

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-572/S-052**

***Trade Name:*** Cubicin® RF

***Generic Name:*** daptomycin for injection

***Sponsor:*** Cubist Pharmaceuticals LLC

***Approval Date:*** July 6, 2016

***Indications:*** For complicated skin and skin structure infections, *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21-572/S-052**

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***APPLICATION NUMBER:***  
**NDA 21-572/S-052**

**APPROVAL LETTER**



NDA 21-572/S-052

**SUPPLEMENT APPROVAL**

Merck Sharp & Dohme Corp., agent for Cubist Pharmaceuticals, LLC  
Attention: Sandra Lynn Wood, PhD  
Director, Global Regulatory Affairs  
351 North Sumneytown Pike  
P.O. Box 1000, Mailstop UG-2D48  
North Wales, PA 19454-2505

Dear Dr. Wood:

Please refer to your Supplemental New Drug Application (sNDA) dated February 9, 2016, received February 9, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cubicin RF (daptomycin for injection), 500 mg/vial.

This Prior Approval supplemental new drug application provides for a re-formulated Cubicin product, Cubicin RF. The package insert (PI) and carton and container labels have been revised accordingly, the former including changes to the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, **DOSAGE AND ADMINISTRATION (2)**, **Preparation of CUBICIN RF for Administration (2.5)**, **Compatible Intravenous Solutions (2.6)**, and **Incompatibilities (2.7)** subsections, **DESCRIPTION (11)** section, and the **HOW SUPPLIED/STORAGE AND HANDLING (16)** section.

Additionally, the following has been added to the **ADVERSE REACTIONS (6)**, **Postmarketing Experience (6.2)** subsection:

- *Blood and lymphatic system disorders: anemia*
- *General and administration site conditions: pyrexia*
- *Renal and urinary disorders: acute kidney injury, renal insufficiency, and renal failure*
- *Skin and Subcutaneous Tissue Disorders: acute generalized exanthematous pustulosis*

Further, the term “single-use” has been replaced with “single-dose” throughout the package insert, cartons and containers.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at:

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 22, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 21-572/S-052.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **MARKET PACKAGE**

Please submit one market package of the drug product when it is available to the following address:

J. Christopher Davi, MS, Senior Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 6230  
10903 New Hampshire Avenue  
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see:

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

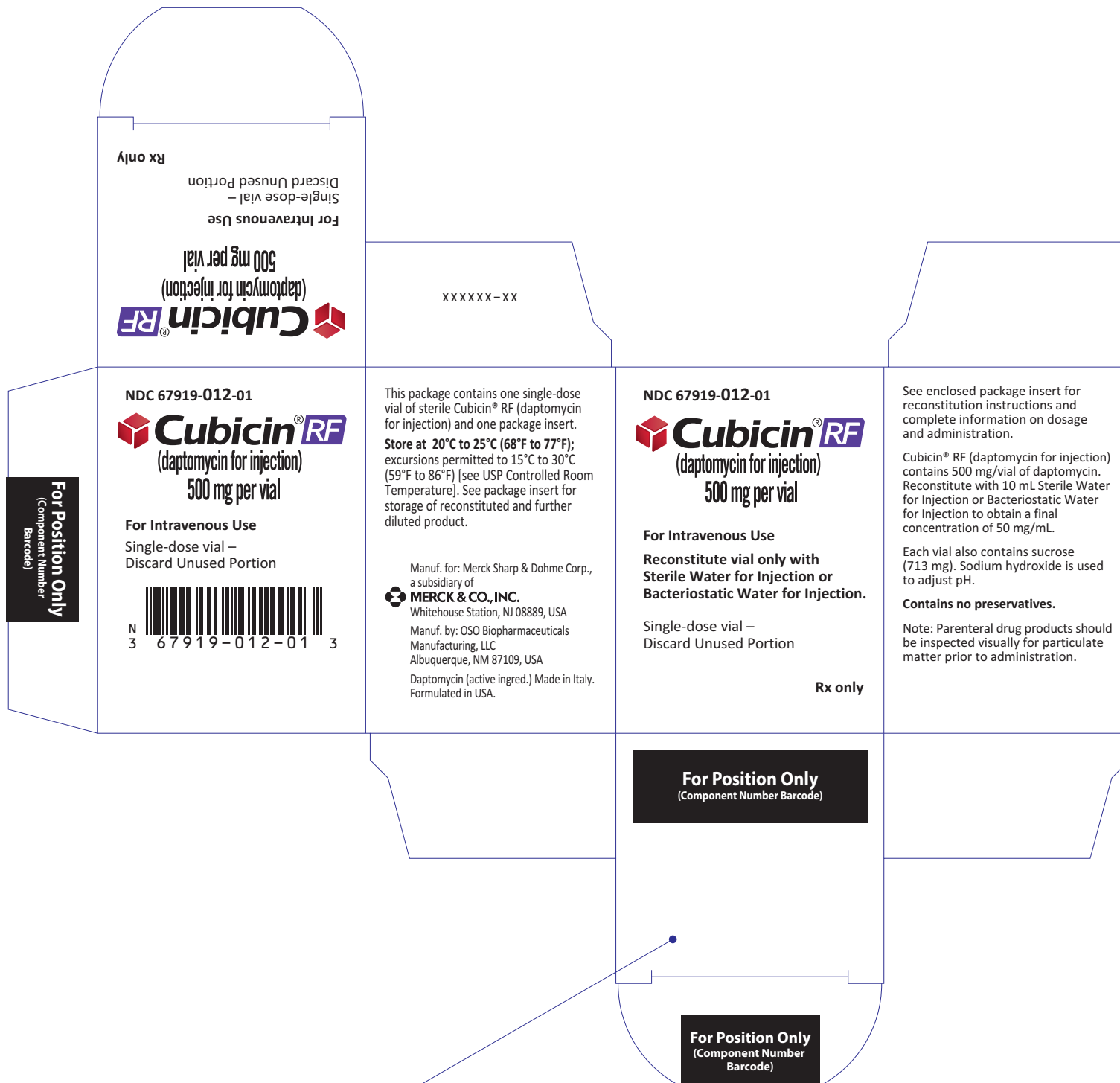
If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

**ENCLOSURES:**      Content of Labeling  
                             Carton and Container Labeling



Lot/Exp. Area: All legends and encoding information to be printed online.



(01)00367919012013

USUAL DOSAGE:  
See Package Insert.  
**Store at 20°C to 25°C (68°F to 77°F).** See package insert for storage of reconstituted and further diluted product.  
**Use 10 mL Sterile or Bacteriostatic Water for Injection for reconstitution only.**  
Manuf. for: Merck Sharp & Dohme Corp.,  
a subsidiary of Merck & Co., Inc.

NDC 67919-012-01

Cubicin<sup>®</sup>RF

(daptomycin for injection)

500 mg per vial

For Intravenous Use  
Single-dose vial –  
Discard Unused Portion

Rx only

XXXXXX-XX

Lot and Expiry Area.  
Legends Printed Online.

Reference ID: 3955674

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUMATHI NAMBIAR  
07/06/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21-572/S-052**

**LABELING**

## 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 <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.

- 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2016

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- 1.2 *Staphylococcus aureus* Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin-Resistant Isolates
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\*Sections or subsections omitted from the full prescribing information are not listed.

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## 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<sub>CR</sub>) 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 <sub>CR</sub> )	Dosage Regimen	
	cSSSI	<i>S. aureus</i> 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.



If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

## 5.7 Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis

Patients with persisting or relapsing *S. aureus* bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus*, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required.

Failure of treatment due to persisting or relapsing *S. aureus* bacteremia/endocarditis may be due to reduced daptomycin susceptibility (as evidenced by increasing MIC of the *S. aureus* isolate) [see *Clinical Trials* (14.2)].

## 5.8 Decreased Efficacy in Patients with Moderate Baseline Renal Impairment

Limited data are available from the two Phase 3 complicated skin and skin structure infection (cSSSI) trials regarding clinical efficacy of CUBICIN treatment in patients with creatinine clearance (CL<sub>CR</sub>) <50 mL/min; only 31/534 (6%) patients treated with CUBICIN in the intent-to-treat (ITT) population had a baseline CL<sub>CR</sub> <50 mL/min. Table 3 shows the number of patients by renal function and treatment group who were clinical successes in the Phase 3 cSSSI trials.

**Table 3: Clinical Success Rates by Renal Function and Treatment Group in Phase 3 cSSSI Trials (Population: ITT)**

CL <sub>CR</sub>	Success Rate n/N (%)	
	CUBICIN 4 mg/kg q24h	Comparator
50-70 mL/min	25/38 (66%)	30/48 (63%)
30-<50 mL/min	7/15 (47%)	20/35 (57%)

In a subgroup analysis of the ITT population in the Phase 3 *S. aureus* bacteremia/endocarditis trial, clinical success rates, as determined by a treatment-blinded Adjudication Committee [see *Clinical Trials* (14.2)], in the CUBICIN-treated patients were lower in patients with baseline CL<sub>CR</sub> <50 mL/min (see Table 4). A decrease of the magnitude shown in Table 4 was not observed in comparator-treated patients.

**Table 4: Adjudication Committee Clinical Success Rates at Test of Cure by Baseline Creatinine Clearance and Treatment Subgroup in the *S. aureus* Bacteremia/Endocarditis Trial (Population: ITT)**

Baseline CL <sub>CR</sub>	Success Rate n/N (%)			
	CUBICIN 6 mg/kg q24h		Comparator	
	Bacteremia	Right-Sided Infective Endocarditis	Bacteremia	Right-Sided Infective Endocarditis
>80 mL/min	30/50 (60%)	7/14 (50%)	19/42 (45%)	5/11 (46%)
50–80 mL/min	12/26 (46%)	1/4 (25%)	13/31 (42%)	1/2 (50%)
30–<50 mL/min	2/14 (14%)	0/1 (0%)	7/17 (41%)	1/1 (100%)

Consider these data when selecting antibacterial therapy for use in patients with baseline moderate to severe renal impairment.

## 5.9 Drug-Laboratory Test Interactions

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay [see *Drug Interactions* (7.2)].

## 5.10 Non-Susceptible Microorganisms

The use of antibacterials may promote the overgrowth of non-susceptible microorganisms. If superinfection occurs during therapy, appropriate measures should be taken.

Prescribing CUBICIN RF in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

## 6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Anaphylaxis/hypersensitivity reactions [see *Warnings and Precautions* (5.1)]
- Myopathy and rhabdomyolysis [see *Warnings and Precautions* (5.2)]
- Eosinophilic pneumonia [see *Warnings and Precautions* (5.3)]
- Peripheral neuropathy [see *Warnings and Precautions* (5.4)]
- Increased International Normalized Ratio (INR)/prolonged prothrombin time [see *Warnings and Precautions* (5.9) and *Drug Interactions* (7.2)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### 6.1 Clinical Trials Experience

Clinical trials enrolled 1,864 patients treated with CUBICIN and 1,416 treated with comparator.

#### Complicated Skin and Skin Structure Infection Trials

In Phase 3 complicated skin and skin structure infection (cSSSI) trials, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse reaction, while comparator was discontinued in 17/558 (3.0%) patients.

The rates of the most common adverse reactions, organized by body system, observed in cSSSI (4 mg/kg CUBICIN) patients are displayed in Table 5.

**Table 5: Incidence of Adverse Reactions that Occurred in  $\geq 2\%$  of Patients in the CUBICIN Treatment Group and  $\geq$  the Comparator Treatment Group in Phase 3 cSSSI Trials**

Adverse Reaction	Patients (%)	
	CUBICIN 4 mg/kg (N=534)	Comparator* (N=558)
<b>Gastrointestinal disorders</b>		
Diarrhea	5.2	4.3
<b>Nervous system disorders</b>		
Headache	5.4	5.4
Dizziness	2.2	2.0

<b>Skin/subcutaneous disorders</b>		
Rash	4.3	3.8
<b>Diagnostic investigations</b>		
Abnormal liver function tests	3.0	1.6
Elevated CPK	2.8	1.8
<b>Infections</b>		
Urinary tract infections	2.4	0.5
<b>Vascular disorders</b>		
Hypotension	2.4	1.4
<b>Respiratory disorders</b>		
Dyspnea	2.1	1.6

\* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

Drug-related adverse reactions (possibly or probably drug-related) that occurred in <1% of patients receiving CUBICIN in the cSSSI trials are as follows:

*Body as a Whole:* fatigue, weakness, rigors, flushing, hypersensitivity

*Blood/Lymphatic System:* leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, increased International Normalized Ratio (INR)

*Cardiovascular System:* supraventricular arrhythmia

*Dermatologic System:* eczema

*Digestive System:* abdominal distension, stomatitis, jaundice, increased serum lactate dehydrogenase

*Metabolic/Nutritional System:* hypomagnesemia, increased serum bicarbonate, electrolyte disturbance

*Musculoskeletal System:* myalgia, muscle cramps, muscle weakness, arthralgia

*Nervous System:* vertigo, mental status change, paresthesia

*Special Senses:* taste disturbance, eye irritation

#### *S. aureus* Bacteremia/Endocarditis Trial

In the *S. aureus* bacteremia/endocarditis trial, CUBICIN was discontinued in 20/120 (16.7%) patients due to an adverse reaction, while comparator was discontinued in 21/116 (18.1%) patients.

Serious Gram-negative infections (including bloodstream infections) were reported in 10/120 (8.3%) CUBICIN-treated patients and 0/115 comparator-treated patients. Comparator-treated patients received dual therapy that included initial gentamicin for 4 days. Infections were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative bacteria.

The rates of the most common adverse reactions, organized by System Organ Class (SOC), observed in *S. aureus* bacteremia/endocarditis (6 mg/kg CUBICIN) patients are displayed in Table 6.

**Table 6: Incidence of Adverse Reactions that Occurred in ≥5% of Patients in the CUBICIN Treatment Group and ≥ the Comparator Treatment Group in the *S. aureus* Bacteremia/Endocarditis Trial**

Adverse Reaction*	Patients n (%)	
	CUBICIN 6 mg/kg (N=120)	Comparator† (N=116)
<b>Infections and infestations</b>		
Sepsis NOS	6 (5%)	3 (3%)
Bacteremia	6 (5%)	0 (0%)
<b>Gastrointestinal disorders</b>		
Abdominal pain NOS	7 (6%)	4 (3%)
<b>General disorders and administration site conditions</b>		
Chest pain	8 (7%)	7 (6%)
Edema NOS	8 (7%)	5 (4%)
<b>Respiratory, thoracic and mediastinal disorders</b>		
Pharyngolaryngeal pain	10 (8%)	2 (2%)
<b>Skin and subcutaneous tissue disorders</b>		
Pruritus	7 (6%)	6 (5%)
Sweating increased	6 (5%)	0 (0%)
<b>Psychiatric disorders</b>		
Insomnia	11 (9%)	8 (7%)
<b>Investigations</b>		
Blood creatine phosphokinase increased	8 (7%)	1 (1%)
<b>Vascular disorders</b>		
Hypertension NOS	7 (6%)	3 (3%)

\* NOS, not otherwise specified.

† Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

The following reactions, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group:

*Blood and Lymphatic System Disorders:* eosinophilia, lymphadenopathy, thrombocytopenia, thrombocytopenia

*Cardiac Disorders:* atrial fibrillation, atrial flutter, cardiac arrest

*Ear and Labyrinth Disorders:* tinnitus

*Eye Disorders:* vision blurred

*Gastrointestinal Disorders:* dry mouth, epigastric discomfort, gingival pain, hypoesthesia oral

*Infections and Infestations:* candidal infection NOS, vaginal candidiasis, fungemia, oral candidiasis, urinary tract infection fungal

*Investigations:* blood phosphorous increased, blood alkaline phosphatase increased, INR increased, liver function test abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, prothrombin time prolonged

*Metabolism and Nutrition Disorders:* appetite decreased NOS

*Musculoskeletal and Connective Tissue Disorders:* myalgia

*Nervous System Disorders:* dyskinesia, paresthesia

*Psychiatric Disorders:* hallucination NOS

*Renal and Urinary Disorders:* proteinuria, renal impairment NOS

*Skin and Subcutaneous Tissue Disorders:* pruritus generalized, rash vesicular

### Other Trials

In Phase 3 trials of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events [see *Indications and Usage* (1.3)].

### Laboratory Changes

#### *Complicated Skin and Skin Structure Infection Trials*

In Phase 3 cSSSI trials of CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients. Of the 534 patients treated with CUBICIN, 1 (0.2%) had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal (ULN). The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after treatment was discontinued [see *Warnings and Precautions* (5.2)]. Table 7 summarizes the CPK shifts from Baseline through End of Therapy in the cSSSI trials.

**Table 7: Incidence of CPK Elevations from Baseline during Therapy in Either the CUBICIN Treatment Group or the Comparator Treatment Group in Phase 3 cSSSI Trials**

Change in CPK	All Patients				Patients with Normal CPK at Baseline			
	CUBICIN 4 mg/kg (N=430)		Comparator* (N=459)		CUBICIN 4 mg/kg (N=374)		Comparator* (N=392)	
	%	n	%	n	%	n	%	n
No Increase	90.7	390	91.1	418	91.2	341	91.1	357
Maximum Value >1× ULN <sup>†</sup>	9.3	40	8.9	41	8.8	33	8.9	35
>2× ULN	4.9	21	4.8	22	3.7	14	3.1	12
>4× ULN	1.4	6	1.5	7	1.1	4	1.0	4
>5× ULN	1.4	6	0.4	2	1.1	4	0.0	0
>10× ULN	0.5	2	0.2	1	0.2	1	0.0	0

Note: Elevations in CPK observed in patients treated with CUBICIN or comparator were not clinically or statistically significantly different.

\* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

<sup>†</sup> ULN (Upper Limit of Normal) is defined as 200 U/L.

### *S. aureus* Bacteremia/Endocarditis Trial

In the *S. aureus* bacteremia/endocarditis trial, at a dose of 6 mg/kg, 11/120 (9.2%) CUBICIN-treated patients, including two patients with baseline CPK levels >500 U/L, had CPK elevations to levels >500 U/L, compared with 1/116 (0.9%) comparator-treated patients. Of the 11 CUBICIN-treated patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Three of these 11 CUBICIN-treated patients discontinued therapy due to CPK elevation, while the one comparator-treated patient did not discontinue therapy [see *Warnings and Precautions* (5.2)].

## **6.2 Post-Marketing Experience**

The following adverse reactions have been identified during post-approval use of CUBICIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Blood and lymphatic system disorders:* anemia

*General and administration site conditions:* pyrexia

*Immune System Disorders:* anaphylaxis; hypersensitivity reactions, including angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia [see *Contraindications* (4), *Warnings and Precautions* (5.1)]

*Infections and Infestations:* *Clostridium difficile*–associated diarrhea [see *Warnings and Precautions* (5.6)]

*Musculoskeletal Disorders:* myoglobin increased; rhabdomyolysis (some reports involved patients treated concurrently with CUBICIN and HMG-CoA reductase inhibitors) [see *Warnings and Precautions* (5.2), *Drug Interactions* (7.1), and *Clinical Pharmacology* (12.3)]

*Respiratory, Thoracic, and Mediastinal Disorders:* cough, eosinophilic pneumonia [see *Warnings and Precautions* (5.3)]

*Nervous System Disorders:* peripheral neuropathy [see *Warnings and Precautions* (5.4)]

*Skin and Subcutaneous Tissue Disorders:* serious skin reactions, including Stevens-Johnson syndrome and vesicubullous rash (with or without mucous membrane involvement), acute generalized exanthematous pustulosis

*Gastrointestinal Disorders:* nausea, vomiting

*Renal and urinary disorders:* acute kidney injury, renal insufficiency, and renal failure

*Special Senses:* visual disturbances

## **7 DRUG INTERACTIONS**

### **7.1 HMG-CoA Reductase Inhibitors**

In healthy subjects, concomitant administration of CUBICIN and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy [see *Clinical Pharmacology* (12.3)].

However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the Phase 3 *S. aureus* bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK [see *Adverse Reactions* (6.1)]. Experience with the coadministration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving CUBICIN RF.

### **7.2 Drug-Laboratory Test Interactions**

Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimized by drawing specimens for PT or INR testing near the time of trough plasma concentrations of daptomycin. However, sufficient daptomycin concentrations may be present at trough to cause interaction.

If confronted with an abnormally high PT/INR result in a patient being treated with CUBICIN RF, it is recommended that clinicians:

1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next CUBICIN RF dose (i.e., at trough concentration). If the PT/INR value obtained at trough remains substantially elevated above what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled trials of CUBICIN RF in pregnant women. Embryofetal development studies performed in rats and rabbits at doses of up to 75 mg/kg (2 and 4 times the 6 mg/kg human dose, respectively, on a body surface area basis) revealed no evidence of harm to the fetus due to daptomycin. Because animal reproduction studies are not always predictive of human response, CUBICIN RF should be used during pregnancy only if the potential benefit outweighs the possible risk.

### 8.3 Nursing Mothers

Daptomycin is present in human milk but is poorly bioavailable orally.

In a single case study, CUBICIN was administered daily for 28 days to a nursing mother at an IV dose of 6.7 mg/kg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 mcg/mL<sup>1</sup>. The calculated maximum daily CUBICIN dose to the infant (assuming mean milk consumption of 150 mL/kg/day) was 0.1% of the maternal dose of 6.7 mg/kg/day [see *Nonclinical Toxicology* (13.2)]. Caution should be exercised when CUBICIN RF is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness of CUBICIN RF in pediatric patients have not been established. 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 [see *Warnings and Precautions* (5.5) and *Nonclinical Toxicology* (13.2)].

### 8.5 Geriatric Use

Of the 534 patients treated with CUBICIN in Phase 3 controlled clinical trials of complicated skin and skin structure infections (cSSSI), 27% were 65 years of age or older and 12% were 75 years of age or older. Of the 120 patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25% were 65 years of age or older and 16% were 75 years of age or older. In Phase 3 clinical trials of cSSSI and *S. aureus* bacteremia/endocarditis, clinical success rates were lower in patients ≥65 years of age than in patients <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years of age than in patients <65 years of age.

The exposure of daptomycin was higher in healthy elderly subjects than in healthy young subjects. However, no adjustment of CUBICIN RF dosage is warranted for elderly patients with creatinine clearance (CL<sub>CR</sub>) ≥30 mL/min [see *Dosage and Administration* (2.4) and *Clinical Pharmacology* (12.3)].

### 8.6 Patients with Renal Impairment

Daptomycin is eliminated primarily by the kidneys; therefore, a modification of CUBICIN RF dosage interval is recommended for patients with CL<sub>CR</sub> <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). In patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently than once weekly [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.2, 5.8), and *Clinical Pharmacology* (12.3)].

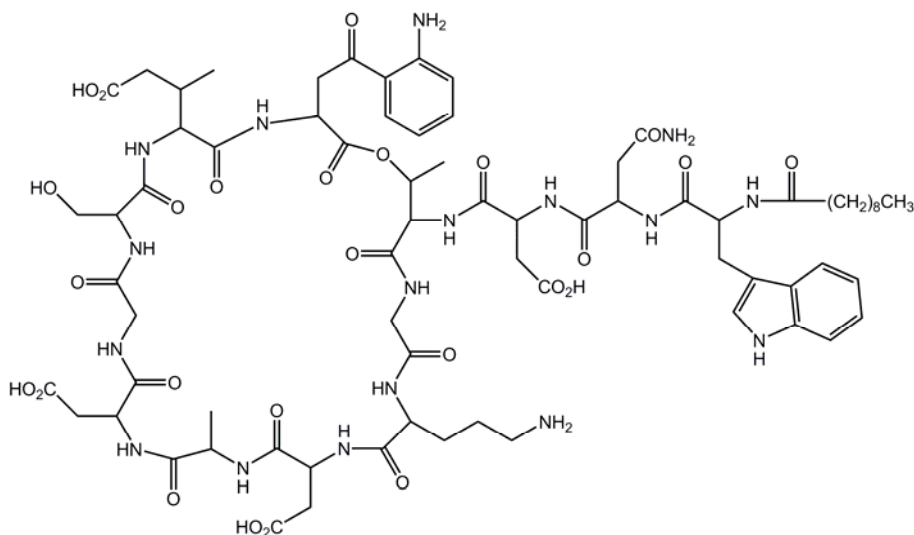
## 10 OVERDOSAGE

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 hours) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 hours). The use of high-flux dialysis

membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with that removed by low-flux membranes.

## 11 DESCRIPTION

CUBICIN RF (daptomycin for injection) contains daptomycin, a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. The chemical name is *N*-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine  $\epsilon_1$ -lactone. The chemical structure is:



The empirical formula is  $C_{72}H_{101}N_{17}O_{26}$ ; the molecular weight is 1620.67. CUBICIN RF is supplied in a single-dose vial as a sterile, preservative-free, pale yellow to light brown, lyophilized powder containing 500 mg of daptomycin for intravenous (IV) use following reconstitution [see *Dosage and Administration* (2.5)]. Each vial also contains 713 mg sucrose and sodium hydroxide is used to adjust the pH. The pH of the solution upon reconstitution is 6.8. Freshly reconstituted solutions of CUBICIN RF range in color from pale yellow to light brown.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Daptomycin is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

### 12.2 Pharmacodynamics

Based on animal models of infection, the antimicrobial activity of daptomycin appears to correlate with the AUC/MIC (area under the concentration-time curve/minimum inhibitory concentration) ratio for certain pathogens, including *S. aureus*. The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with CUBICIN RF.

### 12.3 Pharmacokinetics

#### CUBICIN Administered over a 30-Minute Period

The mean and standard deviation (SD) pharmacokinetic parameters of daptomycin at steady-state following intravenous (IV) administration of CUBICIN over a 30-minute period at 4 to 12 mg/kg q24h to healthy young adults are summarized in Table 8.

**Table 8: Mean (SD) Daptomycin Pharmacokinetic Parameters in Healthy Volunteers at Steady-State**



Dose*† (mg/kg)	Pharmacokinetic Parameters‡				
	AUC <sub>0-24</sub> (mcg•h/mL)	t <sub>1/2</sub> (h)	V <sub>ss</sub> (L/kg)	CL <sub>T</sub> (mL/h/kg)	C <sub>max</sub> (mcg/mL)
4 (N=6)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 (N=6)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 (N=6)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 (N=9)	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 (N=9)	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

\* CUBICIN was administered by IV infusion over a 30-minute period.

† Doses of CUBICIN in excess of 6 mg/kg have not been approved.

‡ AUC<sub>0-24</sub>, area under the concentration-time curve from 0 to 24 hours; t<sub>1/2</sub>, elimination half-life; V<sub>ss</sub>, volume of distribution at steady-state; CL<sub>T</sub>, total plasma clearance; C<sub>max</sub>, maximum plasma concentration.

Daptomycin pharmacokinetics were generally linear and time-independent at CUBICIN doses of 4 to 12 mg/kg q24h administered by IV infusion over a 30-minute period for up to 14 days. Steady-state trough concentrations were achieved by the third daily dose. The mean (SD) steady-state trough concentrations attained following the administration of 4, 6, 8, 10, and 12 mg/kg q24h were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9), and 13.7 (5.2) mcg/mL, respectively.

#### CUBICIN Administered over a 2-Minute Period

Following IV administration of CUBICIN over a 2-minute period to healthy volunteers at doses of 4 mg/kg (N=8) and 6 mg/kg (N=12), the mean (SD) steady-state systemic exposure (AUC) values were 475 (71) and 701 (82) mcg•h/mL, respectively. Values for maximum plasma concentration (C<sub>max</sub>) at the end of the 2-minute period could not be determined adequately in this study. However, using pharmacokinetic parameters from 14 healthy volunteers who received a single dose of CUBICIN 6 mg/kg IV administered over a 30-minute period in a separate study, steady-state C<sub>max</sub> values were simulated for CUBICIN 4 and 6 mg/kg IV administered over a 2-minute period. The simulated mean (SD) steady-state C<sub>max</sub> values were 77.7 (8.1) and 116.6 (12.2) mcg/mL, respectively.

#### Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding ranges from 90 to 93%.

In clinical studies, mean serum protein binding in subjects with creatinine clearance (CL<sub>CR</sub>) ≥30 mL/min was comparable to that observed in healthy subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among subjects with CL<sub>CR</sub> <30 mL/min (88%), including those receiving hemodialysis (86%) and continuous ambulatory peritoneal dialysis (CAPD) (84%). The protein binding of daptomycin in subjects with moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

The volume of distribution at steady-state (V<sub>ss</sub>) of daptomycin in healthy adult subjects was approximately 0.1 L/kg and was independent of dose.

#### Metabolism

In *in vitro* studies, daptomycin was not metabolized by human liver microsomes.

