- Pediatric *S. aureus* bacteremia Patients: The most common adverse reactions that occurred in ≥5% of pediatric patients receiving CUBICIN were vomiting and elevated CPK. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Complicated Skin and Skin Structure Infections (cSSSI)

CUBICIN® RF is indicated for the treatment of adult and pediatric patients (1 to 17 years of age) with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

1.2 *Staphylococcus aureus* Bloodstream Infections (Bacteremia) in Adult Patients, Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates

CUBICIN RF is indicated for the treatment of adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia), including adult patients with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

1.3 *Staphylococcus aureus* Bloodstream Infections (Bacteremia) in Pediatric Patients (1 to 17 Years of Age)

CUBICIN RF is indicated for the treatment of pediatric patients (1 to 17 years of age) with *Staphylococcus aureus* bloodstream infections (bacteremia).

1.4 Limitations of Use

CUBICIN RF is not indicated for the treatment of pneumonia.

CUBICIN RF is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. The clinical trial of CUBICIN in adult patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor *[see Clinical Studies (14.2)].* CUBICIN has not been studied in patients with prosthetic valve endocarditis.

CUBICIN RF is not recommended in pediatric patients younger than 1 year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs *[see Warnings and Precautions (5.7) and Nonclinical Toxicology (13.2)]*.

1.5 Usage

Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN RF and other antibacterial drugs, CUBICIN RF should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

When culture and susceptibility information is available, it 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. Empiric therapy may be initiated while awaiting test results.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Duration Instructions

Adults

Administer the appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL) **to adult patients** intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period *[see Dosage and Administration (2.2, 2.4, 2.7)]*.

Pediatric Patients (1 to 17 Years of Age)

Unlike in adults, do NOT administer CUBICIN RF by injection over a two (2) minute period to pediatric patients.

- Pediatric Patients 7 to 17 years of Age: Administer CUBICIN RF intravenously by infusion over a 30-minute period *[see Dosage and Administration (2.3, 2.5, 2.7)]*.
- Pediatric Patients 1 to 6 years of Age: Administer CUBICIN RF intravenously by infusion over a 60-minute period *[see Dosage and Administration (2.3, 2.5, 2.7)]*.

2.2 Dosage in Adults for cSSSI

Administer CUBICIN RF 4 mg/kg to adult patients intravenously once every 24 hours for 7 to 14 days.

2.3 Dosage in Pediatric Patients (1 to 17 Years of Age) for cSSSI

The recommended dosage regimens based on age for pediatric patients with cSSSI are shown in Table 1. Administer CUBICIN RF intravenously once every 24 hours for up to 14 days.

Table 1: Recommended Dosage of CUBICIN RF in Pediatric Patients (1 to 17 Years of Age) with cSSSI, Based on Age

Age Range	Dosage Regimen*	Duration of therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to less than 2 years	10 mg/kg once every 24 hours infused over 60 minutes	
*Recommended dosage regimen is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.		

2.4 Dosage in Adult Patients with *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates

Administer CUBICIN RF 6 mg/kg to adult patients intravenously once every 24 hours for 2 to 6 weeks. There are limited safety data for the use of CUBICIN for more than 28 days of therapy. In the Phase 3 trial, there were a total of 14 adult patients who were treated with CUBICIN for more than 28 days.

2.5 Dosage in Pediatric Patients (1 to 17 Years of Age) with *Staphylococcus aureus* Bloodstream Infections (Bacteremia)

The recommended dosage regimens based on age for pediatric patients with *S. aureus* bloodstream infections (bacteremia) are shown in Table 2. Administer CUBICIN RF intravenously in 0.9% sodium chloride injection once every 24 hours for up to 42 days.

Table 2: Recommended Dosage of CUBICIN RF in Pediatric Patients (1 to 17 Years of Age) with *S. aureus* Bacteremia, Based on Age

Age group	Dosage*	Duration of therapy
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	
*Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.		

2.6 Dosage in Patients with Renal Impairment

Adult Patients:

No dosage adjustment is required in adult patients with creatinine clearance (CL_{CR}) greater than or equal to 30 mL/min. The recommended dosage regimen for CUBICIN RF in adult patients with CL_{CR} less than 30 mL/min, including adult patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours (Table 3). When possible, CUBICIN RF should be administered following the completion of hemodialysis on hemodialysis days *[see Warnings and Precautions (5.2, 5.10), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Table 3: Recommended Dosage of CUBICIN RF in Adult Patients

Creatinine Clearance (CL_{CR})	**Dosage Regimen in Adults**	
	cSSSI	***S. aureus* Bloodstream Infections**
Greater than or equal to 30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
Less than 30 mL/min, including hemodialysis and CAPD	4 mg/kg once every 48 hours*	6 mg/kg once every 48 hours*

*When possible, administer CUBICIN RF following the completion of hemodialysis on hemodialysis days.

