Cubicin®

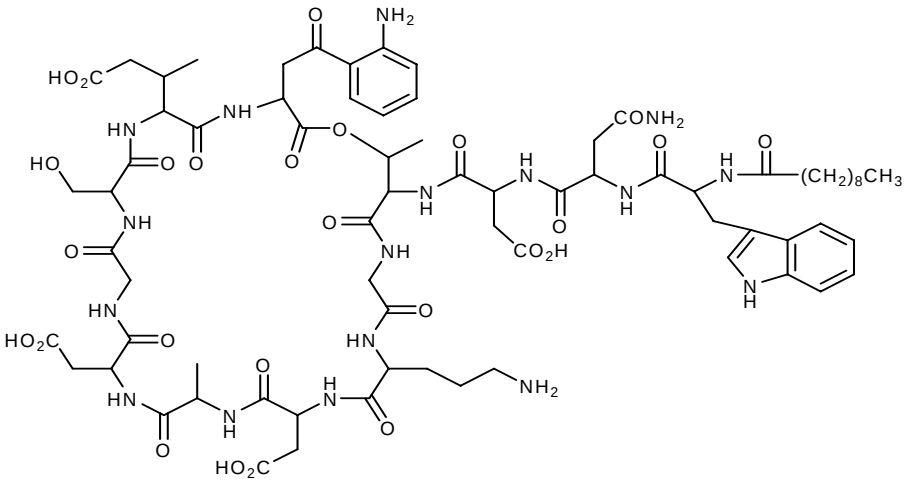
(daptomycin for injection)

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-D-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 (IV) 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 at steady-state following IV administration of 4 to 12 mg/kg q24h to healthy young adults are summarized in Table 1.

Daptomycin pharmacokinetics were generally linear and time-independent at doses of 4 to 12 mg/kg q24h. Steady-state trough concentrations were achieved by the third daily dose. The mean (SD) steady-state trough concentrations attained following administration of 4, 6, 8, 10, and 12 mg/kg q24h were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9), and 13.7 (5.2) µg/mL, respectively.

Table 1. Mean (SD) CUBICIN Pharmacokinetic Parameters in Healthy Volunteers at Steady-State

Dose[b] (mg/kg)	Pharmacokinetic Parameters[a]				
	AUC_{0-24} (µg*h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (mL/h/kg)	C_{max} (µg/mL)
4 (N=6)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 (N=6)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 (N=6)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 (N=9)	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 (N=9)	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

a. AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; $t_{½}$, terminal elimination half-life; V_{ss}, volume of distribution at steady-state; CL_T, plasma clearance; C_{max}, maximum plasma concentration.

b. Doses of CUBICIN in excess of 6 mg/kg have not been approved.

Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding ranged from 90 to 93%.

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 those receiving hemodialysis (85.9%) and continuous ambulatory peritoneal dialysis (CAPD) (83.5%). The protein binding of daptomycin in subjects with hepatic impairment (Child-Pugh B) was similar to that in healthy adult subjects.

The volume of distribution at steady-state (V_{ss}) of daptomycin in healthy adult subjects was approximately 0.10 L/kg and was independent of dose.

Metabolism

In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. In *in vitro* studies, daptomycin was not metabolized by human liver microsomes. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the P450 system.

In 5 healthy young adults after infusion of radiolabeled ^{14}C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay. In a separate

study, no metabolites were observed in plasma on Day 1 following administration of CUBICIN at 6 mg/kg to subjects. Inactive metabolites have been detected in urine, as determined by the difference in total radioactive concentrations and microbiologically active concentrations. Minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Excretion

Daptomycin is excreted primarily by the kidney. In a mass balance study of 5 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 9 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 infected patients (complicated skin and skin structure infections and *S. aureus* bacteremia) and noninfected subjects with varying degrees of renal function (Table 2). Plasma clearance (CL_T), elimination half-life ($t_{1/2}$), and volume of distribution (V_{ss}) were similar in patients with complicated skin and skin structure infections compared with those with *S. aureus* bacteremia. Following the administration of CUBICIN 4 mg/kg q24h, the mean CL_T was 9%, 22%, and 46% lower among subjects and patients with mild (CL_{CR} 50-80 mL/min), moderate (CL_{CR} 30-50 mL/min), and severe (CL_{CR} <30 mL/min) renal impairment, respectively, than in those with normal renal function (CL_{CR} >80 mL/min). The mean steady-state systemic exposure (AUC), $t_{1/2}$, and V_{ss} increased with decreasing renal function, although the mean AUC was not markedly different for patients with CL_{CR} 30-80 mL/min compared with those with normal renal function. The mean AUC for patients with CL_{CR} <30 mL/min and for patients on hemodialysis (dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function. Following the administration of CUBICIN 4 mg/kg q24h, the mean C_{max} ranged from 60 to 70 µg/mL in patients with CL_{CR} ≥30 mL/min, while the mean C_{max} for patients with CL_{CR} <30 mL/min ranged from 41 to 58 µg/mL. The mean C_{max} ranged from 80 to 114 µg/mL in patients with mild-to-moderate renal impairment and was similar to that of patients with normal renal function after the administration of CUBICIN 6 mg/kg q24h. In patients with renal insufficiency, both renal function and creatine phosphokinase (CPK) should be monitored more frequently. CUBICIN should be administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE AND ADMINISTRATION** for recommended dosage regimens).