In 5 healthy adults after infusion of radiolabeled <sup>14</sup>C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference between total radioactive concentrations and microbiologically active concentrations. In a separate study, no metabolites were observed in plasma on Day 1 following the administration of CUBICIN at 6 mg/kg to subjects. Minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

#### Excretion

Daptomycin is excreted primarily by the kidneys. In a mass balance study of 5 healthy subjects using radiolabeled daptomycin, approximately 78% of the administered dose was recovered from urine based on total radioactivity

(approximately 52% of the dose based on microbiologically active concentrations), and 5.7% of the administered dose was recovered from feces (collected for up to 9 days) based on total radioactivity.

### Specific Populations

#### Renal Impairment

Population-derived pharmacokinetic parameters were determined for infected patients (complicated skin and skin structure infections [cSSSI] and *S. aureus* bacteremia) and noninfected subjects with various degrees of renal function (Table 9). Total plasma clearance ( $CL_T$ ), elimination half-life ( $t_{1/2}$ ), and volume of distribution at steady-state ( $V_{ss}$ ) in patients with cSSSI were similar to those in patients with *S. aureus* bacteremia. Following administration of CUBICIN 4 mg/kg q24h by IV infusion over a 30-minute period, the mean  $CL_T$  was 9%, 22%, and 46% lower among subjects and patients with mild ( $CL_{CR}$  50–80 mL/min), moderate ( $CL_{CR}$  30–<50 mL/min), and severe ( $CL_{CR}$  <30 mL/min) renal impairment, respectively, than in those with normal renal function ( $CL_{CR}$  >80 mL/min). The mean steady-state systemic exposure (AUC),  $t_{1/2}$ , and  $V_{ss}$  increased with decreasing renal function, although the mean AUC for patients with  $CL_{CR}$  30–80 mL/min was not markedly different from the mean AUC for patients with normal renal function. The mean AUC for patients with  $CL_{CR}$  <30 mL/min and for patients on dialysis (CAPD and hemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function. The mean  $C_{max}$  ranged from 60 to 70 mcg/mL in patients with  $CL_{CR} \geq 30$  mL/min, while the mean  $C_{max}$  for patients with  $CL_{CR}$  <30 mL/min ranged from 41 to 58 mcg/mL. After administration of CUBICIN 6 mg/kg q24h by IV infusion over a 30-minute period, the mean  $C_{max}$  ranged from 80 to 114 mcg/mL in patients with mild to moderate renal impairment and was similar to that of patients with normal renal function.

**Table 9: Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following Infusion of CUBICIN 4 mg/kg or 6 mg/kg to Infected Patients and Noninfected Subjects with Various Degrees of Renal Function**

Renal Function	Pharmacokinetic Parameters*					
	$t_{1/2}^{\dagger}$ (h) 4 mg/kg	$V_{ss}^{\dagger}$ (L/kg) 4 mg/kg	$CL_T^{\dagger}$ (mL/h/kg) 4 mg/kg	$AUC_{0-\infty}^{\dagger}$ (mcg·h/mL) 4 mg/kg	$AUC_{ss}^{\ddagger}$ (mcg·h/mL) 6 mg/kg	$C_{min,ss}^{\ddagger}$ (mcg/mL) 6 mg/kg
Normal ( $CL_{CR}$ >80 mL/min)	9.39 (4.74) N=165	0.13 (0.05) N=165	10.9 (4.0) N=165	417 (155) N=165	545 (296) N=62	6.9 (3.5) N=61
Mild Renal Impairment ( $CL_{CR}$ 50– 80 mL/min)	10.75 (8.36) N=64	0.12 (0.05) N=64	9.9 (4.0) N=64	466 (177) N=64	637 (215) N=29	12.4 (5.6) N=29
Moderate Renal Impairment ( $CL_{CR}$ 30– <50 mL/min)	14.70 (10.50) N=24	0.15 (0.06) N=24	8.5 (3.4) N=24	560 (258) N=24	868 (349) N=15	19.0 (9.0) N=14
Severe Renal Impairment ( $CL_{CR}$ <30 mL/min)	27.83 (14.85) N=8	0.20 (0.15) N=8	5.9 (3.9) N=8	925 (467) N=8	1050, 892 N=2	24.4, 21.4 N=2
Hemodialysis	30.51 (6.51) N=16	0.16 (0.04) N=16	3.9 (2.1) N=16	1193 (399) N=16	NA	NA
CAPD	27.56 (4.53) N=5	0.11 (0.02) N=5	2.9 (0.4) N=5	1409 (238) N=5	NA	NA

Note: CUBICIN was administered over a 30-minute period.

\*  $CL_{CR}$ , creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight; CAPD, continuous ambulatory peritoneal dialysis;  $AUC_{0-\infty}$ , area under the concentration-time curve extrapolated to infinity;  $AUC_{ss}$ , area under the concentration-time curve calculated over the 24-hour dosing interval at steady-state;  $C_{min,ss}$ , trough concentration at steady-state; NA, not applicable.

- † Parameters obtained following a single dose from patients with complicated skin and skin structure infections and healthy subjects.
- ‡ Parameters obtained at steady-state from patients with *S. aureus* bacteremia.

Because renal excretion is the primary route of elimination, adjustment of CUBICIN RF dosage interval is necessary in patients with severe renal impairment ( $CL_{CR} < 30$  mL/min) [see *Dosage and Administration* (2.4)].

#### *Hepatic Impairment*

The pharmacokinetics of daptomycin were evaluated in 10 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with those in healthy volunteers (N=9) matched for gender, age, and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when CUBICIN RF is administered to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

#### *Gender*

No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when CUBICIN RF is administered.

#### *Geriatric*

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects ( $\geq 75$  years of age) and 11 healthy young controls (18 to 30 years of age). Following administration of a single 4 mg/kg dose of CUBICIN by IV infusion over a 30-minute period, the mean total clearance of daptomycin was approximately 35% lower and the mean  $AUC_{0-\infty}$  was approximately 58% higher in elderly subjects than in healthy young subjects. There were no differences in  $C_{max}$  [see *Use in Specific Populations* (8.5)].

#### *Obesity*

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m<sup>2</sup>) and 6 extremely obese (BMI  $\geq 40$  kg/m<sup>2</sup>) subjects and controls matched for age, gender, and renal function. Following administration of CUBICIN by IV infusion over a 30-minute period as a single 4 mg/kg dose based on total body weight, the total plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in moderately obese subjects and 23% lower in extremely obese subjects than in nonobese controls. The  $AUC_{0-\infty}$  of daptomycin was approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in nonobese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No adjustment of CUBICIN RF dosage is warranted in obese patients.

#### *Pediatric*

The pharmacokinetics of daptomycin in pediatric populations (<18 years of age) have not been established [see *Nonclinical Toxicology* (13.2)].

### Drug-Drug Interactions

#### *In Vitro Studies*

*In vitro* studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized by the P450 system.

#### *Aztreonam*

In a study in which 15 healthy adult subjects received a single dose of CUBICIN 6 mg/kg IV and a combination dose of CUBICIN 6 mg/kg IV and aztreonam 1 g IV, administered over a 30-minute period, the  $C_{max}$  and  $AUC_{0-\infty}$  of daptomycin were not significantly altered by aztreonam.

#### *Tobramycin*

In a study in which 6 healthy adult males received a single dose of CUBICIN 2 mg/kg IV, tobramycin 1 mg/kg IV, and both in combination, administered over a 30-minute period, the mean  $C_{max}$  and  $AUC_{0-\infty}$  of daptomycin were 12.7% and 8.7% higher, respectively, when CUBICIN was coadministered with tobramycin. The mean  $C_{max}$  and  $AUC_{0-\infty}$  of tobramycin were 10.7% and 6.6% lower, respectively, when tobramycin was coadministered with CUBICIN. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of CUBICIN RF is unknown.

#### *Warfarin*

In 16 healthy subjects, administration of CUBICIN 6 mg/kg q24h by IV infusion over a 30-minute period for 5 days, with coadministration of a single oral dose of warfarin (25 mg) on the 5th day, had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio).

#### *Simvastatin*

In 20 healthy subjects on a stable daily dose of simvastatin 40 mg, administration of CUBICIN 4 mg/kg q24h by IV infusion over a 30-minute period for 14 days (N=10) had no effect on plasma trough concentrations of simvastatin and was not associated with a higher incidence of adverse events, including skeletal myopathy, than in subjects receiving placebo once daily (N=10) [see *Warnings and Precautions* (5.2) and *Drug Interactions* (7.1)].

#### *Probenecid*

Concomitant administration of probenecid (500 mg 4 times daily) and a single dose of CUBICIN 4 mg/kg by IV infusion over a 30-minute period did not significantly alter the  $C_{max}$  or  $AUC_{0-\infty}$  of daptomycin.

## **12.4 Microbiology**

Daptomycin belongs to the cyclic lipopeptide class of antibacterials. Daptomycin has clinical utility in the treatment of infections caused by aerobic, Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive bacteria *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC (minimum bactericidal concentration/minimum inhibitory concentration) ratios using broth dilution methodology. Daptomycin maintained bactericidal activity *in vitro* against stationary phase *S. aureus* in simulated endocardial vegetations. The clinical significance of this is not known.

#### Mechanism of Action

The mechanism of action of daptomycin is distinct from that of any other antibacterial. Daptomycin binds to bacterial cell membranes and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death.

#### Mechanism of Resistance

The mechanism(s) of daptomycin resistance is not fully understood. Currently, there are no known transferable elements that confer resistance to daptomycin.

#### Complicated Skin and Skin Structure Infection (cSSSI) Trials

The emergence of daptomycin non-susceptible isolates occurred in 2 infected patients across the set of Phase 2 and pivotal Phase 3 clinical trials of cSSSI. In one case, a non-susceptible *S. aureus* was isolated from a patient in a Phase 2 trial who received CUBICIN at less than the protocol-specified dose for the initial 5 days of therapy. In the second case, a non-susceptible *Enterococcus faecalis* was isolated from a patient with an infected chronic decubitus ulcer who was enrolled in a salvage trial.

#### *S. aureus* Bacteremia/Endocarditis and Other Post-Approval Trials

In subsequent clinical trials, non-susceptible isolates were recovered. *S. aureus* was isolated from a patient in a compassionate-use trial and from 7 patients in the *S. aureus* bacteremia/endocarditis trial [see *Clinical Trials* (14.2)]. An *E. faecium* was isolated from a patient in a vancomycin-resistant enterococci trial.

#### Interactions with Other Antibacterials

*In vitro* studies have investigated daptomycin interactions with other antibacterials. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions of daptomycin with aminoglycosides,  $\beta$ -lactam antibacterials, and rifampin have been shown against some isolates of staphylococci (including some methicillin-resistant isolates) and enterococci (including some vancomycin-resistant isolates).

#### Activity *In Vitro* and *In Vivo*

Daptomycin has been shown to be active against most isolates of the following Gram-positive bacteria both *in vitro* and in clinical infections, as described in *Indications and Usage* (1).

#### **Gram-Positive Bacteria**

*Enterococcus faecalis* (vancomycin-susceptible isolates only)  
*Staphylococcus aureus* (including methicillin-resistant isolates)  
*Streptococcus agalactiae*  
*Streptococcus dysgalactiae* subsp. *equisimilis*  
*Streptococcus pyogenes*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following Gram-positive bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for daptomycin versus the bacterial genus (Table 10). However, the efficacy of CUBICIN RF in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

#### **Gram-Positive Bacteria**

*Corynebacterium jeikeium*  
*Enterococcus faecalis* (vancomycin-resistant isolates)  
*Enterococcus faecium* (including vancomycin-resistant isolates)  
*Staphylococcus epidermidis* (including methicillin-resistant isolates)  
*Staphylococcus haemolyticus*

#### Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility tests for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

#### *Dilution Techniques*

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized broth test method<sup>2,3</sup> with the broth adjusted to a calcium content of 50 mg/L. The use of the agar dilution method is not recommended with daptomycin<sup>3</sup>. The MICs should be interpreted according to the criteria listed in Table 10.

**Table 10: Susceptibility Interpretive Criteria for Daptomycin**

Pathogen	Broth Dilution MIC* (mcg/mL)		
	S	I	R
<i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin-resistant)	≤1	(†)	(†)
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	≤1	(†)	(†)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤4	(†)	(†)

Note: S, Susceptible; I, Intermediate; R, Resistant.

- \* The MIC interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.
- † The current absence of data on daptomycin-resistant isolates precludes defining any categories other than “Susceptible.” Isolates yielding test results suggestive of a “Non-Susceptible” category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit the growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen.

#### Diffusion Technique

Quantitative methods that require measurement of zone diameters have not been shown to provide reproducible estimates of the susceptibility of bacteria to daptomycin. The use of the disk diffusion method is not recommended with daptomycin<sup>3,4</sup>.

#### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>2,3</sup>. Standard daptomycin powder should provide the ranges of MIC values noted in Table 11.

**Table 11: Acceptable Quality Control Ranges for Daptomycin to Be Used in Validation of Susceptibility Test Results**

Quality Control Strain	Broth Dilution MIC Range* (mcg/mL)
<i>Enterococcus faecalis</i> ATCC 29212	1–4
<i>Staphylococcus aureus</i> ATCC 29213	0.12–1
<i>Streptococcus pneumoniae</i> ATCC 49619 <sup>†</sup>	0.06–0.5

- \* The quality control ranges for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the quality control range for *Streptococcus pneumoniae* is applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

- † This strain may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of CUBICIN. However, neither mutagenic nor clastogenic potential was found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an *in vivo* micronucleus assay, an *in vitro* DNA repair assay, and an *in vivo* sister chromatid exchange assay in Chinese hamsters.

Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the estimated human exposure level based upon AUCs.

## 13.2 Animal Toxicology and/or Pharmacology

### Adult Animals

In animals, daptomycin administration has been associated with effects on skeletal muscle. However, there were no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by microscopic degenerative/regenerative changes and variable elevations in creatine phosphokinase (CPK). No fibrosis or rhabdomyolysis was evident in repeat-dose studies up to the highest doses tested in rats (150 mg/kg/day) and dogs (100 mg/kg/day). The degree of skeletal myopathy showed no increase when treatment was extended from 1 month to up to 6 months. Severity was dose-dependent. All muscle effects, including microscopic changes, were fully reversible within 30 days following the cessation of dosing.

In adult animals, effects on peripheral nerve (characterized by axonal degeneration and frequently accompanied by significant losses of patellar reflex, gag reflex, and pain perception) were observed at daptomycin doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks after the start of treatment at 40 mg/kg/day (9 times the human  $C_{max}$  at the 6 mg/kg/day dose), with some clinical improvement noted within 2 weeks after the cessation of dosing. However, at 75 mg/kg/day for 1 month, 7 of 8 dogs failed to regain full patellar reflex responses within a 3-month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted at 6 months after the cessation of dosing. However, recovery of peripheral nerve function was evident.

