Cubicin™

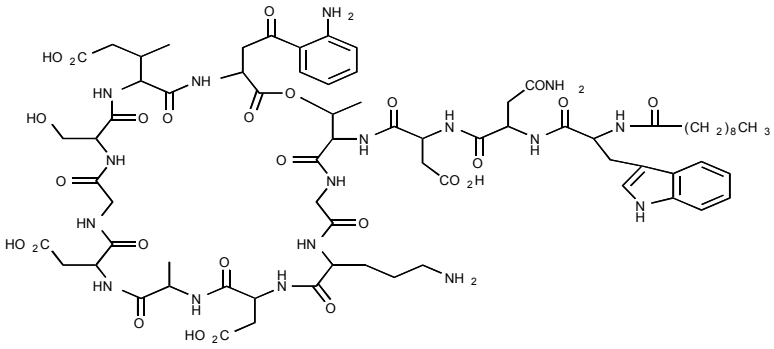
(daptomycin for injection)

Rx 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.

DESCRIPTION

Cubicin contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. The chemical name is *N*-decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine ε_1-lactone. The chemical structure is:



The empirical formula is $C_{72}H_{101}N_{17}O_{26}$; the molecular weight is 1620.67. Cubicin is supplied as a sterile, preservative-free, pale yellow to light brown, lyophilized cake containing approximately 900 mg/g of daptomycin for intravenous use following reconstitution with 0.9% sodium chloride injection. The only inactive ingredient is sodium hydroxide which is used in minimal quantities for pH adjustment. Freshly reconstituted solutions of Cubicin range in color from pale yellow to light brown.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The mean (SD) pharmacokinetic parameters of daptomycin on Day 7 following the intravenous administration of 4 mg/kg, 6 mg/kg, and 8 mg/kg q24h to healthy young adults (mean age 35.8 years) are summarized in Table 1.

Table 1. Mean (SD) Daptomycin Pharmacokinetic Parameters in Healthy Volunteers on Day 7

Dose mg/kg	C_{max} (μg/mL)	T_{max}* (h)	AUC_{0-24} (μg*h/mL)	$t_{1/2}$ (h)	V_d (L/kg)	CL_T (mL/h/kg)	CL_R (mL/h/kg)	Ae_{24} %
4 (n=6)	57.8 (3.0)	0.8 (0.5, 1.0)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	4.8 (1.3)	53.0 (10.8)
6 (n=6)	98.6 (12)	0.5 (0.5,1.0)	747 (91)	8.9 (1.3)	0.104 (0.013)	8.1 (1.0)	4.4 (0.3)	47.4 (11.5)
8 (n=6)	133 (13.5)	0.5 (0.5,1.0)	1130 (117)	9.0 (1.2)	0.092 (0.012)	7.2 (0.8)	3.7 (0.5)	52.1 (5.19)

*Median (minimum, maximum)

C_{max} = Maximum plasma concentration; T_{max} = Time to C_{max}; AUC_{0-24} = Area under concentration-time curve from 0 to 24 hours; $t_{½}$ = Terminal elimination half-life; V_d = Apparent volume of distribution; CL_T = Systemic clearance; CL_R = renal clearance; Ae_{24} = Percent of dose recovered in urine over 24 hours as unchanged daptomycin following the first dose.

Daptomycin pharmacokinetics are nearly linear and time-independent at doses up to 6 mg/kg administered once daily for 7 days. Steady-state concentrations are achieved by the third daily dose. The mean (SD) steady-state trough concentrations (Days 4 to 8) attained following administration of 4, 6, and 8 mg/kg q24h are 5.9 (1.6), 9.4 (2.5) and 14.9 (2.9) μg/mL, respectively.

Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean serum protein binding of daptomycin was approximately 92% in healthy adults after the administration of 4 mg/kg or 6 mg/kg. Serum protein binding was not altered as a function of daptomycin concentration, dose, or number of doses received.