Pediatric Patients:

The dosage regimen for CUBICIN RF in pediatric patients with renal impairment has not been established.

2.7 Preparation and Administration of CUBICIN RF

There are two formulations of daptomycin that have differences concerning storage and reconstitution. Carefully follow the reconstitution and storage procedures in labeling.

Reconstitution of CUBICIN RF Vial

CUBICIN RF must be reconstituted within the vial only with either Sterile Water for Injection or Bacteriostatic Water for Injection.

Do **NOT** use saline based diluents for the reconstitution in the vial because this will result in a hyperosmotic solution that may result in infusion site reactions if the reconstituted product is administered as an intravenous injection over a period of 2 minutes.

CUBICIN RF is supplied in single-dose vials, each containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a CUBICIN RF vial should be reconstituted, using aseptic technique, to 50 mg/mL as follows:

1. Remove the polypropylene flip-off cap from the CUBICIN RF vial to expose the central portion of the rubber stopper.
2. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
3. Transfer 10 mL of Sterile Water for Injection or Bacteriostatic Water for Injection through the center of the rubber stopper into the CUBICIN RF vial. Use a beveled sterile transfer needle that is 21 gauge or smaller in diameter, pointing the transfer needle toward the wall of the vial.
4. Rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.

Administration Instructions

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

Slowly remove reconstituted liquid (50 mg daptomycin/mL) from the vial using a beveled sterile needle that is 21 gauge or smaller in diameter. Administer as an intravenous injection or infusion as described below:

Adults

Intravenous Injection over a period of 2 minutes

- For intravenous (IV) injection over a period of 2 minutes in adult patients **only**: Administer the appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL).

Intravenous Infusion over a period of 30 minutes

- For IV infusion over a period of 30 minutes in adult patients: The appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection.

Pediatric Patients (1 to 17 Years of Age)

Intravenous Infusion over a period of 30 or 60 minutes

- **Unlike in Adults, do NOT administer CUBICIN RF by injection over a two (2) minute period to pediatric patients** *[see Dosage and Administration (2.1)]*.
- *For Intravenous infusion over a period of 60 minutes in pediatric patients 1 to 6 years of age:* The appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into an intravenous infusion bag containing 25 mL of 0.9% sodium chloride injection. The infusion rate should be maintained at 0.42 mL/minute over the 60-minute period.
- *For Intravenous infusion over a period of 30 minutes in pediatric patients 7 to 17 years of age*: The appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. The infusion rate should be maintained at 1.67 mL/minute over the 30-minute period.

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Table 4 below provides in-use storage conditions for reconstituted CUBICIN RF in acceptable intravenous diluents in the syringe, vial and intravenous bag (for reconstitution and dilution). Do not exceed the listed shelf-life of reconstituted and diluted solutions of CUBICIN RF. Discard unused portions of CUBICIN RF.

Table 4: In-Use Storage Conditions for CUBICIN RF Once Reconstituted in Acceptable Intravenous Diluents

Container	Diluent	In-Use Shelf-Life	
		Room Temperature (20°C–25°C, 68°F–77°F)	Refrigerated (2°C–8°C, 36°F–46°F)
Vial	Sterile Water for Injection	1 Day	3 Days
	Bacteriostatic Water for Injection	2 Days	3 Days
Syringe*	Sterile Water for Injection	1 Day	3 Days
	Bacteriostatic Water for Injection	2 Days	5 Days
Intravenous Bag	Reconstitution: Sterile Water for Injection for immediate dilution with 0.9% sodium chloride injection	19 Hours	3 Days
	Reconstitution: Bacteriostatic Water for Injection for immediate dilution with 0.9% sodium chloride injection	2 Days	5 Days

*Polypropylene syringe with elastomeric plunger stopper.

2.8 Compatible Intravenous Solutions

Reconstituted CUBICIN RF is compatible with Sterile Water for Injection, Bacteriostatic Water for Injection, and 0.9% sodium chloride injection. *[See Dosage and Administration (2.7).]*

2.9 Incompatibilities

CUBICIN RF is not compatible with dextrose-containing diluents.