Tissue distribution studies in rats showed that daptomycin is retained in the kidney but appears to penetrate the blood-brain barrier only minimally following single and multiple doses.

### Juvenile Animals

Target organs of daptomycin-related effects in 7-week-old juvenile dogs were skeletal muscle and nerve, the same target organs as in adult dogs. In juvenile dogs, nerve effects were noted at lower daptomycin blood concentrations than in adult dogs following 28 days of dosing. In contrast to adult dogs, juvenile dogs also showed evidence of effects in nerves of the spinal cord as well as peripheral nerves after 28 days of dosing. No nerve effects were noted in juvenile dogs following 14 days of dosing at doses up to 75 mg/kg/day.

Administration of daptomycin to 7-week-old juvenile dogs for 28 days at doses of 50 mg/kg/day produced minimal degenerative effects on the peripheral nerve and spinal cord in several animals, with no corresponding clinical signs. A dose of 150 mg/kg/day for 28 days produced minimal degeneration in the peripheral nerve and spinal cord as well as minimal to mild degeneration of the skeletal muscle in a majority of animals, accompanied by slight to severe muscle weakness evident in most dogs. Following a 28-day recovery phase, microscopic examination revealed recovery of the skeletal muscle and the ulnar nerve effects, but nerve degeneration in the sciatic nerve and spinal cord was still observed in all 150 mg/kg/day dogs.

Following once-daily administration of daptomycin to juvenile dogs for 28 days, microscopic effects in nerve tissue were noted at a  $C_{max}$  value of 417 mcg/mL, which is approximately 3-fold less than the  $C_{max}$  value associated with nerve effects in adult dogs treated once daily with daptomycin for 28 days (1308 mcg/mL).

### Neonatal Animals

Neonatal dogs (4 to 31 days old) were more sensitive to daptomycin-related adverse nervous system and/or muscular system effects than either juvenile or adult dogs. In neonatal dogs, adverse nervous system and/or muscular system effects were associated with a  $C_{max}$  value approximately 3-fold less than the  $C_{max}$  in juvenile dogs, and 9-fold less than the  $C_{max}$  in adult dogs following 28 days of dosing. At a dose of 25 mg/kg/day with associated  $C_{max}$  and  $AUC_{inf}$  values of 147 mcg/mL and 717 mcg·h/mL, respectively (1.6 and 1.0-fold the adult human  $C_{max}$  and  $AUC$ , respectively, at the 6 mg/kg/day dose), mild clinical signs of twitching and one incidence of muscle rigidity were observed with no corresponding effect on body weight. These effects were found to be reversible within 28 days after treatment had stopped.

At higher dose levels of 50 and 75 mg/kg/day with associated  $C_{max}$  and  $AUC_{inf}$  values of  $\geq 321$  mcg/mL and  $\geq 1470$  mcg·h/mL, respectively, marked clinical signs of twitching, muscle rigidity in the limbs, and impaired use of limbs were observed. Resulting decreases in body weights and overall body condition at doses  $\geq 50$  mg/kg/day necessitated early discontinuation by PND19.

Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle or other tissues assessed, at any dose level.

No adverse effects were observed in the dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated  $C_{max}$  and  $AUC_{inf}$  values of 62 mcg/mL and 247 mcg·h/mL, respectively (or 0.6 and 0.4-fold the adult human  $C_{max}$  and AUC, respectively at the 6 mg/kg dose).

## 14 CLINICAL TRIALS

### 14.1 Complicated Skin and Skin Structure Infections

Adult patients with clinically documented complicated skin and skin structure infections (cSSSI) (Table 12) were enrolled in two randomized, multinational, multicenter, investigator-blinded trials comparing CUBICIN (4 mg/kg IV q24h) with either vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g IV per day). Patients could switch to oral therapy after a minimum of 4 days of IV treatment if clinical improvement was demonstrated. Patients known to have bacteremia at baseline were excluded. Patients with creatinine clearance ( $CL_{CR}$ ) between 30 and 70 mL/min were to receive a lower dose of CUBICIN as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of CUBICIN adjusted.

**Table 12: Investigator's Primary Diagnosis in the cSSSI Trials (Population: Intent-to-Treat)**

Primary Diagnosis	Patients (CUBICIN / Comparator*)		
	Study 9801 N=264 / N=266	Study 9901 N=270 / N=292	Pooled N=534 / N=558
Wound Infection	99 (38%) / 116 (44%)	102 (38%) / 108 (37%)	201 (38%) / 224 (40%)
Major Abscess	55 (21%) / 43 (16%)	59 (22%) / 65 (22%)	114 (21%) / 108 (19%)
Ulcer Infection	71 (27%) / 75 (28%)	53 (20%) / 68 (23%)	124 (23%) / 143 (26%)
Other Infection <sup>†</sup>	39 (15%) / 32 (12%)	56 (21%) / 51 (18%)	95 (18%) / 83 (15%)

\* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

<sup>†</sup> The majority of cases were subsequently categorized as complicated cellulitis, major abscesses, or traumatic wound infections.

One trial was conducted primarily in the United States and South Africa (study 9801), and the second was conducted at non-US sites only (study 9901). The two trials were similar in design but differed in patient characteristics, including history of diabetes and peripheral vascular disease. There were a total of 534 patients treated with CUBICIN and 558 treated with comparator in the two trials. The majority (89.7%) of patients received IV medication exclusively.

The efficacy endpoints in both trials were the clinical success rates in the intent-to-treat (ITT) population and in the clinically evaluable (CE) population. In study 9801, clinical success rates in the ITT population were 62.5% (165/264) in patients treated with CUBICIN and 60.9% (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population were 76.0% (158/208) in patients treated with CUBICIN and 76.7% (158/206) in patients treated with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4% (217/270) in patients treated with CUBICIN and 80.5% (235/292) in patients treated with comparator drugs. Clinical success rates in the CE population were 89.9% (214/238) in patients treated with CUBICIN and 90.4% (226/250) in patients treated with comparator drugs.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 13.

**Table 13: Clinical Success Rates by Infecting Pathogen in the cSSSI Trials (Population: Microbiologically Evaluable)**

Pathogen	Success Rate n/N (%)	
	CUBICIN	Comparator*



Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA) <sup>†</sup>	170/198 (86%)	180/207 (87%)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) <sup>†</sup>	21/28 (75%)	25/36 (69%)
<i>Streptococcus pyogenes</i>	79/84 (94%)	80/88 (91%)
<i>Streptococcus agalactiae</i>	23/27 (85%)	22/29 (76%)
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	8/8 (100%)	9/11 (82%)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	27/37 (73%)	40/53 (76%)

\* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g/day IV in divided doses).

<sup>†</sup> As determined by the central laboratory.

## 14.2 *S. aureus* Bacteremia/Endocarditis

The efficacy of CUBICIN in the treatment of patients with *S. aureus* bacteremia was demonstrated in a randomized, controlled, multinational, multicenter, open-label trial. In this trial, adult patients with at least one positive blood culture for *S. aureus* obtained within 2 calendar days prior to the first dose of study drug and irrespective of source were enrolled and randomized to either CUBICIN (6 mg/kg IV q24h) or standard of care [an anti-staphylococcal semi-synthetic penicillin 2 g IV q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g IV q12h, each with initial gentamicin 1 mg/kg IV every 8 hours for first 4 days]. Of the patients in the comparator group, 93% received initial gentamicin for a median of 4 days, compared with 1 patient (<1%) in the CUBICIN group. Patients with prosthetic heart valves, intravascular foreign material that was not planned for removal within 4 days after the first dose of study medication, severe neutropenia, known osteomyelitis, polymicrobial bloodstream infections, creatinine clearance <30 mL/min, and pneumonia were excluded.

Upon entry, patients were classified for likelihood of endocarditis using the modified Duke criteria (Possible, Definite, or Not Endocarditis). Echocardiography, including a transesophageal echocardiogram (TEE), was performed within 5 days following study enrollment. The choice of comparator agent was based on the oxacillin susceptibility of the *S. aureus* isolate. The duration of study treatment was based on the investigator's clinical diagnosis. Final diagnoses and outcome assessments at Test of Cure (6 weeks after the last treatment dose) were made by a treatment-blinded Adjudication Committee, using protocol-specified clinical definitions and a composite primary efficacy endpoint (clinical and microbiological success) at the Test of Cure visit.

A total of 246 patients ≥18 years of age (124 CUBICIN, 122 comparator) with *S. aureus* bacteremia were randomized from 48 centers in the US and Europe. In the ITT population, 120 patients received CUBICIN and 115 received comparator (62 received an anti-staphylococcal semi-synthetic penicillin and 53 received vancomycin). Thirty-five patients treated with an anti-staphylococcal semi-synthetic penicillin received vancomycin initially for 1 to 3 days, pending final susceptibility results for the *S. aureus* isolates. The median age among the 235 patients in the ITT population was 53 years (range: 21 to 91 years); 30/120 (25%) in the CUBICIN group and 37/115 (32%) in the comparator group were ≥65 years of age. Of the 235 ITT patients, there were 141 (60%) males and 156 (66%) Caucasians across the two treatment groups. In addition, 176 (75%) of the ITT population had systemic inflammatory response syndrome (SIRS) at baseline and 85 (36%) had surgical procedures within 30 days prior to onset of the *S. aureus* bacteremia. Eighty-nine patients (38%) had bacteremia caused by methicillin-resistant *S. aureus* (MRSA). Entry diagnosis was based on the modified Duke criteria and comprised 37 (16%) Definite, 144 (61%) Possible, and 54 (23%) Not Endocarditis. Of the 37 patients with an entry diagnosis of Definite Endocarditis, all (100%) had a final diagnosis of infective endocarditis, and of the 144 patients with an entry diagnosis of Possible Endocarditis, 15 (10%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee. Of the 54 patients with an entry diagnosis of Not Endocarditis, 1 (2%) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee.

In the ITT population, there were 182 patients with bacteremia and 53 patients with infective endocarditis as assessed by the Adjudication Committee, including 35 with right-sided endocarditis and 18 with left-sided endocarditis. The 182 patients with bacteremia comprised 121 with complicated *S. aureus* bacteremia and 61 with uncomplicated *S. aureus* bacteremia.

Complicated bacteremia was defined as *S. aureus* isolated from blood cultures obtained on at least 2 different calendar days, and/or metastatic foci of infection (deep tissue involvement), and classification of the patient as not having endocarditis according to the modified Duke criteria. Uncomplicated bacteremia was defined as *S. aureus* isolated from blood culture(s) obtained on a single calendar day, no metastatic foci of infection, no infection of prosthetic material, and

classification of the patient as not having endocarditis according to the modified Duke criteria. The definition of right-sided infective endocarditis (RIE) used in the clinical trial was Definite or Possible Endocarditis according to the modified Duke criteria and no echocardiographic evidence of predisposing pathology or active involvement of either the mitral or aortic valve. Complicated RIE comprised patients who were not intravenous drug users, had a positive blood culture for MRSA, serum creatinine  $\geq 2.5$  mg/dL, or evidence of extrapulmonary sites of infection. Patients who were intravenous drug users, had a positive blood culture for methicillin-susceptible *S. aureus* (MSSA), had serum creatinine  $< 2.5$  mg/dL, and were without evidence of extrapulmonary sites of infection were considered to have uncomplicated RIE.

The coprimary efficacy endpoints in the trial were the Adjudication Committee success rates at the Test of Cure visit (6 weeks after the last treatment dose) in the ITT and Per Protocol (PP) populations. The overall Adjudication Committee success rates in the ITT population were 44.2% (53/120) in patients treated with CUBICIN and 41.7% (48/115) in patients treated with comparator (difference = 2.4% [95% CI -10.2, 15.1]). The success rates in the PP population were 54.4% (43/79) in patients treated with CUBICIN and 53.3% (32/60) in patients treated with comparator (difference = 1.1% [95% CI -15.6, 17.8]).

Adjudication Committee success rates are shown in Table 14.

**Table 14: Adjudication Committee Success Rates at Test of Cure in the *S. aureus* Bacteremia/Endocarditis Trial (Population: ITT)**

Population	Success Rate n/N (%)		Difference: CUBICIN-Comparator (Confidence Interval)
	CUBICIN 6 mg/kg	Comparator*	
Overall	53/120 (44%)	48/115 (42%)	2.4% (-10.2, 15.1) <sup>†</sup>
Baseline Pathogen			
Methicillin-susceptible <i>S. aureus</i>	33/74 (45%)	34/70 (49%)	-4.0% (-22.6, 14.6) <sup>‡</sup>
Methicillin-resistant <i>S. aureus</i>	20/45 (44%)	14/44 (32%)	12.6% (-10.2, 35.5) <sup>‡</sup>
Entry Diagnosis <sup>§</sup>			
Definite or Possible Infective Endocarditis	41/90 (46%)	37/91 (41%)	4.9% (-11.6, 21.4) <sup>‡</sup>
Not Infective Endocarditis	12/30 (40%)	11/24 (46%)	-5.8% (-36.2, 24.5) <sup>‡</sup>
Final Diagnosis			
Uncomplicated Bacteremia	18/32 (56%)	16/29 (55%)	1.1% (-31.7, 33.9) <sup>¶</sup>
Complicated Bacteremia	26/60 (43%)	23/61 (38%)	5.6% (-17.3, 28.6) <sup>¶</sup>
Right-Sided Infective Endocarditis	8/19 (42%)	7/16 (44%)	-1.6% (-44.9, 41.6) <sup>¶</sup>
Uncomplicated Right-Sided Infective Endocarditis	3/6 (50%)	1/4 (25%)	25.0% (-51.6, 100.0) <sup>¶</sup>
Complicated Right-Sided Infective Endocarditis	5/13 (39%)	6/12 (50%)	-11.5% (-62.4, 39.4) <sup>¶</sup>
Left-Sided Infective Endocarditis	1/9 (11%)	2/9 (22%)	-11.1% (-55.9, 33.6) <sup>¶</sup>

\* Comparator: vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin.

- † 95% Confidence Interval
- ‡ 97.5% Confidence Interval (adjusted for multiplicity)
- § According to the modified Duke criteria<sup>5</sup>
- ¶ 99% Confidence Interval (adjusted for multiplicity)

Eighteen (18/120) patients in the CUBICIN arm and 19/116 patients in the comparator arm died during the trial. These comprise 3/28 CUBICIN-treated patients and 8/26 comparator-treated patients with endocarditis, as well as 15/92 CUBICIN-treated patients and 11/90 comparator-treated patients with bacteremia. Among patients with persisting or relapsing *S. aureus* infections, 8/19 CUBICIN-treated patients and 7/11 comparator-treated patients died.