In clinical studies, mean serum protein binding in subjects with CL_{CR} ≥30 mL/min was comparable to that observed in healthy subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among subjects with CL_{CR} <30 mL/min (87.6%) including hemodialysis patients (85.9%) and CAPD patients (83.5%). The protein binding of daptomycin in subjects with hepatic impairment (Child-Pugh B) was similar to healthy adult subjects.

The apparent volume of distribution of daptomycin at steady-state in healthy adult subjects was approximately 0.09 L/kg.

Metabolism

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome (CYP) P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs

metabolized by the CYP P450 system. It is unknown whether daptomycin is a substrate of the CYP P450 system.

In five healthy young adults after infusion of radiolabeled ^{14}C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites of daptomycin have been detected in the urine, as determined by the difference in total radiolabeled concentrations and microbiologically active concentrations. The site of metabolism has not been identified.

Excretion

Daptomycin is excreted primarily by the kidney. In a mass balance study of five healthy subjects using radiolabeled daptomycin, approximately 78% of the administered dose was recovered from urine based on total radioactivity (approximately 52% of the dose based on microbiologically active concentrations) and 5.7% of the dose was recovered from feces (collected for up to nine days) based on total radioactivity.

Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with severe renal insufficiency (CL_{CR} < 30 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Special Populations

Renal Insufficiency

Population derived pharmacokinetic parameters were determined for patients with skin and skin structure infections and healthy non-infected subjects with varying degrees of renal function (n=282). Following the administration of a single 4 mg/kg IV dose of daptomycin, the plasma clearance (CL_T) was reduced and the systemic exposure ($AUC_{0-\infty}$) was increased with decreasing renal function (see Table 2). The mean $AUC_{0-\infty}$ was not markedly different for subjects and patients with CL_{CR} 30-80 mL/min as compared to those with normal renal function (CL_{CR} >80mL/min). The mean $AUC_{0-\infty}$ values for subjects and patients with CL_{CR} <30 mL/min and hemodialysis (dosed post dialysis)/CAPD subjects were approximately 2- and 3-times higher, respectively, than the values in individuals with normal renal function. The mean C_{max} ranged from 59.6 μg/mL to 69.6 μg/mL in subjects with $CL_{CR} \geq$ 30 mL/min while those with CL_{CR} <30 mL/min ranged from 41.1 μg/mL to 57.7 μg/mL. In 11 non-infected adult subjects undergoing dialysis, approximately 15% and 11% of the administered dose was removed by 4 hours of hemodialysis and 48 hours of CAPD, respectively. The recommended dosing regimen is 4 mg/kg once every 24 hours for patients with $CL_{CR} \geq$ 30 mL/min and 4 mg/kg once every 48 hours for CL_{CR} <30 mL/min, including those on hemodialysis and CAPD. Daptomycin should be administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE AND ADMINISTRATION**).

Table 2. Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following a Single 30-Minute Intravenous Infusion of 4 mg/kg to Infected Patients and Non-Infected Subjects with Varying Degrees of Renal Function

Renal Function	$AUC_{0-\infty}$ (μg*h/mL)	$t_{1/2}$ (h)	Vss (L/kg)	CL_T (mL/h/kg)
Normal (CL_{CR} >80 mL/min) (N=165)	417 (155)	9.39 (4.74)	0.13 (0.05)	10.9 (4.0)
Mild Renal Impairment (CL_{CR} 50-80 mL/min) (N=64)	466 (177)	10.75 (8.36)	0.12 (0.05)	9.9 (4.0)
Moderate Renal Impairment (CL_{CR} 30-<50 mL/min) (N=24)	560 (258)	14.70 (10.50)	0.15 (0.06)	8.5 (3.4)
Severe Renal Impairment (CL_{CR} <30 mL/min) (N=8)	925 (467)	27.83 (14.85)	0.20 (0.15)	5.9 (3.9)
Hemodialysis and CAPD (N=21)	1244 (374)	29.81 (6.13)	0.15 (0.04)	3.7 (1.9)

Note: CL_{CR} = Creatinine clearance estimated using the Cockroft-Gault equation with actual body weight.

