HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CUBICIN RF safely and effectively. See full prescribing information for CUBICIN RF.

CUBICIN® RF (daptomycin for injection), for intravenous use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------
CUBICIN RF is a lipopeptide antibacterial indicated for the treatment of:
- Complicated skin and skin structure infections (cSSSI) (1.1)
- *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis (1.2)

CUBICIN RF is not indicated for the treatment of pneumonia. (1.3)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN RF and other antibacterial drugs, CUBICIN RF should be used to treat infections that are proven or strongly suspected to be caused by bacteria. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended dosage regimen for adult patients (2.2, 2.3, 2.4):

Creatinine Clearance (CL_{CR})	Dosage Regimen	
	cSSSI For 7 to 14 days	*S. aureus* Bacteremia For 2 to 6 weeks
≥30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
<30 mL/min, including hemodialysis and CAPD	4 mg/kg once every 48 hours*	6 mg/kg once every 48 hours*

*Administered following hemodialysis on hemodialysis days.
- Administered intravenously, either by injection over a 2-minute period or by infusion over a 30-minute period. (2.1, 2.5)
- Do not use in conjunction with ReadyMED® elastomeric infusion pumps. (2.7)

---------- DOSAGE FORMS AND STRENGTHS ----------
500 mg lyophilized powder for reconstitution in a single-dose vial (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to daptomycin (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Anaphylaxis/hypersensitivity reactions (including life-threatening): Discontinue CUBICIN RF and treat signs/symptoms. (5.1)
- Myopathy and rhabdomyolysis: Monitor CPK levels and follow muscle pain or weakness; if elevated CPK or myopathy occurs, consider discontinuation of CUBICIN RF. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN RF and consider treatment with systemic steroids. (5.3)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.4)
- Potential nervous system and/or muscular system effects in pediatric patients younger than 12 months: Avoid use of CUBICIN RF in this age group. (5.5)
- *Clostridium difficile*–associated diarrhea: Evaluate patients if diarrhea occurs. (5.6)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.7)
- Decreased efficacy was observed in patients with moderate baseline renal impairment. (5.8)

---------- ADVERSE REACTIONS ----------
The most clinically significant adverse reactions observed with CUBICIN 4 mg/kg (cSSSI trials) and 6 mg/kg (*S. aureus* bacteremia/endocarditis trial) were abnormal liver function tests, elevated CPK, and dyspnea. (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: 7/2016

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

CUBICIN® RF is indicated for the treatment of 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), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates

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

1.3 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 patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor *[see Clinical Trials (14.2)].* CUBICIN has not been studied in patients with prosthetic valve endocarditis.

1.4 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 Administration Duration

CUBICIN RF should be administered intravenously either by injection over a two (2) minute period or by infusion over a thirty (30) minute period.

2.2 Complicated Skin and Skin Structure Infections

CUBICIN RF 4 mg/kg should be administered intravenously once every 24 hours for 7 to 14 days.

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

CUBICIN RF 6 mg/kg should be administered 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 patients who were treated with CUBICIN for more than 28 days.

2.4 Patients with Renal Impairment

The recommended dosage regimen for patients with creatinine clearance (CL_{CR}) less than 30 mL/min, including 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 1). When possible, CUBICIN RF should be administered following the completion of hemodialysis on hemodialysis days *[see Warnings and Precautions (5.2, 5.8), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Table 1: Recommended Dosage of CUBICIN RF in Adult Patients

Creatinine Clearance (CL_{CR})	Dosage Regimen	
	cSSSI	*S. aureus* Bloodstream Infections
≥30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
<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.

2.5 Preparation of CUBICIN RF for Administration

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 containing daptomycin (50 mg/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:

Intravenous Injection over a period of 2 minutes

For intravenous (IV) injection over a period of 2 minutes, administer the appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL).

Intravenous Infusion over a period of 30 minutes

For intravenous (IV) infusion over a period of 30 minutes, the appropriate volume of the reconstituted CUBICIN RF (concentration of 50 mg/mL) should be further diluted, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. This transfer should be done using aseptic technique involving a beveled sterile needle that is 21 gauge or smaller in diameter.

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Table 2 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 2: 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.

2.6 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 (2.5).]*

2.7 Incompatibilities

CUBICIN RF is incompatible 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

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 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, 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. 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 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.

5.5 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)].*

5.6 *Clostridium difficile*-Associated Diarrhea

Clostridium 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.

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