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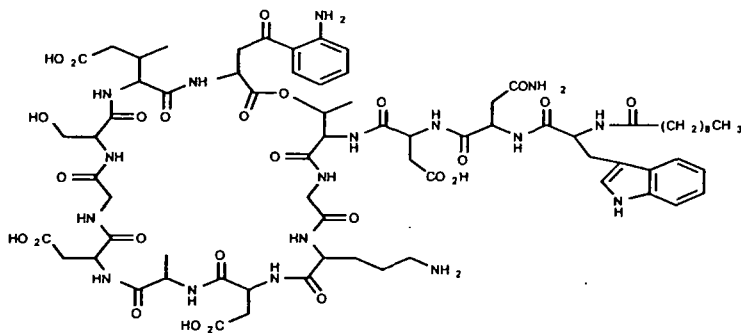
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2 **Cubicin™**
3 (daptomycin for injection)
4 Rx only

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_1 -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.

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 $\text{CL}_{\text{CR}} 30\text{-}80 \text{ mL/min}$ 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**).

151 **Probenecid**

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

156 **MICROBIOLOGY**

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

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

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

170 **Mechanism of Action**

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

175 **Resistance**

176 *Mechanisms of Resistance*

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

180 *Cross Resistance*

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

182 *Other*

183 The emergence of resistance to daptomycin occurred in 2 of more than 1000
184 (<0.2%) infected subjects across the entire set of Phase 2 and 3 clinical trials. In
185 one case, a resistant *S. aureus* was isolated from a patient in a Phase 2 study who

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

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

192 **Aerobic and facultative Gram-positive microorganisms:**

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

198 The following *in vitro* data are available, but their clinical significance is unknown. Greater than
 199 90% of the following microorganisms demonstrate an *in vitro* MIC less than or equal to the
 200 susceptible breakpoint for daptomycin versus the bacterial genus. The efficacy of daptomycin in
 201 treating clinical infections due to these microorganisms has not been established in adequate and
 202 well-controlled clinical trials.

203 **Aerobic and facultative Gram-positive microorganisms:**

204 *Corynebacterium jeikeium*
 205 *Enterococcus faecalis* (vancomycin-resistant strains)
 206 *Enterococcus faecium* (including vancomycin-resistant strains)
 207 *Staphylococcus epidermidis* (including methicillin-resistant strains)
 208 *Staphylococcus haemolyticus*

209 **Susceptibility Testing Methods**

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

214 **Dilution technique**

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

221 **Diffusion technique**

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

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

227 **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
<i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin-resistant)	≤1	(c)	(c)	≥16	(c)	(c)
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	≤1	(c)	(c)	≥16	(c)	(c)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤4	(c)	(c)	≥11	(c)	(c)

- 228
 229 a. The MIC interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth
 230 microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive
 231 criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth
 232 microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5%
 233 lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24
 234 hours.
 235 b. The zone diameter interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to
 236 tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in
 237 5% CO₂ at 35°C for 20 to 24 hours.
 238 c. The current absence of data on daptomycin resistant strains precludes defining any categories other than
 239 “Susceptible”. Strains yielding test results suggestive of a “non-susceptible” category should be retested, and if
 240 the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

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

243 **Quality Control**

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

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

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

- 252
 253 a. Quality control ranges reflect MICs obtained when Mueller-Hinton broth is supplemented with calcium to a
 254 final concentration of 50 mg/L.
 255 b. Some lots of Mueller-Hinton agar are deficient in calcium and give small zone diameters.
 256 c. This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other
 257 than *S. pneumoniae*.
 258 d. This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using
 259 cation adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension
 260 and incubated in ambient air at 35°C for 20 to 24 hours.
 261 e. This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar
 262 supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in
 263 5% CO₂ at 35°C for 20 to 24 hours.

264 INDICATIONS AND USAGE

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

272 Daptomycin is not indicated for the treatment of pneumonia.

273 Appropriate specimens for microbiological examination should be obtained in order to isolate
 274 and identify the causative pathogens and to determine their susceptibility to daptomycin.
 275 Empiric therapy may be initiated while awaiting test results. Antimicrobial therapy should be
 276 adjusted as needed based upon test results.

277 To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cubicin
 278 and other antibacterial drugs, Cubicin should be used only to treat or prevent infections that are

279 proven or strongly suspected to be caused by susceptible bacteria. When culture and
280 susceptibility information are available, they should be considered in selecting or modifying
281 antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns
282 may contribute to the empiric selection of therapy.

