN. Patients who develop unexplained elevations in CPK while receiving daptomycin should be monitored more frequently. Among patients with abnormal CPK (>500 U/L) at baseline, 2/19% (10.5%) treated with CUBICIN and 4/24 (16.6%) treated with comparator developed further increases in CPK while on therapy. In this same population, no patients developed myopathy. Daptomycin-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).
>
> CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000U/L (~5x ULN), or in patients without reported symptoms who have marked elevations in CPK (≥10x UNL). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN."

Broadening of Indication

Your website implies that Cubicin is safe and effective, and FDA-approved, for the treatment of all infections caused by *Staphylococcus aureus* (including methicillin-resistant strains).

For example, the following claims appear on the first page of your website:

- "CUBICIN is the only once-daily, rapidly bactericidal antibiotic proven effective against both MRSA [methicillin-resistant Staphylococcus aureus]and MSSA [methicillin-susceptible Staphylococcus aureus]"
- "Serious against Staph"
- "Proven clinically successful against MRSA and MSSA"
- "Bactericidal against MRSA and MSSA"
- "Once a day—the only QD agent approved for treatment of MRSA and MSSA"

These claims are misleading because they imply that Cubicin is safe and effective, and FDA-approved, for all infections caused by MRSA and MSSA (e.g., endocarditis and pneumonia), when this has not been demonstrated by substantial evidence or substantial clinical experience. The PI specifically states that Cubicin is indicated for "the treatment of complicated skin and skin structure infections [cSSSI] caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimillis* and *Enterococcus faecalis* (vancomycin-susceptible strains only) (emphasis added). Also, the PI specifically states that "Daptomycin is not indicated for the treatment of pneumonia" (emphasis added). The Adverse Reactions section of the PI also describes an important reason for this limitation: "In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events" (emphasis added).

FDA is not aware of substantial evidence or substantial clinical experience to support the efficacy of Cubicin in non-cSSSI infections. Blurring the distinction between cSSSI and non-cSSSI infections by statements that combine and generalize all *Staphylococcus aureus* infections, such as "Proven clinically successful against MRSA and MSSA," and suggesting that Cubicin is proven safe and effective, and approved by FDA, to treat all such infections is misleading and poses a significant public health risk because such practice could lead to therapeutic failure and death.

Failure to Reveal Important Risk Information

The ad and website fail to reveal material facts in light of representations made and with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the main part of the ad presents effectiveness claims for Cubicin, such as "New AGAINST STAPH" and "The only once-daily bactericidal antibiotic---with a distinct mechanism of action---proven effective against both MRSA and MSSA," but fails to provide any risk information. For example, you fail to include information on the risk of increased CPK levels and the risk for development of muscle pain or weakness, which is described in the precautions section of the PI for Cubicin. This information is necessary to qualify the effectiveness claims appearing in the main part of the ad. The main part of the ad includes a reference to the brief summary of prescribing information; however, this statement is not sufficient to provide the appropriate qualification or pertinent information for the claims made in the main part of the ad. See 21 CFR 202.1(e)(3)(i).

The website is similarly misleading because it fails to reveal important risk information necessary for context on pages containing information about the efficacy of Cubicin. For example, you fail to include information on the risk of increased CPK levels and the risk for development of muscle pain or weakness, which is described in the Precautions section of the PI for Cubicin.

DDMAC had previously objected, in an untitled letter dated November 22, 2000, to your failure to disclose facts that are material in light of the representations made in promotion about CUBICIN. Specifically, Cubist failed to disclose important risk information about Cubicin on your website. We are concerned that you are continuing to promote Cubicin in a similarly violative manner.

Misleading Comparative Claim

Promotional materials are false or misleading if they suggest that a drug is superior to other products when such has not been demonstrated by substantial evidence or substantial clinical experience. Your website includes the claim "Bactericidal antibiotics are generally regarded as superior to bacteriostatic agents for the treatment of most infections." This claim implies that, because Cubicin is a bactericidal antibiotic, it is superior to other antibiotics intended for the same conditions when such has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, as noted in the Adverse Reactions section of the PI and previously described, Cubicin was determined to be inferior to comparator agents in the treatment of CAP. FDA is not aware of substantial evidence or substantial clinical experience to support the superior efficacy of bactericidal antibiotics compared to bacteriostatic agents. Furthermore, the statement in your website, "However, clinical data to support this position are lacking except in specific indications," does not adequately correct this misleading presentation.