CUBICIN RF should not be used in conjunction with ReadyMED® elastomeric infusion pumps. Stability studies of CUBICIN solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the CUBICIN solution.

Because only limited data are available on the compatibility of CUBICIN RF with other IV substances, additives and other medications should not be added to CUBICIN RF single-dose vials or infusion bags, or infused simultaneously with CUBICIN RF through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed with a compatible intravenous solution before and after infusion with CUBICIN RF.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 500 mg daptomycin as a sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-dose vial.

4 CONTRAINDICATIONS

CUBICIN RF is contraindicated in patients with known hypersensitivity to daptomycin.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis/Hypersensitivity Reactions

Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including CUBICIN, and may be life-threatening. If an allergic reaction to CUBICIN RF occurs, discontinue the drug and institute appropriate therapy *[see Adverse Reactions (6.2)].*

5.2 Myopathy and Rhabdomyolysis

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), has been reported with the use of CUBICIN. Rhabdomyolysis, with or without acute renal failure, has been reported *[see Adverse Reactions (6.2)]*.

Patients receiving CUBICIN RF should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN RF, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with CUBICIN RF.

In adult patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*

In Phase 1 studies and Phase 2 clinical trials in adults, CPK elevations appeared to be more frequent when CUBICIN was dosed more than once daily. Therefore, CUBICIN RF should not be dosed more frequently than once a day.

CUBICIN RF should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without reported symptoms who have marked elevations in CPK, with levels >2,000 U/L (≥10× ULN). In addition, consideration should be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving CUBICIN RF *[see Drug Interactions (7.1)].*

5.3 Eosinophilic Pneumonia

Eosinophilic pneumonia has been reported in patients receiving CUBICIN *[see Adverse Reactions (6.2)].* In reported cases associated with CUBICIN, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organizing pneumonia. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting CUBICIN and improved when CUBICIN was discontinued and steroid therapy was initiated. Recurrence of eosinophilic pneumonia upon re-exposure has been reported. Patients who develop these signs and symptoms while receiving CUBICIN RF should undergo prompt medical evaluation, and CUBICIN RF should be discontinued immediately. Treatment with systemic steroids is recommended.

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in post-marketing experience with CUBICIN *[see Adverse Reactions (6.2)]*. Patients who develop skin rash, fever, peripheral eosinophilia, and systemic organ (for example, hepatic, renal, pulmonary) impairment while receiving CUBICIN RF should undergo medical evaluation. If DRESS is suspected, discontinue CUBICIN RF promptly and institute appropriate treatment.

5.5 Tubulointerstitial Nephritis (TIN)

TIN has been reported in post-marketing experience with CUBICIN *[see Adverse Reactions (6.2)]*. Patients who develop new or worsening renal impairment while receiving CUBICIN RF should undergo

medical evaluation. If TIN is suspected, discontinue CUBICIN RF promptly and institute appropriate treatment.

5.6 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported during the CUBICIN postmarketing experience *[see Adverse Reactions (6.2)].* Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving CUBICIN RF. Monitor for neuropathy and consider discontinuation.

5.7 Potential Nervous System and/or Muscular System Effects in Pediatric Patients Younger than 12 Months

Avoid use of CUBICIN RF in pediatric patients younger than 12 months due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs with intravenous daptomycin *[see Nonclinical Toxicology (13.2)].*

5.8 *Clostridioides difficile*-Associated Diarrhea

Clostridioides difficile–associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including CUBICIN, and may range in severity from mild diarrhea to fatal colitis *[see Adverse Reactions (6.2)].* Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.9 Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis

Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus*, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required.

Failure of treatment due to persisting or relapsing *S. aureus* bacteremia/endocarditis may be due to reduced daptomycin susceptibility (as evidenced by increasing MIC of the *S. aureus* isolate) *[see Clinical Studies (14.2)].*

5.10 Decreased Efficacy in Patients with Moderate Baseline Renal Impairment

Limited data are available from the two Phase 3 complicated skin and skin structure infection (cSSSI) trials regarding clinical efficacy of CUBICIN treatment in adult patients with creatinine clearance (CL_{CR}) <50 mL/min; only 31/534 (6%) patients treated with CUBICIN in the intent-to-treat (ITT) population had a baseline CL_{CR} <50 mL/min. Table 5 shows the number of adult patients by renal function and treatment group who were clinical successes in the Phase 3 cSSSI trials.