Overall, there was no difference in time to clearance of *S. aureus* bacteremia between CUBICIN and comparator. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (16%) CUBICIN-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (10%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with an anti-staphylococcal semi-synthetic penicillin). Among all failures, isolates from 6 CUBICIN-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing during or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention [see *Warnings and Precautions* (5.7)].

## 15 REFERENCES

1. Buitrago MI, Crompton JA, Bertolami S, North DS, Nathan RA. Extremely low excretion of daptomycin into breast milk of a nursing mother with methicillin-resistant *Staphylococcus aureus* pelvic inflammatory disease. *Pharmacotherapy* 2009;29(3):347–351.
2. Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—ninth edition. CLSI Document M07-A9; Wayne, PA. 2012.
3. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; twenty-second informational supplement. CLSI Document M100-S22; Wayne, PA. 2012.
4. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial disk susceptibility tests; approved standard—eleventh edition. CLSI Document M02-A11; Wayne, PA. 2012.
5. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–638.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

CUBICIN RF (daptomycin for injection) is supplied as a sterile pale yellow to light brown lyophilized powder in a single-dose 10 mL vial containing 500 mg of daptomycin: Package of 1 (NDC 67919-012-01).

Store original packages at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] [see *Dosage and Administration* (2.5)].

## 17 PATIENT COUNSELING INFORMATION

Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Patients should report any previous allergic reactions to daptomycin. [See *Warnings and Precautions* (5.1).]

Patients should be advised to report muscle pain or weakness, especially in the forearms and lower legs, as well as tingling or numbness. [See *Warnings and Precautions* (5.2, 5.4).]

Patients should be advised to report any symptoms of cough, breathlessness, or fever. [See *Warnings and Precautions* (5.3).]

Diarrhea is a common problem caused by antibacterials that usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without

stomach cramps and fever), even as late as 2 or more months after having received the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible. [See *Warnings and Precautions* (5.6).]

Patients should be counseled that antibacterial drugs, including CUBICIN RF, should be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CUBICIN RF is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be administered exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CUBICIN RF or other antibacterial drugs in the future.

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uspi-mk3009-rf-16XXr000

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-572/S-052**

**PHARMACOLOGY REVIEW(S)**

**DIVISION OF ANTI-INFECTIVE PRODUCTS  
PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

**DATE:** 4/19/2016

Application number: 21572

Supporting document/s: Supplement-52 (Manufacturing), SDN #: 625

Sponsor's letter date: 2/9/2016

CDER stamp date: 2/9/2016

Product: Cubicin® (daptomycin for injection) 500 mg/vial

Indication: For treatment of complicated skin and soft tissue infections and *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided ineffective endocarditis

Sponsor: Cubist Pharmaceuticals, Inc.

Review Division: Division of Anti-Infective Products

Reviewer: Terry J. Miller, Ph.D.

Supervisor/Team Leader: Wendelyn Schmidt, Ph.D.

Division Director: Sumathi Nambiar, M.D.

Project Manager: Christopher Davi, M.S.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21572 are owned by Cubist Pharmaceuticals, Inc. Any information or data necessary for approval of NDA 21572 that Cubist Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21572.

**Recommendations:**

Pharmacology/Toxicology has no objection to the approval of NDA 21572 Supplement 52, to modify the formulation of the approved drug product Cubicin® (daptomycin for injection) 500 mg/vial to include the new (b) (4), Sucrose (b) (4) mg). Other than the product name from Cubicin® to Cubicin® RF, the Applicant recommended no changes

to the pharmacology/toxicology relevant sections of the labeling. There are no additional nonclinical recommendations at this time.

### **Information from the NDA Submission:**

The current submission is a Supplemental New Drug Application (Suppl. 052; SDN 625; Feb 9, 2016) to NDA 21572 containing the Sponsor's proposed CMC manufacturing reformulation of Cubicin® (daptomycin for injection, lyophilized powder, for solution) 500 mg/vial to include sucrose. The Sponsor (b) (4)

(b) (4). The proposed reformulated drug product is intended to be nearly (b) (4) product Cubicin® (daptomycin for injection, 500 mg; Merck and Co., Inc.) with (b) (4), concentration, dosage form, route, and indication. The addition of sucrose is the (b) (4). The proposed new formulation is (b) (4). The impurities and degradants detected in the final drug product (b) (4) to the currently marketed product. Please refer to the Product Quality review by Dr. David Lewis in DARRTS for information on the impurity profile of the revised formulation.

Each vial of the proposed reformulated product (Cubicin®RF) will contain 500 mg daptomycin and (b) (4) mg sucrose, reconstituted to 50 mg/mL daptomycin and (b) (4) (w/v; (b) (4) mg/mL) sucrose. The reformulated product will be administered clinically at  $\leq$  (b) (4) % (w/v; (b) (4) mg/mL) sucrose after initial dilution in sterile water to 50 mg/mL daptomycin, and further dilution with (b) (4) as needed. The Sponsor has proposed labeling changes to alter the product name from Cubicin® to Cubicin® RF and has identified saline to be incompatible as the initial diluent for reconstitution of the reformulated product; water should be used for reconstitution (b) (4)

(b) (4) There are no proposed changes to any of the pharmacology/toxicology relevant sections of the labeling except to the name of the drug product.

The proposed sucrose level in the reformulated product before reconstitution is (b) (4) %. As mentioned, the reformulated product will be administered clinically at  $\leq$  (b) (4) % (w/v; (b) (4) mg/mL) sucrose after reconstitution and further dilutions in sterile water and (b) (4), respectively. (b) (4) for sucrose (b) (4)

(NDA 20955; Ferrlecit® (sodium ferric gluconate complex injection); Sanofi-Aventis, Approved 1999). Sucrose (b) (4)

(b) (4) The Applicant compared the sucrose level in the reformulated daptomycin drug product to sucrose levels found in 3 approved drugs, Actemra™, Remicade™, and Ruconest™. Based on an assumed body weight of 80 kg, the Applicant calculated the daily administered sucrose levels for these products to range between 1600 to 2000 mg. In comparison, the Applicant noted that the reformulated daptomycin drug product would deliver less than 750 mg of sucrose/day. Therefore, the Applicant claimed that the reformulated daptomycin product does not represent a safety concern to patients when administered at the currently approved dose levels of 4 and 6 mg/kg/day.

*(Reviewer's comment: The level of sucrose added in the reformulation of daptomycin for injection is acceptable. There are no safety concerns for sucrose in the new formulation).*

The current application contains new pharmacology/toxicology studies conducted to support the new sucrose formulation (Cubicin® RF) including the following studies:

- Single dose IV pharmacokinetic study in dogs comparing the reformulated daptomycin product (RDP) to the original marketed product (OMP)
- In vitro protein binding study comparing the RDP to OMP
- Exploratory single-dose intravenous tolerability study in rats with the RDP
- 14-day intravenous toxicity study in rats with the RDP
- 14-day intravenous toxicity study in rats with the OMP (for comparison)
- In vitro hemolysis study in human blood comparing the RDP to OMP
- In vitro flocculation study in human blood with the RDP to OMP

Cubicin® injection is an approved intravenous drug (approved in 2003; NDA 21572) for treatment of complicated skin and soft tissue infections (cSSSI) and *Staphylococcus aureus* (*S.aureus*) bloodstream infections, including those with right-sided ineffective endocarditis. Recommended dosage regimen for adult patients is 4 to 6 mg/kg daily every 24 or 48 hours (based on renal clearance) for 7 to 14 days (cSSSI) or 2 to 6 weeks (*S.aureus* bacteremia). The reported human mean AUC<sub>0-24h</sub> and C<sub>max</sub> values for Cubicin® administered at 6 mg/kg once daily for 14 days was 632 mcg\*h/mL and 93.9 mcg/mL, respectively. At this dose and duration to patients, human plasma clearance, volume of distribution, and terminal elimination half-life (t<sub>1/2</sub>) for Cubicin® was 9.1 hr/mL/kg, 0.101 L/kg, and 7.9 hours, respectively. Safety and effectiveness of Cubicin in pediatric patients (< 18 years) have not been established.

### **Pharmacokinetics**

The pharmacokinetics of daptomycin have been well characterized (see pharmacology/toxicology review for NDA 21572 by Dr. Wendelyn Schmidt in DARRTS 8/19/2003). The Sponsor has submitted the following studies to compare the pharmacokinetics of the reformulated daptomycin product containing sucrose to the currently approved product:

1. Single dose IV pharmacokinetic study in dogs comparing the reformulated daptomycin product (RDP) to the original marketed product (OMP)
2. In vitro protein binding study comparing the RDP to OMP

Briefly, results of these studies demonstrated no difference in mean plasma concentrations, plasma clearance, volume of distribution at steady state, and half-life between the RDP and OMP formulations. Similarly, daptomycin concentrations of 10 and 100 mcg/mL showed similar % protein binding between formulations, ranging from 90-95% at either drug concentration. Both the pharmacokinetic data and protein binding values were consistent with historical data. Overall, the addition of sucrose in



Cubicin® RF does not appear to affect the established distribution and excretion properties of daptomycin. A review of these nonclinical studies can be found below.

**1. Study title: Comparison of the Pharmacokinetics of Daptomycin in Dogs Dosed with the Reformulated and Original Marketed Products**

Study no.: PK001  
Study report location: Merck Research Laboratories, Boston, MA.  
Conducting laboratory and location: Not reported  
Date of study initiation: Not reported  
GLP compliance: No  
QA statement: Yes  
Drug, lot #, and % purity: Cubicin® (OMP); Lot #PA053; purity 95.1%  
Cubicin® RF (RFP); Lot #CDH001, #CDH003; purity 107%

**Methods**

Doses: Single intravenous bolus dose with RDP on Day 1, followed by a single intravenous bolus dose with OMP on Day 8  
Frequency of dosing: Single dose on Days 1 and 8  
Route of administration: I.V. bolus injection  
Dose: 15 mg/kg  
Dose volume: Not reported  
Formulation/Vehicle: Distilled water (RDP) or Saline (OMP) diluted to 15 mg/mL  
Species/Strain: Beagle dogs  
Number/Sex/Group: 6 males  
Age: Not reported  
Weight: Not reported  
Satellite groups: None  
Unique study design: None  
Deviation from study protocol: Not reported

**Objective:** *To compare the pharmacokinetics of daptomycin in dogs following a single IV dose of RDP and OMP.*

**Methods and Results**

**Mortality**

None reported.

**Clinical Signs**

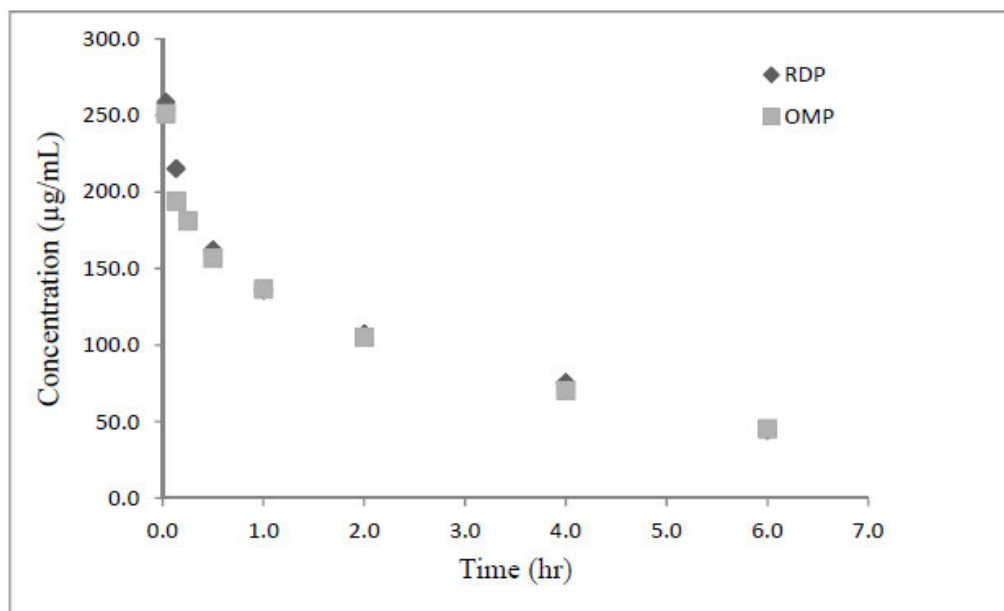
Not reported.

**Pharmacokinetics**

Heparin treated plasma was collected at different timepoints from 2 min to 24 hours after each dose. The vessel from which blood was collected was not reported. The storage of blood samples was not reported, but was likely  $\leq -70^{\circ}\text{C}$ , typical for storage of samples for pharmacokinetic analysis.

Plasma concentrations of daptomycin in dogs dosed with RDP or OMP at 15 mg/kg IV are shown in Figure 1, and the pharmacokinetic parameters are summarized in Table 1. There were no significant differences in the plasma concentrations, or any pharmacokinetic parameters, including AUC and  $C_{\text{max}}$ , measured between RDP and OMP, indicating that the addition of sucrose had no clear impact on the distribution and elimination properties of daptomycin. The reported mean AUC<sub>0-∞</sub> and  $C_{\text{max}}$  values were 768 mcg\*h/mL and 258 mcg/mL, respectively for the RDP, and 807 mcg\*h/mL and 251 mcg/mL, respectively for the OMP. The reported mean values for plasma clearance, volume of distribution at steady state, and terminal elimination half-life ( $t_{1/2}$ ) of daptomycin were 0.33 mL/min/kg, 80 mL/kg, and 2.8 hours, respectively, for the RDP, and 0.32 mL/min/kg, 90 mL/kg, and 3.4 hours, respectively for the OMP.

