

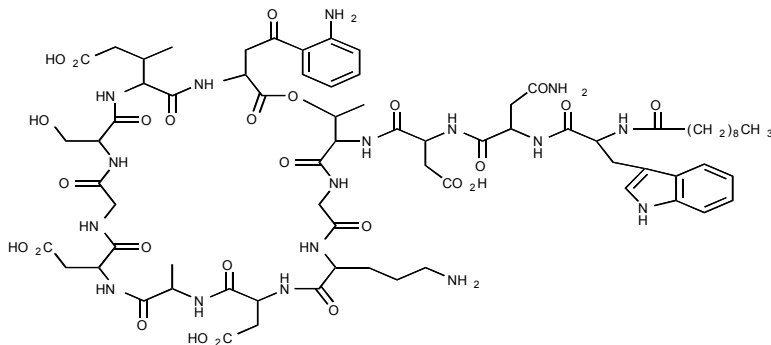
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2 **Cubicin™**
3 (daptomycin for injection)
4 Rx only

5 To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cubicin
6 and other antibacterial drugs, Cubicin should be used only to treat or prevent infections caused
7 by bacteria.

8 DESCRIPTION

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



13

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

20 CLINICAL PHARMACOLOGY

21 Pharmacokinetics

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

1

25 **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)

26 *Median (minimum, maximum)

27 C_{max} = Maximum plasma concentration; T_{max} = Time to C_{max}; AUC₀₋₂₄ = Area under concentration-time curve from 0
 28 to 24 hours; t_{1/2} = Terminal elimination half-life; V_d = Apparent volume of distribution; CL_T = Systemic clearance;
 29 CL_R = renal clearance; Ae₂₄ = Percent of dose recovered in urine over 24 hours as unchanged daptomycin following
 30 the first dose.

31 Daptomycin pharmacokinetics are nearly linear and time-independent at doses up to 6 mg/kg
 32 administered once daily for 7 days. Steady-state concentrations are achieved by the third daily
 33 dose. The mean (SD) steady-state trough concentrations (Days 4 to 8) attained following
 34 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,
 35 respectively.

36 **Distribution**

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

42 In clinical studies, mean serum protein binding in subjects with CL_{CR} ≥30 mL/min was
 43 comparable to that observed in healthy subjects with normal renal function. However, there was
 44 a trend toward decreasing serum protein binding among subjects with CL_{CR} <30 mL/min
 45 (87.6%) including hemodialysis patients (85.9%) and CAPD patients (83.5%). The protein
 46 binding of daptomycin in subjects with hepatic impairment (Child-Pugh B) was similar to
 47 healthy adult subjects.

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

50 **Metabolism**

51 In vitro studies with human hepatocytes indicate that daptomycin does not inhibit or induce the
 52 activities of the following human cytochrome (CYP) P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6,
 53 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs

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

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

61 Excretion

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

67 Because renal excretion is the primary route of elimination, dosage adjustment is necessary in
68 patients with severe renal insufficiency ($\text{CL}_{\text{CR}} < 30 \text{ mL/min}$) (see **DOSAGE AND**
69 **ADMINISTRATION**).

70 Special Populations

71 Renal Insufficiency

72 Population derived pharmacokinetic parameters were determined for patients with skin and skin
73 structure infections and healthy non-infected subjects with varying degrees of renal function
74 ($n=282$). Following the administration of a single 4 mg/kg IV dose of daptomycin, the plasma
75 clearance (CL_{T}) was reduced and the systemic exposure ($\text{AUC}_{0-\infty}$) was increased with decreasing
76 renal function (see Table 2). The mean $\text{AUC}_{0-\infty}$ was not markedly different for subjects and
77 patients with CL_{CR} 30-80 mL/min as compared to those with normal renal function (CL_{CR}
78 $>80\text{mL/min}$). The mean $\text{AUC}_{0-\infty}$ values for subjects and patients with $\text{CL}_{\text{CR}} <30 \text{ mL/min}$ and
79 hemodialysis (dosed post dialysis)/CAPD subjects were approximately 2- and 3-times higher,
80 respectively, than the values in individuals with normal renal function. The mean C_{max} ranged
81 from 59.6 $\mu\text{g/mL}$ to 69.6 $\mu\text{g/mL}$ in subjects with $\text{CL}_{\text{CR}} \geq 30 \text{ mL/min}$ while those with $\text{CL}_{\text{CR}} <30$
82 mL/min ranged from 41.1 $\mu\text{g/mL}$ to 57.7 $\mu\text{g/mL}$. In 11 non-infected adult subjects undergoing
83 dialysis, approximately 15% and 11% of the administered dose was removed by 4 hours of
84 hemodialysis and 48 hours of CAPD, respectively. The recommended dosing regimen is 4 mg/kg
85 once every 24 hours for patients with $\text{CL}_{\text{CR}} \geq 30 \text{ mL/min}$ and 4 mg/kg once every 48 hours for
86 $\text{CL}_{\text{CR}} <30 \text{ mL/min}$, including those on hemodialysis and CAPD. Daptomycin should be
87 administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE**
88 **AND ADMINISTRATION**).

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

Renal Function	AUC _{0-∞} (μg*h/mL)	t _{1/2} (h)	V _{ss} (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)

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

93 **Hepatic Insufficiency**

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

100 **Gender**

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

104 **Geriatric**

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

111 **Obesity**

112 The pharmacokinetics of daptomycin were evaluated in six moderately obese (Body Mass Index
 113 [BMI] 25-39.9 kg/m²) and six extremely obese (BMI ≥40 kg/m²) subjects and controls matched
 114 for age, sex, and renal function. Following administration of a single intravenous 4 mg/kg dose

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

121 **Pediatric**

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

124 **Drug-Drug Interactions**

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

127 **Aztreonam**

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

133 **Tobramycin**

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

141 **Warfarin**

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

146 **Simvastatin**

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

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