Table 5: Clinical Success Rates by Renal Function and Treatment Group in Phase 3 cSSSI Trials in Adult Patients (Population: ITT)

CL_{CR}	Success Rate

	n/N (%)	
	CUBICIN 4 mg/kg q24h	**Comparator**
50-70 mL/min	25/38 (66%)	30/48 (63%)
30-<50 mL/min	7/15 (47%)	20/35 (57%)

In a subgroup analysis of the ITT population in the Phase 3 *S. aureus* bacteremia/endocarditis trial, clinical success rates, as determined by a treatment-blinded Adjudication Committee *[see Clinical Studies (14.2)]*, in the CUBICIN-treated adult patients were lower in patients with baseline CL_{CR} <50 mL/min (see Table 6). A decrease of the magnitude shown in Table 6 was not observed in comparator-treated patients.

Table 6: Adjudication Committee Clinical Success Rates at Test of Cure by Baseline Creatinine Clearance and Treatment Subgroup in the *S. aureus* Bacteremia/Endocarditis Trial in Adult Patients (Population: ITT)

Baseline CL_{CR}	**Success Rate n/N (%)**			
	CUBICIN 6 mg/kg q24h		**Comparator**	
	Bacteremia	**Right-Sided Infective Endocarditis**	**Bacteremia**	**Right-Sided Infective Endocarditis**
>80 mL/min	30/50 (60%)	7/14 (50%)	19/42 (45%)	5/11 (46%)
50–80 mL/min	12/26 (46%)	1/4 (25%)	13/31 (42%)	1/2 (50%)
30–<50 mL/min	2/14 (14%)	0/1 (0%)	7/17 (41%)	1/1 (100%)

Consider these data when selecting antibacterial therapy for use in adult patients with baseline moderate to severe renal impairment.

5.11 Drug-Laboratory Test Interactions

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay *[see Drug Interactions (7.2)]*.

5.12 Non-Susceptible Microorganisms

The use of antibacterials may promote the overgrowth of non-susceptible microorganisms. If these infections occur during therapy, appropriate measures should be taken.

Prescribing CUBICIN RF in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Anaphylaxis/hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Myopathy and rhabdomyolysis *[see Warnings and Precautions (5.2)]*

- Eosinophilic pneumonia *[see Warnings and Precautions (5.3)]*
- Drug reaction with eosinophilia and systemic symptoms *[see Warnings and Precautions (5.4)]*
- Tubulointerstitial nephritis *[see Warnings and Precautions (5.5)]*
- Peripheral neuropathy *[see Warnings and Precautions (5.6)]*
- Increased International Normalized Ratio (INR)/prolonged prothrombin time *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trial Experience in Adult Patients

Clinical trials enrolled 1,864 adult patients treated with CUBICIN and 1,416 treated with comparator.

Complicated Skin and Skin Structure Infection Trials in Adults

In Phase 3 complicated skin and skin structure infection (cSSSI) trials in adult patients, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse reaction, while comparator was discontinued in 17/558 (3.0%) patients.

The rates of the most common adverse reactions, organized by body system, observed in adult patients with cSSSI (receiving 4 mg/kg CUBICIN) are displayed in Table 7.

Table 7: Incidence of Adverse Reactions that Occurred in ≥2% of Adult Patients in the CUBICIN Treatment Group and ≥ the Comparator Treatment Group in Phase 3 cSSSI Trials

Adverse Reaction	Adult Patients (%)	
	CUBICIN 4 mg/kg (N=534)	Comparator* (N=558)
Gastrointestinal disorders		
Diarrhea	5.2	4.3
Nervous system disorders		
Headache	5.4	5.4
Dizziness	2.2	2.0
Skin/subcutaneous disorders		
Rash	4.3	3.8
Diagnostic investigations		
Abnormal liver function tests	3.0	1.6

Elevated CPK	2.8	1.8
Infections		
Urinary tract infections	2.4	0.5
Vascular disorders		
Hypotension	2.4	1.4
Respiratory disorders		
Dyspnea	2.1	1.6

*Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

Drug-related adverse reactions (possibly or probably drug-related) that occurred in <1% of adult patients receiving CUBICIN in the cSSSI trials are as follows:

Body as a Whole: fatigue, weakness, rigors, flushing, hypersensitivity

Blood/Lymphatic System: leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased International Normalized Ratio (INR)

Cardiovascular System: supraventricular arrhythmia

Dermatologic System: eczema

Digestive System: abdominal distension, stomatitis, jaundice, increased serum lactate dehydrogenase

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

Musculoskeletal System: myalgia, muscle cramps, muscle weakness, arthralgia

Nervous System: vertigo, mental status change, paresthesia

Special Senses: taste disturbance, eye irritation

S. aureus Bacteremia/Endocarditis Trial in Adults

In the *S. aureus* bacteremia/endocarditis trial involving adult patients, CUBICIN was discontinued in 20/120 (16.7%) patients due to an adverse reaction, while comparator was discontinued in 21/116 (18.1%) patients.

Serious Gram-negative infections (including bloodstream infections) were reported in 10/120 (8.3%) CUBICIN-treated patients and 0/115 comparator-treated patients. Comparator-treated patients received dual therapy that included initial gentamicin for 4 days. Infections were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative bacteria.

The rates of the most common adverse reactions, organized by System Organ Class (SOC), observed in adult patients with *S. aureus* bacteremia/endocarditis (receiving 6 mg/kg CUBICIN) are displayed in Table 8.

Table 8: Incidence of Adverse Reactions that Occurred in ≥5% of Adult Patients in the CUBICIN Treatment Group and ≥ the Comparator Treatment Group in the *S. aureus* Bacteremia/Endocarditis Trial

Adverse Reaction*	Adult Patients n (%)	
	CUBICIN 6 mg/kg (N=120)	Comparator† (N=116)
Infections and infestations		
Sepsis NOS	6 (5%)	3 (3%)
Bacteremia	6 (5%)	0 (0%)
Gastrointestinal disorders		
Abdominal pain NOS	7 (6%)	4 (3%)
General disorders and administration site conditions		
Chest pain	8 (7%)	7 (6%)
Edema NOS	8 (7%)	5 (4%)
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	10 (8%)	2 (2%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (6%)	6 (5%)
Sweating increased	6 (5%)	0 (0%)
Psychiatric disorders		
Insomnia	11 (9%)	8 (7%)
Investigations		
Blood creatine phosphokinase increased	8 (7%)	1 (1%)
Vascular disorders		
Hypertension NOS	7 (6%)	3 (3%)

*NOS, not otherwise specified.

†Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

The following reactions, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group:

Blood and Lymphatic System Disorders: eosinophilia, lymphadenopathy, thrombocythemia, thrombocytopenia

Cardiac Disorders: atrial fibrillation, atrial flutter, cardiac arrest

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: vision blurred

Gastrointestinal Disorders: dry mouth, epigastric discomfort, gingival pain, hypoesthesia oral

Infections and Infestations: candidal infection NOS, vaginal candidiasis, fungemia, oral candidiasis, urinary tract infection fungal

Investigations: blood phosphorous increased, blood alkaline phosphatase increased, INR increased, liver function test abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, prothrombin time prolonged

Metabolism and Nutrition Disorders: appetite decreased NOS

Musculoskeletal and Connective Tissue Disorders: myalgia

Nervous System Disorders: dyskinesia, paresthesia

Psychiatric Disorders: hallucination NOS

Renal and Urinary Disorders: proteinuria, renal impairment NOS

Skin and Subcutaneous Tissue Disorders: pruritus generalized, rash vesicular

Other Trials in Adults

In Phase 3 trials of community-acquired pneumonia (CAP) in adult patients, the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events *[see Indications and Usage (1.4)].*

Laboratory Changes in Adults

Complicated Skin and Skin Structure Infection Trials in Adults

In Phase 3 cSSSI trials of adult patients receiving CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients. Of the 534 patients treated with CUBICIN, 1 (0.2%) had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal (ULN). The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after treatment was discontinued *[see Warnings and Precautions (5.2)].* Table 9 summarizes the CPK shifts from Baseline through End of Therapy in the cSSSI adult trials.

