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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Approved Labeling

Cubicin™

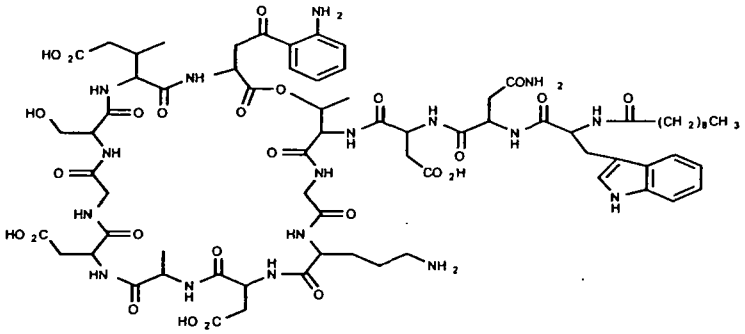
(daptomycin for injection)

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

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