Hepatic Insufficiency

The pharmacokinetics of daptomycin were evaluated in 10 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with healthy volunteers (n=9) matched for gender, age and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when administering daptomycin to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency have not been evaluated.

Gender

No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed between healthy male and female subjects. No dosage adjustment is warranted based on gender when administering daptomycin.

Geriatric

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥ 75 years of age) and 11 healthy young matched controls (18-30 years of age). Following administration of a single intravenous 4 mg/kg dose, the mean total clearance of daptomycin was reduced approximately 35% and the mean $AUC_{0-\infty}$ increased approximately 58% in elderly subjects compared to young healthy subjects. There were no differences in C_{max}. No dosage adjustment is warranted for elderly patients with normal (for age) renal function.

Obesity

The pharmacokinetics of daptomycin were evaluated in six moderately obese (Body Mass Index [BMI] 25-39.9 kg/m^2) and six extremely obese (BMI ≥40 kg/m^2) subjects and controls matched for age, sex, and renal function. Following administration of a single intravenous 4 mg/kg dose

based on total body weight, the plasma clearance of daptomycin increased approximately 18% in moderately obese subjects and 46% in extremely obese subjects compared with non-obese controls. The $AUC_{0-\infty}$ of daptomycin increased approximately 30% in moderately obese and 31% in extremely obese subjects compared with non-obese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No dosage adjustment of daptomycin is warranted in obese subjects.

Pediatric

The pharmacokinetics of daptomycin in pediatric populations (<18 years of age) have not been established.

Drug-Drug Interactions

Drug-drug interaction studies were performed with daptomycin and other drugs that are likely to either be co-administered or associated with overlapping toxicity.

Aztreonam

In a study in which 15 healthy adult subjects received a single dose of daptomycin IV 6 mg/kg, aztreonam 1,000 mg IV, and both in combination, the C_{max} and $AUC_{0-\infty}$ of daptomycin were not significantly altered by aztreonam; the C_{max} and $AUC_{0-\infty}$ of aztreonam were also not significantly altered by daptomycin. No dosage adjustment of either antibiotic is warranted when co-administered.

Tobramycin

In a study in which 6 healthy adult males received a single dose of daptomycin IV 2 mg/kg, tobramycin IV 1 mg/kg, and both in combination, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin increased 12.7% and 8.7%, respectively, when administered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin decreased 10.7% and 6.6%, respectively, when administered with daptomycin. None of these differences was statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of daptomycin (4 mg/kg) is unknown. Caution is warranted when daptomycin is co-administered with tobramycin.

Warfarin

In 16 healthy subjects, concomitant administration of daptomycin 6 mg/kg once daily for 5 days followed by a single oral dose of warfarin (25 mg) had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio). (see **PRECAUTIONS, Drug Interactions**)

Simvastatin

In 20 healthy subjects on a stable daily dose of simvastatin 40 mg, administration of daptomycin IV 4 mg/kg once daily for 14 days (n=10) was not associated with a higher incidence of adverse events than subjects receiving placebo once daily (n=10) (see **PRECAUTIONS, Drug Interactions**).

Probenecid

Concomitant administration of probenecid (500 mg four times daily) and a single dose of daptomycin IV 4 mg/kg did not significantly alter the C_{max} and $AUC_{0-\infty}$ of daptomycin. No dosage adjustment of daptomycin is warranted when daptomycin is co-administered with probenecid.

MICROBIOLOGY

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. Daptomycin is a natural product which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria. Daptomycin retains potency against antibiotic resistant Gram-positive bacteria including isolates resistant to methicillin, vancomycin, and linezolid.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro.* This has been demonstrated both by time-kill curves and by MBC/MIC ratios using broth dilution methodology.