Table 9: Incidence of CPK Elevations from Baseline during Therapy in Either the CUBICIN Treatment Group or the Comparator Treatment Group in Phase 3 cSSSI Adult Trials

Change in CPK		All Adult Patients				Adult Patients with Normal CPK at Baseline			
		CUBICIN 4 mg/kg (N=430)		Comparator* (N=459)		CUBICIN 4 mg/kg (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	>1× ULN†	9.3	40	8.9	41	8.8	33	8.9	35
	>2× ULN	4.9	21	4.8	22	3.7	14	3.1	12
	>4× ULN	1.4	6	1.5	7	1.1	4	1.0	4
	>5× ULN	1.4	6	0.4	2	1.1	4	0.0	0

>10× ULN	0.5	2	0.2	1	0.2	1	0.0	0

Note: Elevations in CPK observed in adult patients treated with CUBICIN or comparator were not clinically or statistically significantly different.

*Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

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

S. aureus Bacteremia/Endocarditis Trial in Adults

In the *S. aureus* bacteremia/endocarditis trial in adult patients, at a dose of 6 mg/kg, 11/120 (9.2%) CUBICIN-treated patients, including two patients with baseline CPK levels >500 U/L, had CPK elevations to levels >500 U/L, compared with 1/116 (0.9%) comparator-treated patients. Of the 11 CUBICIN-treated patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Three of these 11 CUBICIN-treated patients discontinued therapy due to CPK elevation, while the one comparator-treated patient did not discontinue therapy *[see Warnings and Precautions (5.2)]*.

Clinical Trial Experience in Pediatric Patients

Complicated Skin and Skin Structure Infection Trial in Pediatric Patients

The safety of CUBICIN was evaluated in one clinical trial (in cSSSI), which included 256 pediatric patients (1 to 17 years of age) treated with intravenous CUBICIN and 133 patients treated with comparator agents. Patients were given age-dependent doses once daily for a treatment period of up to 14 days (median treatment period was 3 days). The doses given by age group were as follows: 10mg/kg for 1 to < 2 years, 9 mg/kg for 2 to 6 years, 7mg/kg for 7 to 11 years and 5 mg/kg for 12 to 17 years of age *[see Clinical Studies (14)]*. Patients treated with CUBICIN were (51%) male, (49%) female and (46%) Caucasian and (32%) Asian.

Adverse Reactions Leading to Discontinuation

In the cSSSI study, CUBICIN was discontinued in 7/256 (2.7%) patients due to an adverse reaction, while comparator was discontinued in 7/133 (5.3%) patients.

Most Common Adverse Reactions

The rates of the most common adverse reactions, organized by body system, observed in these pediatric patients with cSSSI are displayed in Table 10.

Table 10: Adverse Reactions that Occurred in ≥2% of Pediatric Patients in the CUBICIN Treatment-Arm and Greater Than or Equal to the Comparator Treatment-Arm in the cSSSI Pediatric Trial

	CUBICIN (N = 256)	**Comparator* (N = 133)**
Adverse Reaction	**n (%)**	**n (%)**
Gastrointestinal disorders		
Diarrhea	18 (7.0)	7 (5.3)
Vomiting	7 (2.7)	1 (0.8)
Abdominal Pain	5 (2.0)	0
Skin and subcutaneous tissue disorders		

Pruritus	8 (3.1)	2 (1.5)
General disorders and administration site conditions		
Pyrexia	10 (3.9)	4 (3.0)
Investigations		
Blood CPK increased	14 (5.5)	7 (5.3)
Nervous system disorders		
Headache	7 (2.7)	3 (2.3)

*Comparators included intravenous therapy with either vancomycin, clindamycin, or an anti-staphylococcal semi-synthetic penicillin (nafcillin, oxacillin or cloxacillin)

The safety profile in the clinical trial of cSSSI pediatric patients was similar to that observed in the cSSSI adult patients.

S. aureus Bacteremia Trial in Pediatric Patients

The safety of CUBICIN was evaluated in one clinical trial (in *S. aureus* bacteremia), which treated 55 pediatric patients with intravenous CUBICIN and 26 patients with comparator agents. Patients were given age-dependent doses once daily for a treatment period of up to 42 days (mean duration of IV treatment was 12 days). The doses by age group were as follows: 12 mg/kg for 1 to <6 years, 9 mg/kg for 7 to 11 years and 7 mg/kg for 12 to 17 years of age *[see Clinical Studies (14)]*. Patients treated with CUBICIN were (69%) male and (31%) female. No patients 1 to <2 years of age were enrolled.

Adverse Reactions Leading to Discontinuation

In the bacteremia study, CUBICIN was discontinued in 3/55 (5.5%) patients due to an adverse reaction, while comparator was discontinued in 2/26 (7.7%) patients.