**Figure 1. Plasma Concentrations of Daptomycin in Dogs (n=6) Dosed with Reformulated (RDP) and Original Product (OMP) at 15 mg/kg IV**



Six male beagle dogs were dosed with RDP on Day 1 and OMP on Day 8. Plasma concentrations of daptomycin were determined at various timepoints from 2 min to 24 hours after each dose. Mean values are plotted. The concentrations at 8 and 24 hours were below the lower limit of quantitation, 3 mcg/mL. (Figure 1 on page 12 of the study report)

**Table 1. Comparison of the Pharmacokinetic Parameters of Daptomycin in Dogs Dosed with the RDP and OMP at 15 mg/kg IV**

Formulation	AUC <sub>0-∞</sub> (μg•hr/mL)	C <sub>max</sub> (μg/mL)	CL <sub>p</sub> (mL/min/kg)	Vd <sub>ss</sub> (mL/kg)	MRT (hr)	T <sub>1/2</sub> (hr)
RDP	768 ± 80.9	258 ± 37.7	0.33 ± 0.04	80 ± 17	4.1 ± 1.1	2.8 ± 0.9
OMP	807 ± 159	251 ± 59.2	0.32 ± 0.06	90 ± 22	4.8 ± 1.3	3.4 ± 1.1

(Table 1 on page 9 of the study report)

### Dosing Solution Analysis

It is not clear from the report if the dosing solutions were analyzed.

**Conclusion:** Overall, the addition of sucrose in Cubicin® RF did not affect the distribution and excretion properties of daptomycin when compared to the originally marketed product (Cubicin®).

*(Reviewer's Comments: The design of this study to compare PK parameters between the RDP and OMP was adequate. The addition of sucrose to daptomycin in the reformulated product had no clear effect on the PK properties of daptomycin at clinically relevant exposures when compared to the marketed product. Additional information from the in-life portion of this study, particularly confirmation of the study location, study initiation date, animal husbandry, and blood sample collection procedure would have been helpful. As this was conducted as a non-GLP study and failed to contain much of the information typically expected in a pivotal GLP toxicology study, this study is considered as informational rather than pivotal in support of the Application.)*

**2. Study title: Comparison of the Human Plasma Protein Binding of the Reformulated Daptomycin Product (RDP) and Original Marketed Product**

Study no.: PK002  
Test article: Cubicin® (OMP), Cubicin® RF (RDP), daptomycin (pure)  
Reconstituted to 50 mg/mL stock, and further diluted to 40 mg/mL, in either saline (OMP, RDP), or DMSO (daptomycin) to 4 mg/mL  
Sample Tested: EDTA-treated plasma (previously frozen)  
Species Tested: Human  
Study report location: Merck Research Laboratories, Boston, MA.  
Conducting laboratory and location: Not reported  
Date of study initiation: Not reported  
GLP compliance: No  
QA statement: No  
Drug, lot #, and % purity: Cubicin® (OMP); Lot #PA053; purity 95.1%  
Cubicin® RF (RDP); Lot #CDH001, #CDH003; purity 107%,  
Daptomycin, Lot # not reported, from (b) (4).

***Objective:*** To assess the impact of reformulation with sucrose on protein binding of daptomycin in human plasma.

**Methods**

Treatment and storage conditions of previously frozen human plasma were not reported.

Plasma protein binding was determined by equilibrium dialysis using (b) (4) dialysis plates (b) (4). Plasma diluted in phosphate buffer was incubated for 6 hours with each of the different daptomycin formulations, in a chamber containing 5% CO<sub>2</sub>. Then aliquots of plasma and buffer were mixed with acetonitrile and analyzed by LC-MS/MS. Incubations were carried out in 4-6 replicates. The reported limit of quantitation for this analytical technique was 10 nM (16.2 ng/mL). The % daptomycin bound in plasma was calculated using the equation below:

$$\% \text{ Bound} = \frac{(\text{Concentration in plasma} - \text{Concentration in buffer}) \times 100}{\text{Concentration in plasma}}$$

**Results**

Protein binding of daptomycin in human plasma was determined using equilibrium dialysis after incubation of the reconstituted formulations as well as the pure API, at final daptomycin concentrations of 10 and 100 mcg/mL. The results expressed as mean ±

standard deviation of the % bound are presented in Table 2. There is very little difference in protein binding in human plasma between the reformulated product, original marketed product, and pure daptomycin at 10 and 100 mcg/mL. At the lower concentration, mean % bound ranged between 89.3 and 93.2% between all three formulations, and at 100 mcg/mL, the mean % bound ranged from 94.4 to 95.3%.

**Conclusion:** Overall, the addition of sucrose had little effect on protein binding when compared to either the marketed product, or pure daptomycin.

**Table 2. Comparison of Protein Binding of Reformulated Daptomycin Product (RDP), Original Marketed Product (OMP), and Pure Daptomycin in Human Plasma**

Formulation	% Bound (Mean $\pm$ SD)	
	10 $\mu$ g/mL	100 $\mu$ g/mL
RDP, lot CDH001	91.9 $\pm$ 0.4 (N=5)	94.8 $\pm$ 0.4 (N=6)
RDP, lot CDH003	90.6 $\pm$ 0.8 (N=6)	95.3 $\pm$ 0.5 (N=6)
RDP, both lots	91.2 $\pm$ 0.9 (N=11)	95.0 $\pm$ 0.5 (N=12)
OMP, lot PA053, vial #1	93.2 $\pm$ 1.0 (N=6)	95.2 $\pm$ 0.6 (N=5)
OMP, lot PA053, vial #2	89.3 $\pm$ 0.3 (N=4)	93.7 $\pm$ 0.7 (N=6)
OMP, both vials	91.6 $\pm$ 2.1 (N=10)	94.4 $\pm$ 1.0 (N=11)
Pure daptomycin	93.0 $\pm$ 0.6 (N=6)	95.3 $\pm$ 0.5 (N=6)

The plasma protein binding of daptomycin was determined using equilibrium dialysis and LC-MS/MS.

Notebook/Page: NB-wolffmi-0375714-0013.

(Table 1 on page 7 of the study report)

*(Reviewer's Comments: The design of this study to compare protein binding of the reformulated daptomycin with sucrose, to the originally marketed product and pure daptomycin was adequate. The addition of sucrose to daptomycin in the reformulated product had no effect on protein binding, as the % bound in human plasma was nearly identical between the three formulations.)*

## **Toxicology**

The toxicity of the current saline formulation of daptomycin has been well characterized (see pharmacology/toxicology review for NDA 21572 by Dr. Wendelyn Schmidt in DARRTS 8/19/2003). The established dose-related targets for intravenous daptomycin toxicity in animals are primarily nerve and muscle. Peripheral nerve axonal degeneration and skeletal muscle myopathy were observed with greater incidence and severity in dogs than rats at clinically relevant doses, particularly in toxicology studies of  $\geq 1$  month duration. Complete recovery in rats was noted 2 months after cessation of dosing; muscle myopathy and neuropathy was more prolonged in dogs with limited recovery noted after a 6 month recovery period. The Sponsor has submitted the following studies to compare the in vitro and in vivo toxicity profile of a new sucrose formulation of daptomycin (Reformulated Daptomycin Product (RDP)) with the Original Marketed Product (OMP), Cubicin®:

1. Exploratory single-dose intravenous tolerability study in rats with the RDP
2. 14-day intravenous toxicity study in rats with the RDP
3. 14-day intravenous toxicity study in rats with the OMP
4. In vitro hemolysis study in human blood comparing the RDP to OMP

#### 5. In vitro flocculation study in human blood with the RDP to OMP

Briefly, results of these studies demonstrated no significant difference in the toxicology profile between daptomycin (Cubicin®RF) with sucrose and daptomycin alone (Cubicin®). No histopathological evaluation was conducted on the rats administered the marketed product for comparison. However, based on prior findings of peripheral nerve axonal degeneration in rats administered IV daptomycin (Cubicin®), as well as nearly identical toxicokinetic results and lack of any new toxicities identified with either formulation, the histopathology is expected to be the same. In vitro assays show no difference in hemolytic or flocculent potential between the current daptomycin formulation and reformulated daptomycin containing sucrose in vitro. A review of these nonclinical studies can be found below.

**1. Study title: MK-3009: Exploratory Single-Dose Intravenous Tolerability Study in Rats (non-GLP; Dose Range Finding Study)**

Study no.: TT #15-1200 (Merck Study No.)  
Study report location: Merck Research Laboratories, West Point, PA, USA  
Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, PA, USA  
Date of study initiation: Not reported  
GLP compliance: No  
QA statement: No  
Drug, lot #, and % purity: MK-3009 (daptomycin-sucrose); Lot #L-000699541-002E; purity: not reported.

**Objective:** *To assess the tolerability of MK-3009 (a cyclic lipopeptide antibiotic) containing sucrose in 0.9% sodium chloride after a single intravenous dose to rats.*

**Methods**

Three male and female Wistar rats (CrI:WI(Han)) approximately 8-9 weeks old (100-300 g) were administered MK-3009-sucrose in 0.9% sodium chloride in a single intravenous injection to the tail vein (dose volume of 5 mL/kg). One male and female injected with 300 mg/kg showed rapid onset of clinical signs and death prompting a reduction of dose to 100 mg/kg for the four remaining rats. Two rats/sex were administered 100 mg/kg MK-3009-sucrose, and monitored for mortality, clinical signs, followed by necropsy and tissue collection 24 hours post-dose. Microscopic evaluation of tissues was not performed.

**Results and Discussion**

One male and one female rat administered a single intravenous injection of MK-3009-sucrose was found dead approximately 5 minutes after dosing. Clinical observations at this high dose included decreased activity, sternally recumbent, hind limb paddling, slow respiration, gasping and/or labored breathing immediately after dosing. The remaining four animals administered MK-3009-sucrose at 100 mg/kg showed no mortality or clinical signs up to 24 hours after dosing. The high dose of 100 mg/kg MK-3009-sucrose was confirmed to be tolerable when administered in a single intravenous injection.

*(Reviewer's Comments: It appears from the study protocol, that this study was originally designed to be a 14-day tolerability study of once daily intravenous injections of MK-3009 (daptomycin) containing sucrose. Based on findings from other toxicity studies, the Applicant planned for the high dose in this study to be 300 mg/kg, but reduce the high dose to 100 mg/kg when 2/2 animals showed severe clinical signs and unscheduled death within 5 minutes after a single high dose. The study was then changed to a single dose intravenous tolerability study with scheduled euthanization of surviving animals 24 hours post-dose. Based*

*solely on the absence of mortality and clinical signs at 100 mg/kg, this dose was selected as the high dose of MK-3009-sucrose for the following 14-day repeat dose toxicity study in rats (Study No. TT #15-1178).*

## 2. Study title: Fourteen-Day Intravenous Toxicity Study in Rats (GLP)

Study no.: TT #15-1178 –RDP (Merck Study No.)  
Study report location: Merck Research Laboratories, West Point, PA, USA  
Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, PA, USA  
Date of study initiation: 10/21/2015  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: MK-3009 (daptomycin-sucrose), Lots #L-000699541-004J002/-004J001; purity: 95.1%/95.1%

### Methods

Doses: 0, 25, 50, 100 mg/kg/day  
Frequency of dosing: Once daily for 14 days; slow bolus 2 mL/min  
Route of administration: Intravenous injection (bolus) to tail vein  
Dose Volume: 1.9 mL/kg  
Formulation/Vehicle: Test article: MK-3009 lyophilized powder in vial containing Cubicin® and 7.5% sucrose; high-dose reconstituted in sterile water for injection pH 6.8; low-dose, mid-dose, and control groups dissolved in 7.5% sucrose in sterile water for injection, pH 6.8.  
Species/Strain: Rats / Wistar Han, Crl:WI(Han)  
Number/Sex/Group: 10 rats/sex for all groups  
Age: 8 weeks old  
Weight: Male: 223.7-271.6 g; Females: 156.2-192.8 g  
Satellite groups: None  
Housing/Diet: Group housed under fluorescent light on a 12 h cycle; food and water ad libitum.  
Deviation from study protocol: None reported that affected the integrity of this study.

**Objective:** *To determine the toxicity and toxicokinetic profile of MK-3009 (Cubicin®) in 7.5% sucrose when administered intravenously to rats once daily for 14 days.*

**Dose Justification:** The high-dose level was based on a previous rat study (Study No. TT #15-1200). The low- and mid-dose levels were intended to provide systemic exposures that are multiples over the anticipated therapeutic exposure.



**Observations and Results****Mortality (Once daily)**

There were no unscheduled deaths.

**Clinical Signs (Once daily):**

There were no test-article related clinical signs observed in any dose group.

**Body Weight (Pre-test, Once weekly):**

There were no test-article related changes in body weights in any dose group.

**Food Consumption (Pre-test, daily, Once weekly):**

There were no test-article related changes in food consumption.

**Hematology / Coagulation (hematology - serum samples collected after overnight fast on Study Day 13 under anesthesia from the jugular vein; coagulation - blood collected at necropsy)**

Test article related changes in hematology was limited to female rats dosed at 100 mg/kg/day that showed slight decrease in total white blood cell counts (-24%) and lymphocyte counts (-26%) when compared to mean values of concurrent controls. These findings were not considered to be toxicologically significant due to the minimal magnitude of change, observation in a single sex, and lack of any correlative histopathology or antemortem effects.

There were no test-article related findings in any coagulation parameters tested.

**Clinical Chemistry (clinical chemistry - serum samples collected after overnight fast on Study Day 13 under anesthesia from the jugular vein)**

Significant test-article related changes observed only in male rats were observed at all doses when compared to mean values of concurrent controls, including a slight mean increase in serum glucose (+29%), triglycerides (+55%), and potassium (+16%) concentrations at 100 mg/kg/day; increased serum triglyceride (+50%) and potassium levels (+9%) at 50 mg/kg/day; and increased triglycerides (+50%) and potassium (+11%) at 25 mg/kg/day. Female rats showed no test-article related serum chemistry findings at doses of MK-3009-sucrose at any dose tested. These findings were not considered to be toxicologically relevance because they were observed in only one sex, and lacked any significant correlative histopathology or antemortem effects.

*(Reviewer's comment: Histomorphologic changes in the kidney included minimal proximal tubular vacuolation that occurred in both sexes of similar incidence. The absence of similar serum chemistry changes in females would suggest vacuolation in the kidney to be unrelated to serum findings.)*

### Urinalysis (overnight urine collection at room temperature with overnight fasting at end of Study Week 2)

No test article related findings were observed in the urinalysis or urine sediment data.