In vitro studies have demonstrated additive or indifferent interactions of daptomycin with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions occurred with aminoglycosides and β-lactam antibiotics against some isolates of staphylococci and enterococci, including some MRSA isolates.

Mechanism of Action

The mechanism of action of daptomycin is distinct from any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death.

Resistance

Mechanisms of Resistance

At this time, no mechanism of resistance to daptomycin has been identified. Currently, there are no known transferable elements that confer resistance to daptomycin.

Cross Resistance

Cross-resistance has not been observed with any other class of antibiotic.

Other

The emergence of resistance to daptomycin occurred in 2 of more than 1000 (<0.2%) infected subjects across the entire set of Phase 2 and 3 clinical trials. In one case, a resistant *S. aureus* was isolated from a patient in a Phase 2 study who

received daptomycin at less than the protocol-specified dose for the initial 5 days of therapy. In the second case, a resistant *E. faecalis* was isolated from a patient with an infected chronic decubitus ulcer enrolled in a salvage trial.

Daptomycin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms:

Enterococcus faecalis (vancomycin-susceptible strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. *equisimilis*
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. Greater than 90% of the following microorganisms demonstrate an *in vitro* MIC less than or equal to the susceptible breakpoint for daptomycin versus the bacterial genus. The efficacy of daptomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms:

Corynebacterium jeikeium
Enterococcus faecalis (vancomycin-resistant strains)
Enterococcus faecium (including vancomycin-resistant strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus

Susceptibility Testing Methods

Susceptibility testing by dilution methods requires the use of daptomycin susceptibility powder. The testing also requires presence of physiological levels of free calcium ions (50 mg/L calcium chloride) in Mueller-Hinton broth medium and a minimum of 28 mg/L calcium chloride in Mueller-Hinton agar medium.

Dilution technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure[2, 3]. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of daptomycin powder. The MIC values should be interpreted according to the criteria in Table 3.

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized

procedure requires the use of standardized inoculum concentrations[1, 3]. This procedure uses paper disks impregnated with 30 µg of daptomycin to test the susceptibility of microorganisms to daptomycin. The disk diffusion interpretive criteria are provided in Table 3.

Table 3. Susceptibility Interpretive Criteria for Daptomycin

Pathogen	Minimal inhibitory concentration (µg/mL)[a]			Disk diffusion zone Diameter (mm)[b]		
	S	I	R	S	I	R
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤1	(c)	(c)	≥16	(c)	(c)
Streptococcus pyogenes, Streptococcus agalactiae, and *Streptococcus dysgalactiae* subsp. *equisimilis*	≤1	(c)	(c)	≥16	(c)	(c)
Enterococcus faecalis (vancomycin–susceptible only)	≤4	(c)	(c)	≥11	(c)	(c)

a. The MIC interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.

b. The zone diameter interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2 at 35ºC for 20 to 24 hours.

c. The current absence of data on daptomycin resistant strains precludes defining any categories other than "Susceptible". Strains yielding test results suggestive of a "non-susceptible" category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the procedures. Standard daptomycin powder should provide the range of values noted in Table 4. Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 4. Acceptable Quality Control Ranges for Daptomycin to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in µg/mL)[a]	**Disk Diffusion (Zone Diameters in mm)** [b]
Enterococcus faecalis ATCC 29212	1-8	Not applicable
Staphylococcus aureus ATCC 29213	0.25-1	Not applicable
Staphylococcus aureus ATCC 25923	Not applicable	18-23
Streptococcus pneumoniae ATCC 49619 [c]	0.06-0.5 [d]	19-26 [e]

a. Quality control ranges reflect MICs obtained when Mueller-Hinton broth is supplemented with calcium to a final concentration of 50 mg/L.
b. Some lots of Mueller-Hinton agar are deficient in calcium and give small zone diameters.
c. This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.
d. This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.
e. This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35ºC for 20 to 24 hours.

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**).

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 (e.g., 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**).

