

**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

**RECENT MAJOR CHANGES**

Indications and Usage (1) 9/2017  
Dosage and Administration (2) 9/2017

**INDICATIONS AND USAGE**

CUBICIN RF is a lipopeptide antibacterial indicated for the treatment of:

- Complicated skin and skin structure infections (cSSSI) in adult and pediatric patients (1 to 17 years of age) (1.1) and,
- *Staphylococcus aureus* bloodstream infections (bacteremia), in adult patients including those with right-sided infective endocarditis, (1.2)
- *Staphylococcus aureus* bloodstream infections (bacteremia) in pediatric patients (1 to 17 years of age). (1.3)

**Limitations of Use:**

- CUBICIN RF is not indicated for the treatment of pneumonia. (1.4)
- CUBICIN RF is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. (1.4)
- CUBICIN RF is not recommended 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. (1.4)

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. (1.5)

**DOSAGE AND ADMINISTRATION**

**Adult Patients**

- Administer to **adult patients** intravenously in 0.9% sodium chloride, either by injection over a 2-minute period or by infusion over a 30-minute period. (2.1, 2.7)
- Recommended dosage regimen for adult patients (2.2, 2.4, 2.6):

Creatinine Clearance (CL <sub>CR</sub> )	Dosage Regimen	
	cSSSI For 7 to 14 days	<i>S. aureus</i> 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.

**Pediatric Patients**

- **Unlike in adults, do NOT administer by injection over a two (2) minute period to pediatric patients.** (2.1, 2.7)
- Administer to pediatric patients intravenously in 0.9% sodium chloride, by infusion over a 30- or 60-minute period, based on age. (2.1, 2.7)
- Recommended dosage regimen for pediatric patients (1 to 17 years of age) with cSSSI, based on age (2.3):

Age group	Dosage*	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 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.

- Recommended dosage regimen for pediatric patients (1 to 17 years of age) with *S. aureus* bacteremia, based on age (2.5):

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.

- There are two formulations of daptomycin that have differences concerning storage and reconstitution. Carefully follow the reconstitution and storage procedures in labeling. (2.7)
- Do not use in conjunction with ReadyMED® elastomeric infusion pumps in adult and pediatric patients. (2.9)

**DOSAGE FORMS AND STRENGTHS**

For Injection: 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 adult patients with moderate baseline renal impairment. (5.8)

**ADVERSE REACTIONS**

- **Adult cSSSI Patients:** The most common adverse reactions that occurred in ≥2% of adult cSSSI patients receiving CUBICIN 4 mg/kg were diarrhea, headache, dizziness, rash, abnormal liver function tests, elevated creatinine phosphokinase (CPK), urinary tract infections hypotension, and dyspnea. (6.1)
- **Pediatric cSSSI Patients:** The most common adverse reactions that occurred in ≥2% of pediatric patients receiving CUBICIN were diarrhea, vomiting, abdominal pain, pruritus, pyrexia, elevated CPK, and headache. (6.1)
- **Adult *S. aureus* bacteremia/endocarditis Patients:** The most common adverse reactions that occurred in ≥5% of *S. aureus* bacteremia/endocarditis patients receiving CUBICIN 6 mg/kg were sepsis, bacteremia, abdominal pain, chest pain, edema, pharyngolaryngeal pain, pruritus, increased sweating, insomnia, elevated CPK, and hypertension. (6.1)
- **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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2017

---

**FULL PRESCRIBING INFORMATION: CONTENTS\*****1 INDICATIONS AND USAGE**

- 1.1 Complicated Skin and Skin Structure Infections (cSSSI)
- 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
- 1.3 *Staphylococcus aureus* Bloodstream Infections (Bacteremia) in Pediatric Patients (1 to 17 Years of Age)
- 1.4 Limitations of Use
- 1.5 Usage

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Important Administration Duration Instructions
- 2.2 Dosage in Adults for cSSSI
- 2.3 Dosage in Pediatric Patients (1 to 17 Years of Age) for cSSSI
- 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
- 2.5 Dosage in Pediatric Patients (1 to 17 Years of Age) with *Staphylococcus aureus* Bloodstream Infections (Bacteremia)
- 2.6 Dosage in Patients with Renal Impairment
- 2.7 Preparation and Administration of CUBICIN RF
- 2.8 Compatible Intravenous Solutions
- 2.9 Incompatibilities

**3 DOSAGE FORMS AND STRENGTHS****4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Anaphylaxis/Hypersensitivity Reactions
- 5.2 Myopathy and Rhabdomyolysis
- 5.3 Eosinophilic Pneumonia
- 5.4 Peripheral Neuropathy
- 5.5 Potential Nervous System and/or Muscular System Effects in Pediatric Patients Younger than 12 Months
- 5.6 *Clostridium difficile*-Associated Diarrhea

- 5.7 Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis
- 5.8 Decreased Efficacy in Patients with Moderate Baseline Renal Impairment
- 5.9 Drug-Laboratory Test Interactions
- 5.10 Non-Susceptible Microorganisms

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

**7 DRUG INTERACTIONS**

- 7.1 HMG-CoA Reductase Inhibitors
- 7.2 Drug-Laboratory Test Interactions

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment

**10 OVERDOSAGE****11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

- 14.1 Complicated Skin and Skin Structure Infections
- 14.2 *S. aureus* Bacteremia/Endocarditis

**15 REFERENCES****16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

\*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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 (5.5)* 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<sub>CR</sub>) greater than or equal to 30 mL/min. The recommended dosage regimen for CUBICIN RF in adult patients with CL<sub>CR</sub> 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, 5.8), *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].

**Table 3: Recommended Dosage of CUBICIN RF in Adult Patients**

Creatinine Clearance (CL <sub>CR</sub> )	Dosage Regimen in Adults	
	cSSSI	<i>S. aureus</i> 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:

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.