### Toxicokinetics (heparinized plasma samples collected on Day 14 at 0.25, 0.5, 1, 4, 7, and 24 hours post-dose; animals were fasted only for the 24 hour timepoint)

**Subgroup A: 3 rats/sex/dose at 15 min and 4 hours post dose**

**Subgroup B: 3 rats/sex/dose at 30 min and 7 hours post dose**

**Subgroup C: 3 rats/sex/dose at 1 and 24 hours post dose**

Toxicokinetic data for MK-3009-sucrose is shown in Table 3. Following daily intravenous administration of MK-3009-sucrose at 25, 50, and 100 mg/kg/day for 14 days, the mean  $AUC_{0-24h}$  values at the end of the study were 560, 1100, and 2350 mcg•h/mL for both sexes combined, respectively, and mean  $C_{max}$  values of 172, 359, and 724 mcg/mL for combined sexes, respectively. As dose increased from 25 to 100 mg/kg/day on Day 14, systemic exposure ( $AUC_{0-24h}$ ) increased in a dose proportional manner in both sexes, with no clear sex differences. Mean maximum plasma concentrations of MK-3009 were reached by 15 min after dosing for all groups, plasma elimination was similarly rapid across all three doses with mean trough (24 hour) concentrations below the lower limit of quantitation (LLQ) by the end of Study Week 2 (LLQ = 3 mcg/mL). Since plasma was not collected on Day 1 of the study, no information on any dose accumulation could be determined from the data.

**Table 3. Plasma MK-3009 Toxicokinetic Parameters in Rats Following Dosing of MK-3009**

Dose (mg/kg/day)	Sex	$AUC_{0-24h}$ (µg/mL*hr)	$C_{max}$ (µg/mL)	$T_{max}$ (hr)
25	Female	507 ± 23.5	153 ± 8.58	0.50 ± NC
	Male	615 ± 25.7	192 ± 4.22	0.25 ± NC
	All	560 ± 20.3	172 ± 13.5	0.25 ± NC
50	Female	1040 ± 36.3	351 ± 7.70	0.25 ± NC
	Male	1150 ± 26.6	367 ± 16.3	0.25 ± NC
	All	1100 ± 24.3	359 ± 8.82	0.25 ± NC
100	Female	2270 ± 152	743 ± 94.3	0.25 ± NC
	Male	2420 ± 127	706 ± 27.3	0.25 ± NC
	All	2350 ± 93.4	724 ± 44.7	0.25 ± NC
NC = Not Calculated				

(Table 1 on pg. 591 of the study report)

### Gross Necropsy (at necropsy on Study Day 15)

No macroscopic changes attributed to MK-3009 were recorded at necropsy.

### Organ Weights (at necropsy)

No test article related organ weight changes were detected at necropsy.

### Histopathology (at necropsy)

**Adequate Battery:** Yes

#### **Routine Tissues Collected:**

Adrenal glands*	Lymph node, mandibular	Skin, inguinal
Aorta	Lymph node (mesenteric)	Small intestine (D,J,I) <sup>3</sup>
Bone (femur/tibia)	Mammary gland	Spinal cord (C,T, L) <sup>1</sup>
Bone marrow	Nerves, sciatic	Spleen*
Brain*	Optic nerve	Stomach
Cervix	Ovaries*	Testes*
Epididymis*	Pancreas	Thymus*
Esophagus	Parathyroid glands	Thyroid glands*
Eyes	Peyer's patch	Tongue
Harderian gland	Pituitary*	Trachea
Heart*	Prostate*	Ulnar Nerve
Injection site	Salivary glands (SM,SL) <sup>2</sup>	Urinary bladder
Kidneys*	Sciatic nerve	Uterus*
Large Intestine (Co, Ce) <sup>4</sup>	Seminal vesicles	Vagina
Liver*	Skeletal muscle, biceps	
Lungs*	Skeletal muscle, quadriceps	

\*Organ weights collected

<sup>1</sup>C= cervical, T = thoracic, L = lumbar

<sup>2</sup>SM = submandibular, SL = sublingual

<sup>3</sup>D = duodenum, J = jejunum, I = ileum

<sup>4</sup>Co = Colon, Ce = Cecum

**Peer Review:** no

### **Histological Findings:**

There were no test article-related gross findings or differences in organ weights in either sex at any dose tested.

Test article-related histomorphologic findings were present in the kidney, sciatic nerve, and ulnar nerve in both sexes as summarized in the table 4 below. Minimal tubular vacuolation was present in the renal cortex of in the kidney of both male and female rats of similar incidence noted at 50 and 100 mg/kg/day. Minimal axonal degeneration was present in the sciatic and ulnar nerves in both sexes at 100 mg/kg/day, with considerably higher incidence noted in males. Reportedly, individual axonal segments appeared swollen, eosinophilic, and fragmented.

**Table 4. Test Article-Related Histologic Findings**

Dose, mg/kg/day Number of Animals	Females			Males		
	25	50	100	25	50	100
	10	10	10	10	10	10
Histomorphology (Incidence)						
Kidney: Tubular vacuolation	-	6	7	-	7	10
Nerve: Axonal degeneration						
Sciatic nerve	NE	-	2	NE	-	10
Ulnar nerve	NE	-	1	NE	-	6
- = No test article-related findings NE = Group not examined.						

Minimal hemorrhage, inflammation, and foreign body granuloma was observed at similar incidence at the injection site in the tails in both sexes in the vehicle control, and 100 mg/kg/day. Injection site reactions are likely related to the injection procedure and therefore are of limited toxicology significance. All other gross and histomorphologic changes were of the type and incidence observed in untreated rats and were considered unrelated to treatment.

#### **Dosing Solution Analysis:**

Dosing solutions analyzed on Study Week 1 and 2 showed assay results within range of theoretical values (90-110% of nominal); all dose formulations appeared accurately prepared. MK3009 was confirmed to be absent from the vehicle control sample.

*(Reviewer's comments: The overall study design was sufficient to evaluate the repeat dose toxicity of MK-3009 containing sucrose in Wistar rats. The amount of sucrose administered between dose levels of the test article and control was the same. The original marketed product Cubicin® was not tested in this study. MK-3009 containing sucrose was generally tolerated with no apparent mortality, clinical signs, or adverse effects on body weight or food consumption. Female rats at 100 mg/kg/day of MK-3009 showed an approximate 25% reduction in lymphocytes and total white blood cell counts with no histological correlates in any hematopoietic or lymphoid tissues; no decrease was noted in males at any dose tested. Male rats at 25, 50, and 100 mg/kg/day of MK-3009 showed slight increases in triglycerides (~ +50%) and potassium (~ +15%); serum glucose was also increased only in males (~ +30%) at 100 mg/kg/day. Minimal proximal tubular vacuolation in the kidneys was noted in both sexes at 50 and 100 mg/kg/day; however the absence of similar serum chemistry changes in females would suggest vacuolation in the kidney to be unrelated to this finding. Minimal axonal degeneration in the sciatic and ulnar peripheral nerves was noted in both sexes at 100 mg/kg/day; however the incidence was greater in males than females. This is an expected finding noted in previously conducted toxicology studies in rats and dogs, particularly with experimental durations that exceed 1 month. There were no reported CNS effects, evidence of muscular weakness or decreased activity, or any histopathologic changes noted in muscle, brain, or spinal cord of rats of both sexes at any dose tested. The Applicant determined the No Observed Adverse Effect Level (NOAEL) was determined*

*to be 25 mg/kg/day when administered once daily for 14 days, based on clinical pathology findings, and evidence of proximal tubular vacuolation observed at higher doses. However, because both the serum chemistry and renal histopathology findings in the rat were minimal, and likely lacked toxicological relevance, the revised NOAEL proposed by the reviewer for the reformulated daptomycin product in this study is 50 mg/kg/day. At this NOAEL, the mean  $AUC_{0-24h}$  and  $C_{max}$  in Week 2 for both sexes combined was 1100 mcg•h/mL and 359 mcg/mL, respectively, just slightly less than twice the clinical AUC and four times the  $C_{max}$  value reported in patients administered 6 mg/kg Cubicin once daily for 14 days in the clinic. In addition, at the NOAEL dose of 50 mg/kg/day, the daily amount of sucrose administered to rats was approximately equivalent to the expected amount of sucrose to be administered to a 60 kg patient when normalized to body surface area).*

### 3. Study title: Fourteen-Day Intravenous Toxicity Study in Rats (GLP)

Study no.:	TT #15-1179 –OMP (Merck Study No.)
Study report location:	Merck Research Laboratories, West Point, PA, USA
Conducting laboratory and location:	Safety Assessment and Laboratory Animal Resources, Merck Research Laboratories, West Point, PA, USA
Date of study initiation:	10/28/2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MK-3009 (daptomycin), Lots #L-000699541-002E001; purity: 94.8%

#### Methods

Doses:	0, 25, 50, 100 mg/kg/day
Frequency of dosing:	Once daily for 14 days; slow bolus 2 mL/min
Route of administration:	Intravenous injection (bolus) to tail vein
Dose Volume:	1.9 mL/kg
Formulation/Vehicle:	Test article: MK-3009 lyophilized powder in vial containing Cubicin® reconstituted in 0.9% saline; Control article: 0.9% saline
Species/Strain:	Rats / Wistar Han, Crl:WI(Han)
Number/Sex/Group:	10 rats/sex for all groups
Age:	8 weeks old
Weight:	Male: 207.5 - 252.8 g; Female: 159.3 – 198.1 g
Satellite groups:	None
Housing/Diet:	Group housed under fluorescent light on a 12 h cycle; food and water ad libitum.
Deviation from study protocol:	None reported that affected the integrity of this study.

**Objective:** *To determine the toxicity and toxicokinetic profile of MK-3009 (Cubicin®) without sucrose when administered intravenously to rats once daily for 14 days (for comparison to Cubicin® + sucrose).*

**Dose Justification:** The high-dose level was based on a previous rat study (Study No. TT #15-1200). The low- and mid-dose levels were intended to provide systemic exposures that are multiples over the anticipated therapeutic exposure.

### **Observations and Results**

#### **Mortality (Once daily)**

There were no unscheduled deaths.

#### **Clinical Signs (Once daily):**

There were no test-article related clinical signs observed in any dose group.

#### **Body Weight (Pre-test, Once weekly):**

There were no test-article related changes in body weights in any dose group.

#### **Food Consumption (Pre-test, daily, Once weekly):**

There were no test-article related changes in food consumption.

#### **Hematology / Coagulation (hematology - serum samples collected after overnight fast on Study Day 13 under anesthesia from the jugular vein; coagulation - blood collected at necropsy)**

There were no test-article related findings on any hematology and coagulation parameters tested.

#### **Clinical Chemistry (clinical chemistry - serum samples collected after overnight fast on Study Day 13 under anesthesia from the jugular vein)**

Test-article related changes were limited to an increase in serum glucose (+29%) observed only in male rats at 100 mg/kg/day; no test article related clinical chemistry changes were observed in male rats at 25 or 50 mg/kg/day, or in female rats at any dose tested. Other changes in biochemistry parameters were considered unrelated to test article due to the minimal magnitude of change, variation in directional change, absence of a dose response and/or biological relevance.

*(Reviewer's comment: Similar magnitude increase in serum glucose was observed only in males at 100 mg/kg/day in the previously reviewed 14-day toxicology study with MK-3009+sucrose reformulated drug product. For comparison, other serum chemistry changes observed with the sucrose formulation including increased serum triglycerides and potassium observed in rats administered the reformulated product were not observed in this study with just Cubicin®. The reason for the different clinical chemistry*

*profiles in rats administered the original and reformulated product daily for 14 days is unknown.)*

### Urinalysis (overnight urine collection at room temperature with overnight fasting at end of Study Week 2)

No test article related findings were observed in the urinalysis or urine sediment data.

### Toxicokinetics (heparinized plasma samples collected on Day 14 at 0.25, 0.5, 1, 4, 7, and 24 hours post-dose; animals were fasted only for the 24 hour timepoint)

**Subgroup A: 3 rats/sex/dose at 15 min and 4 hours post dose**

**Subgroup B: 3 rats/sex/dose at 30 min and 7 hours post dose**

**Subgroup C: 3 rats/sex/dose at 1 and 24 hours post dose**

Toxicokinetic data for MK-3009 is shown in Table 5. Following daily intravenous administration of MK-3009 at 25, 50, and 100 mg/kg/day for 14 days, the mean  $AUC_{0-24h}$  values at the end of the study were 497, 1160, and 2500 mcg•h/mL for both sexes combined, respectively, and mean  $C_{max}$  values of 197, 374, and 759 mcg/mL for combined sexes, respectively. As dose increased from 25 to 100 mg/kg/day on Day 14, systemic exposure ( $AUC_{0-24h}$ ) increased in a dose proportional manner in both sexes, with no clear sex differences. Mean maximum plasma concentrations of MK-3009 were reached 15 min after dosing for all groups, plasma elimination was similarly rapid across all three doses with no measureable plasma concentrations above the lower limit of quantitation (LLQ = 3 mcg/mL) after 7 hours post-dose. Since plasma was not collected on Day 1 of the study, no information on dose accumulation could be determined from the data.

**Table 5. Plasma MK-3009 Toxicokinetic Parameters in Rats Following Dosing of MK-3009**

Dose (mg/kg/day)	Sex	$AUC_{0-24h}$ (µg/mL*hr)	$C_{max}$ (µg/mL)	$T_{max}$ (hr)
25	Female	441 ± 41.7	185 ± 5.96	0.25 ± NC
	Male	552 ± 76.6	209 ± 13.5	0.25 ± NC
	All	497 ± 41.5	197 ± 8.48	0.25 ± NC
50	Female	1120 ± 54.9	369 ± 17.0	0.25 ± NC
	Male	1190 ± 32.6	378 ± 10.1	0.25 ± NC
	All	1160 ± 32.1	374 ± 9.08	0.25 ± NC
100	Female	2060 ± 210	698 ± 60.1	0.25 ± NC
	Male	2950 ± 112	819 ± 10.9	0.25 ± NC
	All	2500 ± 161	759 ± 38.5	0.25 ± NC
NC = Not Calculated a MK-3009 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 3 µg/mL) of the bioanalytical method.				

(Table on pg. 467 of the study report)

### Gross Necropsy (at necropsy on Study Day 15)

No macroscopic changes attributed to MK-3009 were recorded at necropsy.

### Organ Weights (at necropsy)

No test article related organ weight changes were detected at necropsy.

