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 (5.5) 11/2014

----------INDICATIONS AND USAGE----------

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

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.

----------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 in 0.9% sodium chloride, 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-use 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 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 Cubist Pharmaceuticals, Inc., at 1-877-282-4786 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

CUBICIN® (daptomycin for injection)

1 INDICATIONS AND USAGE

CUBICIN is indicated for the treatment of the infections listed below.

1.1 Complicated Skin and Skin Structure Infections

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

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 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 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 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 Administration Duration

CUBICIN 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 4 mg/kg should be administered intravenously in 0.9% sodium chloride injection 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 6 mg/kg should be administered 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 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}) <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 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 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 following the completion of hemodialysis on hemodialysis days.

2.5 Preparation of CUBICIN for Administration

CUBICIN is supplied in single-use 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:

Note: To minimize foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.

1. Remove the polypropylene flip-off cap from the CUBICIN vial to expose the central portion of the rubber stopper.
2. 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.
3. Ensure that all of the CUBICIN powder is wetted by gently rotating the vial.
4. Allow the wetted product to stand undisturbed for 10 minutes.
5. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.

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

For IV infusion over a period of 30 minutes, 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.

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

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature and up to 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F).

The diluted solution is stable in the infusion bag for 12 hours at room temperature and 48 hours if stored under refrigeration. The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) should not exceed 12 hours at room temperature or 48 hours under refrigeration.

CUBICIN vials are for single use only.

2.6 Compatible Intravenous Solutions

CUBICIN is compatible with 0.9% sodium chloride injection and lactated Ringer's injection.

2.7 Incompatibilities

CUBICIN is not compatible with dextrose-containing diluents.

CUBICIN should not be used in conjunction with ReadyMED® elastomeric infusion pumps (Cardinal Health, Inc.). 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 with other IV substances, additives and other medications should not be added to CUBICIN single-use vials or infusion bags, or infused simultaneously with CUBICIN 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.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

CUBICIN 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 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 should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, 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.

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 should not be dosed more frequently than once a day.

CUBICIN 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 [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

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