Most Common Adverse Reactions

The rates of the most common adverse reactions, organized by body system, observed in these pediatric patients with bacteremia are displayed in Table 11.

Table 11: Incidence of Adverse Reactions that Occurred in ≥5% of Pediatric Patients in the CUBICIN Treatment-Arm and Greater Than or Equal to the Comparator Treatment-Arm in the Pediatric Bacteremia Trial

	CUBICIN (N = 55)	**Comparator (N = 26)**
Adverse Reaction	**n (%)**	**n (%)**
Gastrointestinal disorders		
Vomiting	6 (10.9)	2 (7.7)
Investigations		
Blood CPK increased	4 (7.3)	0

*Comparators included intravenous therapy with either vancomycin, cefazolin, or an anti-staphylococcal semi-synthetic penicillin (nafcillin, oxacillin or cloxacillin)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of CUBICIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: anemia, thrombocytopenia

General and administration site conditions: pyrexia

Immune System Disorders: anaphylaxis; hypersensitivity reactions, including angioedema, pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia *[see Contraindications (4), Warnings and Precautions (5.1)]*

Infections and Infestations: Clostridioides difficile–associated diarrhea *[see Warnings and Precautions (5.8)]*

Laboratory Investigations: platelet count decreased

Musculoskeletal Disorders: myoglobin increased; rhabdomyolysis (some reports involved patients treated concurrently with CUBICIN and HMG-CoA reductase inhibitors) *[see Warnings and Precautions (5.2), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*

Respiratory, Thoracic, and Mediastinal Disorders: cough, eosinophilic pneumonia, organizing pneumonia *[see Warnings and Precautions (5.3)]*

Nervous System Disorders: peripheral neuropathy *[see Warnings and Precautions (5.6)]*

Skin and Subcutaneous Tissue Disorders: serious skin reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement), acute generalized exanthematous pustulosis *[see Warnings and Precautions (5.4)]*

Gastrointestinal Disorders: nausea, vomiting

Renal and urinary disorders: acute kidney injury, renal insufficiency, renal failure, and tubulointerstitial nephritis (TIN) *[see Warnings and Precautions (5.5)]*

Special Senses: visual disturbances

7 DRUG INTERACTIONS

7.1 HMG-CoA Reductase Inhibitors

In healthy adult subjects, concomitant administration of CUBICIN and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy *[see Clinical Pharmacology (12.3)].*

However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the adult Phase 3 *S. aureus* bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK *[see Adverse Reactions (6.1)].* Experience with the coadministration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving CUBICIN RF.

7.2 Drug-Laboratory Test Interactions

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimized by drawing specimens for PT or INR testing near the time of trough plasma

concentrations of daptomycin. However, sufficient daptomycin concentrations may be present at trough to cause interaction.

If confronted with an abnormally high PT/INR result in a patient being treated with CUBICIN RF, it is recommended that clinicians:

1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next CUBICIN RF dose (i.e., at trough concentration). If the PT/INR value obtained at trough remains substantially elevated above what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data on use of CUBICIN RF in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies performed in rats and rabbits daptomycin was administered intravenously during organogenesis at doses 2 and 4–times, respectively, the recommended 6 mg/kg human dose (on a body surface area basis). No evidence of adverse developmental outcomes was observed.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant rats, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 18. Maternal body weight gain was decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than in humans at the recommended maximum dose of 6mg/kg (based on body surface area).

In pregnant rabbits, daptomycin was administered intravenously at doses of 5, 20, or 75 mg/kg/day during the gestation days 6 to 15. Maternal body weight gain and food consumption were decreased at 75 mg/kg/day. No embryo/fetal effects were noted at the highest dose of 75 mg/kg/day, a dose approximately 4-fold higher than in humans at the maximum recommended dose of 6mg/kg (based on body surface area).

In a combined fertility and pre/postnatal development study, daptomycin was administered intravenously to female rats at doses of 2, 25, 75 mg/kg/day from 14-days pre-mating through lactation/postpartum day 20). No effects on pre/postnatal development were observed up to the highest dose of 75 mg/kg/day, a dose approximately 2-fold higher than the maximum recommended human dose of 6 mg/kg (based on body surface area)[1].

