

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

Warnings and Precautions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (5.4) 8/2020
 Warnings and Precautions, Tubulointerstitial Nephritis (TIN) (5.5) 8/2020

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	
	<u>cSSSI</u> For 7 to 14 days	<u>S. aureus Bacteremia</u> 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)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue CUBICIN and institute appropriate treatment. (5.4)
- Tubulointerstitial Nephritis (TIN): Discontinue CUBICIN and institute appropriate treatment. (5.5)
- Peripheral neuropathy: Monitor for neuropathy and consider discontinuation. (5.6)
- Potential nervous system and/or muscular system effects in pediatric patients younger than 12 months: Avoid use of CUBICIN in this age group. (5.7)
- *Clostridioides difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.8)
- Persisting or relapsing *S. aureus* bacteremia/endocarditis: Perform susceptibility testing and rule out sequestered foci of infection. (5.9)
- Decreased efficacy was observed in adult patients with moderate baseline renal impairment. (5.10)

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.

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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
- 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- 5.5 Tubulointerstitial Nephritis (TIN)
- 5.6 Peripheral Neuropathy

- 5.7 Potential Nervous System and/or Muscular System Effects in Pediatric Patients Younger than 12 Months
- 5.8 *Clostridioides difficile*-Associated Diarrhea
- 5.9 Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis
- 5.10 Decreased Efficacy in Patients with Moderate Baseline Renal Impairment
- 5.11 Drug-Laboratory Test Interactions
- 5.12 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® 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 (5.7)* 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 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, 5.10), *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	<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 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.

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