Conclusion and Requested Action

Your ad and website fail to reveal material facts regarding important risk information associated with the use of Cubicin in accordance with 21 U.S.C. 321(n), 352(a), (n); 21 C.F.R. 202.1(e)(3)(i). Furthermore, your website suggests that Cubicin is useful in all infections caused by MRSA and MSSA when such has not been demonstrated by substantial evidence or substantial clinical experience and makes an unsubstantiated comparative claim in violation of 21 U.S.C. 201(n), 352(a), (n).

DDMAC requests that Cubist immediately cease the dissemination of violative promotional materials for Cubicin such as those described above. Please submit a written response to this letter on or before August 31, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Cubicin such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12433 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Cubicin comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Chong
8/17/04 03:37:37 PM

The only once-daily bactericidal antibiotic—with a distinct mechanism of action—proven effective against both MRSA and MSSA.

Once-A-Day
CUBICIN™
(daptomycin for injection)

CUBICIN is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible strains only).

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 caused by bacteria.

CUBICIN is not indicated for the treatment of pneumonia.

Please see brief summary of prescribing information on previous page.

CUBIST PHARMACEUTICALS

CUBICIN™
(daptomycin for injection)

Brief summary of prescribing information.

INDICATIONS AND USAGE

CUBICIN (daptomycin for injection) is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms (see also **DOSAGE AND ADMINISTRATION**): *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp *equisimilis* and *Enterococcus faecalis* (vancomycin-susceptible strains only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms (see **CLINICAL STUDIES** in full prescribing information).

Daptomycin 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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including daptomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

If a diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C difficile*.

PRECAUTIONS

General: The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Skeletal Muscle: In Phase 3 complicated skin and skin structure infection (cSSSI) trials, elevations in serum creatine phosphokinase (CPK) were reported as clinical adverse events in 15/534 (2.8%) daptomycin-treated patients, compared to 10/558 (1.8%) comparator-treated patients. Skeletal muscle effects associated with daptomycin were observed in animals (see **ANIMAL PHARMACOLOGY**).

Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. CPK levels should be monitored weekly in patients who receive CUBICIN. Patients who develop unexplained elevations in CPK while receiving daptomycin should be monitored more frequently. 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. Daptomycin-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).

CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000 U/L (~5x ULN), or in patients without reported symptoms who have marked elevations in CPK (≥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 small number of patients in Phase 1 and Phase 2 studies, 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 CAP studies, 7/989 (0.7%) daptomycin-treated patients and 7/1018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In animals, effects of daptomycin on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving CUBICIN.

Drug Interactions: **Warfarin** Concomitant administration of daptomycin (6 mg/kg once every 24 hours 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 daptomycin and warfarin is limited to volunteer studies, anticoagulant activity in patients receiving daptomycin 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 I trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with daptomycin (4 mg/kg once every 24 hours) for 14 days. 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.

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, 3 and 6 times the human dose, respectively, on a body surface area basis, have revealed no evidence of harm to the fetus due to CUBICIN. 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 complicated skin and skin structure infection, 27.0% were 65 years of age or older and 12.4% were 75 years or older. In the two Phase 3 clinical studies in patients with cSSSI, lower clinical success rates were seen in patients ≥65 years of age compared to 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 in both cSSSI studies.

ANIMAL PHARMACOLOGY

In animals, daptomycin administration has been associated with effects on skeletal muscle with no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by degenerative/regenerative changes and variable elevations in CPK. No fibrosis or rhabdomyolysis was evident in repeat dose studies up to the highest doses tested in rats (150 mg/kg/day) and dogs (100 mg/kg/day). The degree of skeletal myopathy showed no increase when treatment was extended from 1 month to up to 6 months. Severity was dose dependent. All muscle effects, including microscopic changes, were fully reversible within 30 days following cessation of dosing.

In adult animals, effects on peripheral nerve (characterized by axonal degeneration and frequently accompanied by significant losses of patellar reflex, gag reflex, and pain perception) were observed at doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks of the start of treatment at 40 mg/kg (3.5 times the human AUC), with some clinical improvement noted within 2 weeks of the cessation of dosing. However, at 75 mg/kg daily for 1 month, 7/8 dogs failed to regain full patellar reflex responses within the duration of a 3 month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted at 6 months after cessation of dosing. However, recovery of peripheral nerve function was evident.

Tissue distribution studies in rats have shown that daptomycin is retained in the kidney but does not appear to penetrate across the blood-brain barrier following single and multiple doses.

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 to 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 1409 patients treated with daptomycin and 1185 treated with comparator. Most adverse events reported in these clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, daptomycin was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients.

The rates of most common adverse events, organized by body system, observed in cSSSI patients are displayed in the following table.