8.2 Lactation

Risk Summary

Limited published data report that daptomycin is present in human milk at infant doses of 0.1% of the maternal dose *[see Data]*[2,3,4]. There is no information on the effects of daptomycin on the breastfed infant or the effects of daptomycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CUBICIN and any potential adverse effects on the breastfed infant from CUBICIN RF or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of CUBICIN RF in the treatment of cSSSI and *S. aureus* bloodstream infections (bacteremia) have been established in the age groups 1 to 17 years of age. Use of CUBICIN RF in these age groups is supported by evidence from adequate and well-controlled studies in adults, with additional data from pharmacokinetic studies in pediatric patients, and from safety, efficacy and PK studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

Safety and effectiveness in pediatric patients below the age of one year have not been established. Avoid use of CUBICIN RF in pediatric patients younger than one year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs *[see Warnings and Precautions (5.7) and Nonclinical Toxicology (13.2)].*

CUBICIN RF is not indicated in pediatric patients with renal impairment because dosage has not been established in these patients.

CUBICIN RF has not been studied in pediatric patients with other bacterial infections.

8.5 Geriatric Use

Of the 534 adult patients treated with CUBICIN in Phase 3 controlled clinical trials of complicated skin and skin structure infections (cSSSI), 27% were 65 years of age or older and 12% were 75 years of age or older. Of the 120 adult patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25% were 65 years of age or older and 16% were 75 years of age or older. In Phase 3 adult clinical trials of cSSSI and *S. aureus* bacteremia/endocarditis, clinical success rates were lower in patients ≥65 years of age than in patients <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years of age than in patients <65 years of age.

The exposure of daptomycin was higher in healthy elderly subjects than in healthy young adult subjects. However, no adjustment of CUBICIN RF dosage is warranted for elderly patients with creatinine clearance (CL_{CR}) ≥30 mL/min *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)].*

8.6 Patients with Renal Impairment

Daptomycin is eliminated primarily by the kidneys; therefore, a modification of CUBICIN RF dosage interval is recommended for adult patients with CL_{CR} <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In adult patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently than once weekly *[see Dosage and Administration (2.6), Warnings and Precautions (5.2, 5.10), and Clinical Pharmacology (12.3)].*

The dosage regimen for CUBICIN RF in pediatric patients with renal impairment has not been established.

10 OVERDOSAGE

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 hours) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with that removed by low-flux membranes.

11 DESCRIPTION

CUBICIN RF (daptomycin for injection) 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:

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. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the P450 system.

Aztreonam

In a study in which 15 healthy adult subjects received a single dose of CUBICIN 6 mg/kg IV and a combination dose of CUBICIN 6 mg/kg IV and aztreonam 1 g IV, administered over a 30-minute period, the C_{max} and $AUC_{0-\infty}$ of daptomycin were not significantly altered by aztreonam.

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, administered over a 30-minute period, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin were 12.7% and 8.7% higher, respectively, when CUBICIN was coadministered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin were 10.7% and 6.6% lower, respectively, when tobramycin was coadministered with CUBICIN. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of CUBICIN RF is unknown.

Warfarin

In 16 healthy adult subjects, administration of CUBICIN 6 mg/kg q24h by IV infusion over a 30-minute period for 5 days, with coadministration of a single oral dose of warfarin (25 mg) on the 5th day, had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio).

Simvastatin

In 20 healthy adult subjects on a stable daily dose of simvastatin 40 mg, administration of CUBICIN 4 mg/kg q24h by IV infusion over a 30-minute period for 14 days (N=10) had no effect on plasma trough concentrations of simvastatin and was not associated with a higher incidence of adverse events, including skeletal myopathy, than in subjects receiving placebo once daily (N=10) *[see Warnings and Precautions (5.2) and Drug Interactions (7.1)].*

Probenecid

Concomitant administration of probenecid (500 mg 4 times daily) and a single dose of CUBICIN 4 mg/kg by IV infusion over a 30-minute period in adults did not significantly alter the C_{max} or $AUC_{0-\infty}$ of daptomycin.

12.4 Microbiology

Daptomycin belongs to the cyclic lipopeptide class of antibacterials. Daptomycin 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 exhibits rapid, concentration-dependent bactericidal activity against Gram-positive bacteria *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC (minimum bactericidal concentration/minimum inhibitory concentration) ratios using broth dilution methodology. Daptomycin maintained bactericidal activity *in vitro* against stationary phase *S. aureus* in simulated endocardial vegetations. The clinical significance of this is not known.

Mechanism of Action

Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death.

Resistance

treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be administered exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CUBICIN RF or other antibacterial drugs in the future.

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