Table 2. Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following Infusion of 4 mg/kg or 6 mg/kg to Infected Patients and Noninfected Subjects with Varying Degrees of Renal Function

Renal Function	$t_{1/2}$[a] (h) 4 mg/kg	V_{ss}[a] (L/kg) 4 mg/kg	CL_T[a] (mL/h/kg) 4 mg/kg	$AUC_{0-\infty}$[a] (µg*h/mL) 4 mg/kg	AUC_{ss}[b] (µg*h/mL) 6 mg/kg	$C_{min,ss}$[b] (µg*h/mL) 6 mg/kg
Normal (CL_{CR} >80 mL/min)	9.39 (4.74) N=165	0.13 (0.05) N=165	10.9 (4.0) N=165	417 (155) N=165	545 (296) N=62	6.9 (3.5) N= 61
Mild Renal Impairment (CL_{CR} 50-80 mL/min)	10.75 (8.36) N=64	0.12 (0.05) N=64	9.9 (4.0) N=64	466 (177) N=64	637 (215) N=29	12.4 (5.6) N=29
Moderate Renal Impairment (CL_{CR} 30-<50 mL/min)	14.70 (10.50) N=24	0.15 (0.06) N=24	8.5 (3.4) N=24	560 (258) N=24	868 (349) N=15	19.0 (9.0) N=14
Severe Renal Impairment (CL_{CR} <30 mL/min)	27.83 (14.85) N=8	0.20 (0.15) N=8	5.9 (3.9) N=8	925 (467) N=8	1050, 892 N=2	24.4, 21.4 N=2
Hemodialysis	29.81 (6.13) N=21	0.15 (0.04) N=21	3.7 (1.9) N=21	1244 (374) N=21	NA	NA

Note: CL_{CR}, creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight; $AUC_{0-\infty}$, area under the concentration-time curve extrapolated to infinity; AUC_{ss}, area under the concentration-time curve calculated over the 24-hour dosing interval at steady-state; $C_{min,ss}$, trough concentration at steady-state; NA, not applicable.

a. Parameters obtained following a single dose from patients with complicated skin and skin structure infections and healthy subjects.

b. Parameters obtained at steady-state from patients with *S. aureus* bacteremia.

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 CUBICIN 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. No dosage adjustment is warranted based on gender when administering CUBICIN.

Geriatric

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥75 years of age) and 11 healthy young controls (18 to 30 years of age). Following administration of a single 4 mg/kg IV dose, the mean total clearance of daptomycin was reduced approximately 35% and the mean $AUC_{0-\infty}$ increased approximately 58% in elderly subjects compared with young healthy

subjects. There were no differences in C_{max}. No dosage adjustment is warranted for elderly patients with normal renal function.

Obesity

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m^2) and 6 extremely obese (BMI ≥40 kg/m^2) subjects and controls matched for age, sex, and renal function. Following administration of a single 4 mg/kg IV dose based on total body weight, the plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in moderately obese subjects and 23% lower in extremely obese subjects compared with nonobese controls. The $AUC_{0-\infty}$ of daptomycin increased approximately 30% in moderately obese and 31% in extremely obese subjects compared with nonobese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No dosage adjustment of CUBICIN 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 CUBICIN and other drugs that are likely to be either co-administered or associated with overlapping toxicity.

Aztreonam

In a study in which 15 healthy adult subjects received a single dose of CUBICIN 6 mg/kg IV, aztreonam 1 g 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 also were 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 CUBICIN 2 mg/kg IV, tobramycin 1 mg/kg IV, 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 CUBICIN. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of CUBICIN is unknown. Caution is warranted when CUBICIN is co-administered with tobramycin.

Warfarin

In 16 healthy subjects, concomitant administration of CUBICIN 6 mg/kg q24h 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**).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.