Incidence (%) of Adverse Events that Occurred in ≥ 2% of Patients in Either Daptomycin or Comparator Treatment Groups in Phase 3 cSSSI Studies

Adverse Event	Daptomycin (N=534)	Comparator* (N=558)
Gastrointestinal disorders		
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General disorders		
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous system disorders		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/subcutaneous disorders		
Rash	4.3%	3.8%
Pruritis	2.8%	3.8%
Diagnostic investigations		
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections		
Fungal infections	2.6%	3.2%
Urinary tract infections	2.4%	0.5%
Vascular disorders		
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/urinary disorders		
Renal failure	2.2%	2.7%
Blood/lymphatic disorders		
Anemia	2.1%	2.3%
Respiratory disorders		
Dyspnea	2.1%	1.6%
Musculoskeletal disorders		
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

*Comparators included vancomycin (1 g IV q12h) and semi-synthetic penicillins (ie, nafcillin, oxacillin, cloxacillin, flucloxacillin; 4-12 g/day in divided doses)

In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**). Additional adverse events that occurred in 1-2% of patients in either daptomycin- or comparator-treatment groups in the cSSSI studies are as follows: edema, cellulitis, hypoglycemia, elevated alkaline phosphatase, cough, back pain, abdominal pain, hypokalemia, hyperglycemia, decreased appetite, anxiety, chest pain, sore throat, cardiac failure, confusion, and Candida infections. These events occurred at rates ranging from 0.2-1.7% in daptomycin-treated patients and at rates of 0.4-1.8% in comparator-treated patients.

Additional drug-related adverse events (possibly or probably related) that occurred in <1% of patients receiving daptomycin in cSSSI trials are as follows:

Body as a Whole: fatigue, weakness, rigors, discomfort, jitteriness, flushing, hypersensitivity

Blood/Lymphatic System: leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased international normalized ratio

Cardiovascular System: supraventricular arrhythmia

Dermatologic System: eczema

Digestive System: abdominal distension, flatulence, stomatitis, jaundice, increased serum lactate dehydrogenase

Metabolic/Nutritional System: hypomagnesemia, increased serum bicarbonate, electrolyte disturbance

Musculoskeletal System: myalgia, muscle cramps, muscle weakness, osteomyelitis

Nervous System: vertigo, mental status change, paraesthesia

Special Senses: taste disturbance, eye irritation

Laboratory Changes

Incidence (%) of Creatine Phosphokinase (CPK) Elevations From Baseline While on Therapy in Either Daptomycin or Comparator Treatment Groups in Phase 3 cSSSI Studies

	All Patients				Patients With Normal CPK at Baseline			
	Daptomycin (N=430)		Comparator (N=459)		Daptomycin (N=374)		Comparator (N=392)	
	%	n	%	n	%	n	%	n
No Increase	90.7	390	91.1	418	91.2	341	91.1	357
Maximum Value >1x ULN*	9.3	40	8.9	41	8.8	33	8.9	35
>2x ULN	4.9	21	4.8	22	3.7	14	3.1	12
>4x ULN	1.4	6	1.5	7	1.1	4	1.0	4
>5x ULN	1.4	6	0.4	2	1.1	4	0.0	0
>10x ULN	0.5	2	0.2	1	0.2	1	0.0	0

*ULN (Upper Limit of Normal) is defined as 200 U/L.

Note: Elevations in CPK observed in patients treated with daptomycin or comparator were not clinically or statistically significantly different ($P < 0.05$).

In clinical trials, 0.2% of patients treated with CUBICIN had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal. The symptoms resolved within 3 days and CPK returned to normal within 7-10 days after discontinuing treatment (see **PRECAUTIONS, Skeletal Muscle**). In Phase 3 comparator-controlled trials, there was no clinically or statistically significant difference ($P < 0.05$) in the frequency of CPK elevations between patients treated with CUBICIN and those treated with comparator. CPK elevations in both groups were generally related to medical conditions, for example, skin and skin structure infection, surgical procedures, or intramuscular injections, and were not associated with muscle symptoms.

There were no substantial differences between CUBICIN and the comparators in the frequency or distribution of changes in other laboratory parameters, regardless of drug relationship.

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 by peritoneal dialysis (approximately 11% recovered over 48 hours).

DOSAGE AND ADMINISTRATION

Complicated Skin and Skin Structure Infections: CUBICIN 4 mg/kg should be administered over a 30-minute period by intravenous infusion in 0.9% sodium chloride injection once every 24 hours for 7-14 days. Doses of CUBICIN higher than 4 mg/kg/day have not been studied in Phase 3 controlled clinical trials. In Phase 1 and 2 clinical studies, CPK elevations appeared to be more frequent when daptomycin was dosed more frequently than once daily. Therefore, CUBICIN should not be dosed more frequently than once a day.