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 1,409 patients treated with daptomycin and 1,185 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 Table 5.

Table 5. 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%
Pruritus	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 anti-staphylococcal penicillins (i.e. 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

Table 6. 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 Table 7. The recommended dosing regimen is 4 mg/kg once every 24 hours for patients with $CL_{CR} \geq 30$ 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**).

Table 7 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.

HOW SUPPLIED

Cubicin (daptomycin for injection) – Pale yellow to light brown lyophilized cake
Single-use 10 mL capacity vials:
500 mg/vial: Packages of 1 (NDC 67919-011-01)
250 mg/vial: Packages of 1 (NDC 67919-010-01)

STORAGE

Store original packages at refrigerated temperatures 2 to 8°C (36 to 46°F); avoid excessive heat.

CLINICAL STUDIES

Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections (Table 8) were enrolled in two randomized, multinational, multicenter, investigator-blinded studies comparing Cubicin (4 mg/kg IV q24h) with either vancomycin (1 g IV q12h) or a semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4-12 g IV per day). Patients known to have bacteremia at baseline were excluded. Patients with creatinine clearance between 30-70 mL/minute were to receive a lower dose of Cubicin as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of daptomycin adjusted. Patients could switch to oral therapy after a minimum of four days of IV treatment if clinical improvement was demonstrated.

One study was conducted primarily in the United States and South Africa (study 9801), and the second (study 9901) was conducted at non-US sites only. Both studies were similar in design, but differed in patient characteristics, including history of diabetes and peripheral vascular disease. There were a total of 534 patients treated with Cubicin and 558 treated with comparator in the two studies. The majority (89.7%) of patients received IV medication exclusively.

The efficacy endpoints in both studies were the clinical success rates in the intent-to treat (ITT) population and in the clinically evaluable (CE) population. In study 9801, clinical success rates in the ITT population were 62.5% (165/264) in patients treated with daptomycin and 60.9 % (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population were 76.0% (158/208) in patients treated with Cubicin and 76.7% (158/206) in patients treated with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4% (217/270) in patients treated with daptomycin and 80.5 % (235/292) in patients treated with comparator drugs. Clinical success rates in the CE population were 89.9% (214/238) in patients treated with daptomycin and 90.4% (226/250) in patients treated with comparator drugs.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 9.

Table 8. Investigator's Primary Diagnosis in the Complicated Skin and Skin Structure Infection Studies (Population: ITT)

Parameters	Study 9801 Cubicin/Comparator[a] N=264/N=266	Study 9901 Cubicin/Comparator[a] N=270/N=292	Pooled Cubicin/Comparator[a] N=534/N=558
Wound Infection	99 (37.5%)/116 (43.6%)	102 (37.8%)/108 (37.0%)	201 (37.6%)/224 (40.1%)
Major Abscess	55 (20.8%)/43 (16.2%)	59 (21.9%)/65 (22.3%)	114 (21.3%)/108 (19.4%)
Ulcer Infection	71 (26.9%)/75 (28.2%)	53 (19.6%)/68 (23.3%)	124 (23.2%)/143 (25.6%)
Other Infection[b]	39 (14.8%)/32 (12.0%)	56 (20.7%)/51 (17.5%)	95 (17.8%)/83 (14.9%)

a.Vancomycin or semi-synthetic penicillins

b. The majority of cases were subsequently categorized as complicated cellulitis, major abscesses or traumatic wound infections.