283 **CONTRAINDICATIONS**

284 Cubicin is contraindicated in patients with known hypersensitivity to daptomycin.

285 **WARNINGS**

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

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

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

298 **PRECAUTIONS**

299 **General**

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

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

305 **Skeletal Muscle**

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

311 Patients receiving Cubicin should be monitored for the development of muscle pain or weakness,
312 particularly of the distal extremities. CPK levels should be monitored weekly in patients who
313 receive Cubicin. Patients who develop unexplained elevations in CPK while receiving

314 daptomycin should be monitored more frequently. Among patients with abnormal CPK (>500
315 U/L) at baseline, 2/19 (10.5%) treated with Cubicin and 4/24 (16.7%) treated with comparator
316 developed further increases in CPK while on therapy. In this same population, no patients
317 developed myopathy. Daptomycin-treated patients with baseline CPK >500 U/L (n=19) did not
318 experience an increased incidence of CPK elevations or myopathy relative to those treated with
319 comparator (n=24).

320 Cubicin should be discontinued in patients with unexplained signs and symptoms of myopathy in
321 conjunction with CPK elevation >1000 U/L (~5X ULN), or in patients without reported
322 symptoms who have marked elevations in CPK (\geq 10X ULN). In addition, consideration should
323 be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA
324 reductase inhibitors, in patients receiving Cubicin.

325 In a small number of patients in Phase 1 and Phase 2 studies, administration of Cubicin was
326 associated with decreases in nerve conduction velocity and with adverse events (e.g.,
327 paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. Nerve
328 conduction deficits were also detected in a similar number of comparator subjects in these
329 studies. In Phase 3 cSSSI and CAP studies 7/989 (0.7%) daptomycin-treated patients and 7/1018
330 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral
331 neuropathy was not diagnosed in any of these patients. In animals, effects of daptomycin on
332 peripheral nerve were observed (see **ANIMAL PHARMACOLOGY**). Therefore, physicians
333 should be alert to the possibility of signs and symptoms of neuropathy in patients receiving
334 Cubicin.

335 **Drug Interactions**

336 **Warfarin**

337 Concomitant administration of daptomycin (6 mg/kg once every 24 hours for 5 days) and
338 warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either
339 drug and the INR was not significantly altered. As experience with the concomitant
340 administration of daptomycin and warfarin is limited to volunteer studies, anticoagulant activity
341 in patients receiving daptomycin and warfarin should be monitored for the first several days after
342 initiating therapy with Cubicin (see **CLINICAL PHARMACOLOGY, Drug-Drug**
343 **Interactions**).

344 **HMG CoA Reductase Inhibitors**

345 Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or
346 weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in
347 a placebo-controlled Phase I trial in which 10 healthy subjects on stable simvastatin therapy were
348 treated concurrently with daptomycin (4 mg/kg once every 24 hours) for 14 days. Experience
349 with co-administration of HMG-CoA reductase inhibitors and Cubicin in patients is limited,
350 therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase
351 inhibitors in patients receiving Cubicin.

352 **Drug-Laboratory Test Interactions**

353 There are no reported drug-laboratory test interactions.

354 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

355 Long-term carcinogenicity studies in animals have not been conducted to evaluate the
356 carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was
357 found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene
358 mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an *in vivo*
359 micronucleus assay, an *in vitro* DNA repair assay, and an *in vivo* sister chromatid exchange
360 assay in Chinese hamsters.

361 Daptomycin did not affect the fertility or reproductive performance of male and female rats when
362 administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the
363 estimated human exposure level based upon AUCs.

364 **Pregnancy**

365 **Teratogenic effects: Pregnancy Category B**

366 Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 3
367 and 6 times the human dose respectively on a body surface area basis, have revealed no evidence
368 of harm to the fetus due to Cubicin. There are, however, no adequate and well controlled studies
369 in pregnant women. Because animal reproduction studies are not always predictive of human
370 response, this drug should be used during pregnancy only if clearly needed.

371 **Nursing Mothers**

372 It is not known if daptomycin is excreted in human milk. Caution should be exercised when
373 Cubicin is administered to nursing women.

374 **Pediatric Use**

375 Safety and efficacy of Cubicin in patients under the age of 18 have not been established.

376 **Geriatric Use**

377 Of the 534 patients treated with Cubicin in Phase 3 controlled clinical trials of complicated skin
378 and skin structure infection, 27.0% were 65 years of age or older and 12.4% were 75 years or
379 older. In the two Phase 3 clinical studies in patients with cSSSI, lower clinical success rates were
380 seen in patients ≥ 65 years of age compared to those < 65 years of age. In addition, treatment-
381 emergent adverse events were more common in patients ≥ 65 years old than in patients < 65 years
382 of age in both cSSSI studies.

