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

CUBICIN® (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 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 is not indicated for the treatment of pneumonia. (1.4)
- CUBICIN is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. (1.4)
- CUBICIN 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 and other antibacterial drugs, CUBICIN 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_{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.		

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 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. (5.2)
- Eosinophilic pneumonia: Discontinue CUBICIN 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 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 creatine 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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

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® 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 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 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 is not indicated for the treatment of pneumonia.

CUBICIN 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 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 and other antibacterial drugs, CUBICIN 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 (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 by injection over a two (2) minute period to pediatric patients.

- Pediatric Patients 7 to 17 years of Age: Administer CUBICIN 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 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 4 mg/kg to adult patients intravenously in 0.9% sodium chloride injection 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 intravenously in 0.9% sodium chloride injection once every 24 hours for up to 14 days.

Table 1: Recommended Dosage of CUBICIN 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 6 mg/kg to adult patients intravenously in 0.9% sodium chloride injection 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 intravenously in 0.9% sodium chloride injection once every 24 hours for up to 42 days.

Table 2: Recommended Dosage of CUBICIN 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 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 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 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 following the completion of hemodialysis on hemodialysis days.

Pediatric Patients:

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

2.7 Preparation and Administration of CUBICIN

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 Vial

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

1. To minimize foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.
2. Remove the polypropylene flip-off cap from the CUBICIN vial to expose the central portion of the rubber stopper.
3. 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.
4. Slowly transfer 10 mL of 0.9% sodium chloride injection through the center of the rubber stopper into the CUBICIN vial, pointing the transfer needle toward the wall of the vial. It is recommended that a beveled sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device is used, pointing the transfer needle toward the wall of the vial.
5. Ensure that all of the CUBICIN powder is wetted by gently rotating the vial.
    1. Allow the wetted product to stand undisturbed for 10 minutes.
    2. Gently 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 (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 (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 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 (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 (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. Do not exceed the In-Use storage conditions of the reconstituted and diluted solutions of CUBICIN described below. Discard unused portions of CUBICIN.

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