Table 9. Clinical Success Rates by Infecting Pathogen, Primary Comparative Complicated Skin and Skin Structure Infection Studies (Population: Microbiologically Evaluable)

Pathogen	Success Rate	
	Cubicin n/N (%)	**Comparator[a] n/N (%)**
Methicillin-susceptible *Staphylococcus aureus (MSSA)*[b]	170/198 (85.9)	180/207 (87.0)
Methicillin-resistant *Staphylococcus aureus (MRSA)*[b]	21/28 (75.0)	25/36 (69.4)
Streptococcus pyogenes	79/84 (94.0)	80/88 (90.9)
Streptococcus agalactiae	23/27 (85.2)	22/29 (75.9)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100)	9/11 (81.8)
Enterococcus faecalis (vancomycin-susceptible only)[b]	27/37 (73.0)	40/53 (75.5)

a. Vancomycin or semi-synthetic penicillins
b. As determined by the central laboratory

Rx only

US Patent Nos. 6,468,967; 5,912,226; 4,885,243; 4,874,843

Cubicin is a trademark of Cubist Pharmaceuticals, Inc.

Manufactured for:

Cubist Pharmaceuticals, Inc.
Lexington, MA 02421

Manufactured by:

Abbott Laboratories
Hospital Products Division
McPherson, KS 67460

For all medical inquiries call: (866) 793-2786

References

1. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests; approved standard-eighth edition. NCCLS document M2-A8, Villanova, (PA). 2003 January.

2. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically; approved standard-sixth edition. NCCLS document M7-A6, Villanova, (PA). 2003 January.

3. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing; thirteenth informational supplement. NCCLS document M100-S13, Villanova, (PA). 2003 January.

Sept. 2003

CUBIST ITEM# 67919-011-01 BLACK PMS 201 PMS 2607 PMS 2757 PMS 300 DIE

NDC 67919-011-01

Store at 2° to 8°C
(36° to 46°F).

CUBIST

Manufactured for:
Cubist Pharmaceuticals, Inc.
Lexington, MA 02421 USA

US Patent Nos. 6,468,967; 5,912,226; 4,885,243; 4,874,843

500 mg

CUBICIN™
(daptomycin for injection)

For intravenous infusion only.
Single-use only.
Rx only

Cubist Pharmaceuticals, Inc. USA

Lot.
Exp.
Part # 1001

67919-011-01

CUBIST ITEM# 67919-011-01

VARNISH

CardinalHealth

Customer Name: **Cubist**

Item #: **67919-011-01**

Date Negative Made: _____ Date Proof Made: _____

❑ **Proof approved as submitted**

❑ **Proof approved with corrections noted**

❑ **Proof not approved (see comments)**

Signature: _____ Date: _____

Comments: _____

CardinalHealth

1st check

2nd check

PLATE # 13070 DIE # 13070

PMS 300 BLUE PMS 201 RUST BLACK

PMS 2607 PURPLE PMS 2757 DK. BLUE

DIE LINE ACRYLIC

CUBICIN™ (daptomycin for injection)

500 mg

One single-use vial

CUBICIN™ (daptomycin for injection) contains approximately 900 mg/g of daptomycin for intravenous use following reconstitution with 0.9% sodium chloride injection, USP. Sodium hydroxide used to adjust pH may be present in trace amounts.

Contains no preservatives.

Store in a refrigerator at 2° to 8° C (36° to 46° F).
Single-use only

N 3 67919-011-01 6

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

1002

This package contains one single-use vial of sterile CUBICIN™ (daptomycin for injection) and one package insert.

CUBICIN™ (daptomycin for injection)

Manufactured by:
Abbott Laboratories
Hospital Products Division
McPherson, KS 64760 USA

Manufactured for:
Cubist Pharmaceuticals, Inc.
Lexington, MA 02421 USA

US Patent Nos. 6,468,967; 5,912,226; 4,885,243; 4,874,843

CH 00

NDC 67919-011-01

One single-use vial

500 mg

CUBICIN™ (daptomycin for injection)

For intravenous infusion only.

Rx only.

CUBIST Cubist Pharmaceuticals, Inc. Lexington, MA 02421 USA

Lot.

Exp.

1002

See enclosed package insert for reconstitution instructions and complete information on dosage and administration.

Reconstitute CUBICIN™ with 0.9% sodium chloride injection, USP.

CUBIST Cubist Pharmaceuticals, Inc. Lexington, MA 02421 USA