383 ANIMAL PHARMACOLOGY

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

392 In adult animals, effects on peripheral nerve (characterized by axonal degeneration and
393 frequently accompanied by significant losses of patellar reflex, gag reflex and pain perception)
394 were observed at doses higher than those associated with skeletal myopathy. Deficits in the dogs'
395 patellar reflexes were seen within 2 weeks of the start of treatment at 40 mg/kg (3.5 times the
396 human AUC), with some clinical improvement noted within 2 weeks of the cessation of dosing.
397 However, at 75 mg/kg daily for 1 month, 7/8 dogs failed to regain full patellar reflex responses
398 within the duration of a 3 month recovery period. In a separate study in dogs receiving doses of
399 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted at 6
400 months after cessation of dosing. However, recovery of peripheral nerve function was evident.

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

403 ADVERSE REACTIONS

404 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
405 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials
406 of another drug and may not reflect the rates observed in practice. The adverse reaction
407 information from clinical trials does, however, provide a basis for identifying the adverse events
408 that appear to be related to drug use and for approximating rates.

409 Clinical studies sponsored by Cubist enrolled 1,409 patients treated with daptomycin and 1,185
410 treated with comparator. Most adverse events reported in these clinical studies were described as
411 mild or moderate in intensity. In Phase 3 cSSSI trials, daptomycin was discontinued in 15/534
412 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%)
413 patients.

414 The rates of most common adverse events, organized by body system, observed in cSSSI patients
415 are displayed in Table 5.

416 **Table 5. Incidence (%) of Adverse Events that Occurred in $\geq 2\%$ of Patients in Either Daptomycin or**
 417 **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%

418 *Comparators included vancomycin (1 g IV q12h) and anti-staphylococcal penicillins (i.e. nafcillin, oxacillin,
 419 cloxacillin, flucloxacillin; 4-12 g/day in divided doses)

420 In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious
 421 cardiorespiratory adverse events were higher in daptomycin-treated patients than in comparator-

422 treated patients. These differences were due to lack of therapeutic effectiveness of daptomycin
 423 in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS**
 424 **AND USAGE**).

425 Additional adverse events that occurred in 1-2% of patients in either daptomycin or comparator
 426 treatment groups in the cSSSI studies are as follows: edema, cellulitis, hypoglycemia, elevated
 427 alkaline phosphatase, cough, back pain, abdominal pain, hypokalemia, hyperglycemia, decreased
 428 appetite, anxiety, chest pain, sore throat, cardiac failure, confusion and Candida infections. These
 429 events occurred at rates ranging from 0.2-1.7% in daptomycin-treated patients and at rates of 0.4-
 430 1.8% in comparator-treated patients.

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

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

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

436 *Cardiovascular System:* supraventricular arrhythmia

437 *Dermatologic System:* eczema

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

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

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

443 *Nervous System:* vertigo, mental status change, paraesthesia

444 *Special Senses:* taste disturbance, eye irritation

445 **Laboratory Changes**

446 **Table 6. Incidence (%) of Creatine Phosphokinase (CPK) Elevations From Baseline While on Therapy in**
 447 **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

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

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

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

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

462 **OVERDOSAGE**

463 In the event of overdosage, supportive care is advised with maintenance of glomerular filtration.
464 Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered
465 over 4 hours) or by peritoneal dialysis (approximately 11% recovered over 48 hours).

466 **DOSAGE AND ADMINISTRATION**

467 **Complicated Skin and Skin Structure Infections**

468 Cubicin 4 mg/kg should be administered over a 30-minute period by intravenous infusion in
469 0.9% sodium chloride injection once every 24 hours for 7-14 days. Doses of Cubicin higher than
470 4 mg/kg/day have not been studied in Phase 3 controlled clinical trials. In Phase 1 and 2 clinical
471 studies, CPK elevations appeared to be more frequent when daptomycin was dosed more
472 frequently than once daily. Therefore, Cubicin should not be dosed more frequently than once a
473 day.

474 Because daptomycin is eliminated primarily by the kidney, a dosage modification is
475 recommended for patients with creatinine clearance < 30 mL/min, including patients receiving
476 hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), as listed in Table 7. The
477 recommended dosing regimen is 4 mg/kg once every 24 hours for patients with $CL_{CR} \geq 30$
478 mL/min and 4 mg/kg once every 48 hours for $CL_{CR} < 30$ mL/min, including those on
479 hemodialysis or CAPD. When possible, Cubicin should be administered following hemodialysis
480 on hemodialysis days (See **CLINICAL PHARMACOLOGY**).