Because daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as listed in the following table. The recommended dosing regimen is 4 mg/kg once every 24 hours for patients with CL_{CR} ≥ 30 mL/min and 4 mg/kg once every 48 hours for CL_{CR} <30 mL/min, including those on hemodialysis or CAPD. When possible, CUBICIN should be administered following hemodialysis on hemodialysis days (see **CLINICAL PHARMACOLOGY** in full prescribing information).

Recommended Dosage of CUBICIN (daptomycin for injection) in Adult Patients With Renal Impairment

Creatinine Clearance	Dosage Regimen
≥30 mL/min	4 mg/kg once every 24 hours
<30 mL/min, including hemodialysis or CAPD	4 mg/kg once every 48 hours

Preparation of Daptomycin for Administration: CUBICIN is supplied in single-use vials containing either 250 or 500 mg daptomycin as a sterile, lyophilized powder. The contents of a CUBICIN 250 mg vial should be reconstituted with 5 mL of 0.9% sodium chloride injection. The contents of a CUBICIN 500 mg vial should be reconstituted with 10 mL of 0.9% sodium chloride injection. Reconstituted CUBICIN should be further diluted with 0.9% sodium chloride injection to be administered by intravenous infusion over a period of 30 minutes.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of final intravenous solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature or up to 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F). The diluted solution is stable in the infusion bag for 12 hours at room temperature or 48 hours if stored under refrigeration. The combined time (vial and infusion bag) at room temperature should not exceed 12 hours; the combined time (vial and infusion bag) under refrigeration should not exceed 48 hours.

CUBICIN vials are for single-use only.

Parenteral drug products should be inspected visually for particulate matter prior to administration.

Because only limited data are available on the compatibility of CUBICIN with other intravenous substances, additives or other medications should not be added to daptomycin single-use vials or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed with a compatible infusion solution before and after infusion with daptomycin.

Compatible Intravenous Solutions: CUBICIN is compatible with 0.9% sodium chloride injection and lactated Ringer's injection. CUBICIN is not compatible with dextrose-containing diluents.

CUBIST PHARMACEUTICALS

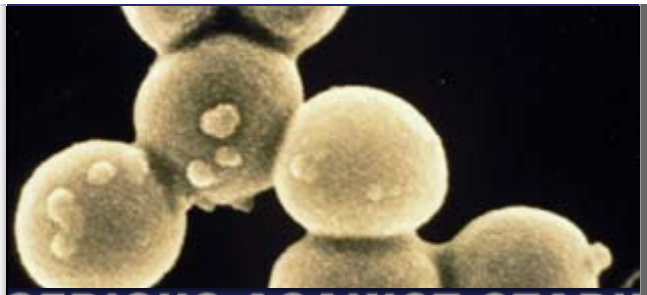
1206112103

CUBICIN™
(daptomycin for injection)

- FACTS ABOUT CUBICIN
- FULL PRESCRIBING INFORMATION
- SUSCEPTIBILITY TESTING INFORMATION
- INFECTIOUS DISEASES NEWS
- EVENTS & EDUCATIONAL OPPORTUNITES
- CLINICAL TRIALS

This site is provided by Cubist Pharmaceuticals for prescribing health-care professionals.

CUBIST PHARMACEUTICALS



SERIOUS AGAINST STAPH

CUBICIN is the only once-daily, rapidly bactericidal antibiotic proven effective against both MRSA and MSSA.

- New class, distinct mechanism of action
- Proven clinically successful against MRSA and MSSA
- Bactericidal against MRSA and MSSA
- Generally well tolerated in clinical trials
- Once a day--the only QD agent approved for treatment of MRSA and MSSA

View our recently launched ad campaign (PDF, 858k)

NEW ON THE SITE

Welcome to the CUBICIN Web site. Here you can find our package insert and information on susceptibility testing guidelines.

FULL PRESCRIBING INFORMATION

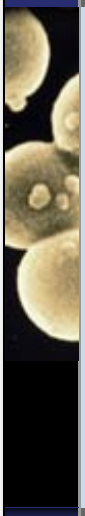
Download Large Version
16 pages (PDF, 328k)

Download Compact Version
3 pages (PDF, 95k)

To view PDF files use the free Adobe Acrobat Reader.

CUBICIN™ (daptomycin for injection)

Bactericidal Action



Bactericidal antibiotics are generally regarded as superior to bacteriostatic agents for the treatment of most infections. However, clinical data to support this position are lacking except in specific indications. This slide set highlights the clinical implications of bactericidal versus bacteriostatic antibiotics.

BACTERICIDAL ACTION DOWNLOADS

Download Bactericidal v. Bacteriostatic Slide Kit
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