481 **Table 7 Recommended Dosage of Cubicin (daptomycin for injection) in Adult Patients with Renal**
 482 **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

483

484 **Preparation Of Daptomycin For Administration**

485 Cubicin is supplied in single-use vials containing either 250 or 500 mg daptomycin as a sterile,
 486 lyophilized powder. The contents of a Cubicin 250 mg vial should be reconstituted with 5 mL of
 487 0.9% sodium chloride injection. The contents of a Cubicin 500 mg vial should be reconstituted
 488 with 10 mL of 0.9% sodium chloride injection. Reconstituted Cubicin should be further diluted
 489 with 0.9% sodium chloride injection to be administered by intravenous infusion over a period of
 490 30 minutes.

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

498 Cubicin vials are for single-use only.

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

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

506 **Compatible Intravenous Solutions**

507 Cubicin is compatible with 0.9% sodium chloride injection and lactated Ringer's injection.
 508 Cubicin is not compatible with dextrose-containing diluents.

509 **HOW SUPPLIED**

510 Cubicin (daptomycin for injection) – Pale yellow to light brown lyophilized cake
 511 Single-use 10 mL capacity vials:
 512 500 mg/vial: Packages of 1 (NDC 67919-011-01)
 513 250 mg/vial: Packages of 1 (NDC 67919-010-01)

514 **STORAGE**

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

516 **CLINICAL STUDIES**517 **Complicated Skin and Skin Structure Infections**

518 Adult patients with clinically documented complicated skin and skin structure infections (Table
519 8) were enrolled in two randomized, multinational, multicenter, investigator-blinded studies
520 comparing Cubicin (4 mg/kg IV q24h) with either vancomycin (1 g IV q12h) or a semi-synthetic
521 penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4-12 g IV per day). Patients
522 known to have bacteremia at baseline were excluded. Patients with creatinine clearance between
523 30-70 mL/minute were to receive a lower dose of Cubicin as specified in the protocol; however,
524 the majority of patients in this subpopulation did not have the dose of daptomycin adjusted.
525 Patients could switch to oral therapy after a minimum of four days of IV treatment if clinical
526 improvement was demonstrated.

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

532 The efficacy endpoints in both studies were the clinical success rates in the intent-to treat (ITT)
533 population and in the clinically evaluable (CE) population. In study 9801, clinical success rates
534 in the ITT population were 62.5% (165/264) in patients treated with daptomycin and 60.9 %
535 (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population
536 were 76.0% (158/208) in patients treated with Cubicin and 76.7% (158/206) in patients treated
537 with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4%
538 (217/270) in patients treated with daptomycin and 80.5 % (235/292) in patients treated with
539 comparator drugs. Clinical success rates in the CE population were 89.9% (214/238) in patients
540 treated with daptomycin and 90.4% (226/250) in patients treated with comparator drugs.

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

542 **Table 8. Investigator's Primary Diagnosis in the Complicated Skin and Skin Structure Infection Studies**
543 **(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%)

544 a. Vancomycin or semi-synthetic penicillins

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

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

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

549

550 a. Vancomycin or semi-synthetic penicillins

551 b. As determined by the central laboratory

552 **Rx only**

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

554 Cubicin is a trademark of Cubist Pharmaceuticals, Inc.

555 **Manufactured for:**

556 Cubist Pharmaceuticals, Inc.

557 Lexington, MA 02421

558 **Manufactured by:**

559 Abbott Laboratories

560 Hospital Products Division

561 McPherson, KS 67460

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

563 **References**

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9/12/03

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- 573 **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)

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

US Patent Nos. 6,448,967; 5,912,276; 4,885,243,
4,874,843

500 mg

CUBICIN™
(daptomycin for injection)

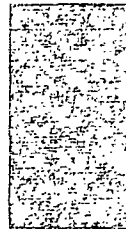
For intravenous infusion only.
Single-use only.
Rx only


CardinalPharmaceuticals Inc. USA

Lot. Exp. Part # 1001

67919-011-01

CUBIST ITEM# 67919-011-01




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

CUBICIN™
(daptomycin for injection)

500 mg
One single-use vial

CUBICIN™ (daptomycin for injection) contains approximately 500 mg 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



3 67919-011-01 6

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

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

NDC 67919-011-01

One single-use vial
500 mg

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

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

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. 5,464,967; 5,912,276;
6,085,243; 6,074,843

CUBIST

CUBICIN™
(daptomycin for injection)

For intravenous
infusion only.

Rx only.

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Cubist Pharmaceuticals, Inc.
Lexington, MA 02421 USA

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