### Histopathology (Tissues Collected/Weighed, Histopathology Not Conducted)

**Adequate Battery:** Yes

#### Routine Tissues Collected:

Adrenal glands*	Lymph node, mandibular	Skin, inguinal
Aorta	Lymph node (mesenteric)	Small intestine (D,J,I) <sup>3</sup>
Bone (femur/tibia)	Mammary gland	Spinal cord (C,T, L) <sup>1</sup>
Bone marrow	Nerves, sciatic	Spleen*
Brain*	Optic nerve	Stomach
Cervix	Ovaries*	Testes*
Epididymis*	Pancreas	Thymus*
Esophagus	Parathyroid glands	Thyroid glands*
Eyes	Peyer's patch	Tongue
Harderian gland	Pituitary*	Trachea
Heart*	Prostate*	Ulnar Nerve
Injection site	Salivary glands (SM,SL) <sup>2</sup>	Urinary bladder
Kidneys*	Sciatic nerve	Uterus*
Large Intestine (Co, Ce) <sup>4</sup>	Seminal vesicles	Vagina
Liver*	Skeletal muscle, biceps	
Lungs*	Skeletal muscle, quadriceps	

\*Organ weights collected

<sup>1</sup>C= cervical, T = thoracic, L = lumbar

<sup>2</sup>SM = submandibular, SL = sublingual

<sup>3</sup>D = duodenum, J = jejunum, I = ileum

<sup>4</sup>Co = Colon, Ce = Cecum

### Dosing Solution Analysis:

Dosing solutions analyzed on Study Week 1 and 2 showed assay results within range of theoretical values (90-110% of nominal); all dose formulations appeared accurately prepared. MK3009 was confirmed to be absent from the vehicle control sample.

*(Reviewer's comments: The overall study design was sufficient to evaluate the repeat dose toxicity of MK-3009 (Cubicin®) in Wistar rats. This study was conducted to establish the toxicity profile of the original marketed product for comparison with results obtained in an independent study with the reformulated daptomycin product containing sucrose, at a dose range of 25 to 100 mg/kg/day. This study was conducted in near identical fashion as the related study with the sucrose containing formulation, except no histopathology was conducted on the tissues in this study. MK-3009 injected into the tail vein of rats daily at a dose up to 100 mg/kg/day for 14 days was generally well tolerated with no mortality, clinical signs, or adverse effects on body weight, food consumption, hematology, coagulation, and urinalysis. Male rats at 100 mg/kg/day of MK-3009 showed an approximate 29% mean increase in serum glucose, with no*



*increase noted in males at lower doses, or in females at any dose tested. This finding was similarly observed in the submitted 14 day rat toxicology study with the reformulated product containing sucrose, indicating increased serum glucose in rats to be unrelated to sucrose administration with the reformulated product. There were no macroscopic changes noted in any collected tissues, and mean organ weights for selected tissues were similar to concurrent controls. No microscopic evaluation of tissues was conducted in this study. Much like with the reformulated daptomycin product containing sucrose, there were no reported CNS effects, evidence of muscular weakness or decreased activity, noted in rats of either sex at any dose tested. The Applicant determined the No Observed Adverse Effect Level (NOAEL) to be 50 mg/kg/day when administered once daily for 14 days, conservatively based on the slight increase in serum glucose observed in males in the high dose group. As in the other study, the lack of histological correlates or any clinical signs suggests the minimal change in serum glucose to be of little toxicological relevance. Because the Applicant decided not to conduct histopathology on collected tissues and prior studies show degeneration of peripheral nerves in rats at 100 mg/kg/day, the NOAEL of 50 mg/kg/day is appropriate for this study. At this NOAEL, the combined mean  $AUC_{0-24h}$  and  $C_{max}$  values in Week 2 for both sexes was 1160 mcg•h/mL and 374 mcg/mL, or at approximately two times greater than the clinical AUC and four times greater  $C_{max}$  values than reported in patients administered 6 mg/kg Cubicin once daily for 14 days in the clinic.)*

**4. Study title: GLP Evaluation of Different Formulations of Daptomycin for Potential to Induce Hemolysis in Human Blood**

Study no.: 0725XC75.007 ( (b) (4) Study No.)  
Test article: Cubicin® (OMP), Cubicin® RF (RDP),  
Reconstituted to 52.5 mg/mL stock in  
saline (OMP) or sterile water (RDP), and  
further diluted to the appropriate dose  
with saline.  
Dose: 100, 200, 400 mcg/mL  
Sample Tested: Heparin-treated plasma (collected fresh  
and tested on collection day)  
Species Tested: Human healthy volunteer (n=1)  
Study report location: Merck Research Laboratories, West  
Point, PA  
Conducting laboratory and location: (b) (4)  
Date of study initiation: 11/17/2015  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: Cubicin® (OMP); Lot #PA053; purity  
95.1%  
Cubicin® RF (RDP); Lot #CDH001,  
#CDH003; purity 107%,  
Daptomycin, Lot # not reported, from (b) (4)

**Objective:** *To assess the hemolytic potential of two formulations of daptomycin in human blood.*

## Methods

1. Fresh whole blood sample from a single healthy human volunteer, was collected into a heparinized tube (tested on collection day).
2. Blood was diluted (1:3) in saline, centrifuged, and analyzed for optical density; supernatant dilutions between 0.8 and 1.2 at 540 nm were used in this study.
3. Daptomycin (OMP and RDP) at 100, 200, or 400 mcg/mL, 7.5% sucrose placebo solution, saline (0.9%), and sterile water for injection were mixed with diluted whole blood (in triplicate). (Note: Sucrose placebo was diluted in saline in the same ratio as the 100, 200, or 400 mcg/mL RDP).
4. Samples were incubated for 30 min at room temperature, and then examined macroscopically and microscopically for precipitation and coagulation.
5. An aliquot was centrifuged and examined visibly for pellet formation; pellets were scored as follows:
  - 0 = negative
  - 1 = very slight precipitation or pellet
  - 2 = minimal precipitation or pellet
  - 3 = moderate precipitation or pellet
  - 4 = significant precipitation or pellet

**Results**

- Vehicle controls were all negative for hemolysis. Percent hemolysis for vehicle diluted samples equivalent to 50, 100, and 200 mcg/mL sucrose was calculated to be 0.3%, 0.2%, and 0.2% hemolysis, respectively.
- Daptomycin with sucrose was negative for hemolysis. Incubation of human blood with Daptomycin containing sucrose at daptomycin concentrations of 50, 100, and 200 mcg/mL resulted in 0.3%, 0%, and 0.3% hemolysis, respectively.
- Currently approved daptomycin was negative for hemolysis. Incubation of human blood with Daptomycin (OMP) at dosing concentrations of 50, 100, and 200 mcg/mL was calculated to be 0%, 0%, and 0.4% hemolysis, respectively.
- Dose formulation analysis showed that all samples (OMP and RDP) met the acceptance criteria for concentration (90-110% of nominal concentration samples > 0.1 mg/mL and 80-120% of nominal concentration for samples  $\leq$  0.1 mg/mL) and criteria for homogeneity.

**Conclusions**

The study design was adequate to determine the hemolytic potential of different formulations of daptomycin. Based on the findings, the current daptomycin formulation (OMP) and reformulated daptomycin formulation containing sucrose (RDP) showed no difference in hemolytic potential at any tested concentrations up to 200 mcg/mL.

**5. Study title: GLP Evaluation of Different Formulations of Daptomycin for Potential to Induce Flocculation in Human Plasma and Serum**

Study no.: 0726XC75.007 (b) (4) Study No.)  
Test article: Cubicin® (OMP), Cubicin® RF (RDP),  
Reconstituted to 52.5 mg/mL stock in  
saline (OMP) or sterile water (RDP), and  
further diluted to the appropriate dose  
with saline.  
Dose: 100, 200, 400 mcg/mL  
Sample Tested: Plasma and Serum collected in  
heparinized tubes and tubes without anti-  
coagulant (collected fresh and tested on  
collection day)  
Species Tested: Human healthy volunteer (n=1)  
Study report location: Merck Research Laboratories, West  
Point, PA  
Conducting laboratory and location: (b) (4)  
Date of study initiation: 11/24/2015  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: Cubicin® (OMP); Lot #PA053; purity  
95.1%  
Cubicin® RF (RDP); Lot #CDH001,  
#CDH003; purity 107%,  
Daptomycin, Lot # not reported, from (b) (4)

**Objective:** *To assess the compatibility of two daptomycin formulations in human plasma and serum.*

### Methods

1. Fresh whole blood sample from a single healthy human volunteer was collected in a heparinized tube and tube without anti-coagulant (tested on collection day).
2. Daptomycin (OMP and RDP) at 100, 200, and 400 mcg/mL, 7.5% sucrose, or 0.9% saline were mixed with an equal volume of plasma, serum, or saline (in triplicate). (Note: Sucrose placebo was diluted in saline in the same ratio as the 100, 200, or 400 mcg/mL RDP).
3. Samples were incubated for 1 hour at 37°C, followed by centrifugation, and then analyzed for hemolysis on a spectrophotometer at 540 nm.

### Results (See Table 6)

- No precipitation or pellet was noted in the saline or sucrose placebo controls (at equivalent dilution ratios as the sucrose daptomycin formulations).
- No precipitation or pellet was observed in the plasma or serum mixed with 100, 200, or 400 mcg/mL of the currently marketed product (OMP) or sucrose daptomycin formulation (RDP).
- Dose formulation analysis showed the marketed Daptomycin product (OMP) met acceptance criteria for concentration (90-110% of nominal concentration samples

> 0.1 mg/mL and 80-120% of nominal concentration for samples  $\leq$  0.1 mg/mL) and criteria for homogeneity. The 0.1 mg/mL sucrose Daptomycin formulation (RDP) met the acceptance criteria for concentration (90-110% of nominal concentration samples > 0.1 mg/mL), but 0.2 and 0.4 mg/mL did not. All sucrose daptomycin formulations met acceptance criteria for homogeneity.

**Table 6. Flocculation Assay in Human Plasma and Serum**

Treatment	Final Concentration (µg/ml)	Plasma			Serum			Saline		
		Macro	Micro	Pellet	Macro	Micro	Pellet	Macro	Micro	Pellet
Saline <sup>a</sup>	-	0	0	0	0	0	0	-	-	-
Sucrose Placebo Solution	- <sup>b</sup>	0	0	0	0	0	0	0	0	0
Sucrose Placebo Solution	- <sup>c</sup>	0	0	0	0	0	0	0	0	0
Sucrose Placebo Solution	- <sup>d</sup>	0	0	0	0	0	0	0	0	0
Current daptomycin formulation	50	0	0	0	0	0	0	0	0	0
Current daptomycin formulation	100	0	0	0	0	0	0	0	0	0
Current daptomycin formulation	200	0	0	0	0	0	0	0	0	0
Sucrose daptomycin formulation	50	0	0	0	0	0	0	0	0	0
Sucrose daptomycin formulation	100	0	0	0	0	0	0	0	0	0
Sucrose daptomycin formulation	200	0	0	0	0	0	0	0	0	0

0 = negative

1 = very slight precipitation or pellet

2 = minimal precipitation or pellet

3 = moderate precipitation or pellet

4 = significant precipitation or pellet

<sup>a</sup> Negative control for flocculation

<sup>b</sup> Sucrose Placebo was diluted in saline in the same ratio as the 100 µg/ml Daptomycin Sucrose dosing formulation

<sup>c</sup> Sucrose Placebo was diluted in saline in the same ratio as the 200 µg/ml Daptomycin Sucrose dosing formulation

<sup>d</sup> Sucrose Placebo was diluted in saline in the same ratio as the 400 µg/ml Daptomycin Sucrose dosing formulation

(Table 1 on page 22 of the study report)

## Conclusions

The study design was adequate to determine the flocculence potential of different formulations of daptomycin. Under these study conditions, the current daptomycin formulation (OMP) and reformulated daptomycin formulation containing sucrose (RDP) showed no difference in flocculence potential at any tested concentrations up to 200 mcg/mL. Both formulations were determined to be compatible with human plasma and serum at concentrations up to 200 mcg/mL.

## Overall Summary and Safety Evaluation

The current manufacturing supplement (S-052) to NDA 21572 (Cubicin®, Merck and Co.) is a proposed manufacturing reformulation of Cubicin® 500 mg/vial (daptomycin for injection, lyophilized powder for solution) to include (b) (4) mg of sucrose, with an associated name change to Cubicin® RF. The Sponsor claims (b) (4)

(b) (4) The dosage form, strength, dose, and route of administration (b) (4) to Cubicin®. The addition of sucrose is (b) (4) to Cubicin®, and the reported impurity and degradant profile of the reformulated product (b) (4) to the approved drug.

The proposed use of sucrose as an (b) (4) in the new formulation of daptomycin is of little safety concern from a pharmacology/toxicology perspective. Sucrose is Generally

Regarded as Safe (GRAS) and is present in several approved parenteral products at higher concentrations than proposed in the new formulation of Cubicin® RF.

Sucrose addition in the new formulation (Cubicin® RF) had no effect on the distribution and elimination properties of daptomycin in rats and dogs in vivo, or on human protein binding in vitro, when compared to the marketed product (Cubicin®). Similar pharmacokinetic (PK) parameters were observed with both formulations when administered in a single IV dose to dogs (15 mg/kg) at clinically relevant exposures.

The reported mean (combined sex)  $AUC_{0-\infty}$  and  $C_{max}$  values in dogs were 768 mcg\*h/mL and 258 mcg/mL, respectively for the reformulated product, and 807 mcg\*h/mL and 251 mcg/mL, respectively for the original marketed product. Also, near identical PK parameters were observed in rats administered a once daily IV injection of either formulation for 14 consecutive days. The reported (combined sex) mean  $AUC_{0-\infty}$  and  $C_{max}$  values for rats were 1100 mcg\*h/mL and 359 mcg/mL, respectively with the reformulated product, compared to 1160 mcg\*h/mL and 375 mcg/mL, respectively with the original marketed product. PK values obtained in the single dose study in dogs (15 mg/kg), and at the NOAEL dose (50 mg/kg) in the 14-day toxicology studies in rats with both formulations were similar to PK values recorded in humans (6 mg/kg) with the marketed product (values from subsection 12.3 of the package insert for Cubicin®). The addition of sucrose had no impact on the comparability of this data across species (Table 7). Protein binding of daptomycin in human plasma was unchanged with the addition of sucrose; mean % bound values in human blood ranged from 89-95% for both formulations and pure daptomycin up to 100 mcg/mL.

**Table 7. Species Comparison of the PK Parameters for the Reformulated Daptomycin Product (RDP) and the Original Marketed Product (OMP)**

Species	Formulation	Dose <sup>1</sup> (mg/kg)	No. of Doses	AUC <sub>0-∞</sub> (mcg*h/mL)	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> <sup>2</sup> (hr)	T <sub>1/2</sub> (hr)
Dog	RDP	15	1	768	258	0.03	2.8
	OMP	15	1	807	251	0.03	3.4

Species	Formulation	Dose <sup>1</sup> (mg/kg)	No. of Doses	AUC <sub>0-24h</sub> (mcg*h/mL)	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> <sup>2</sup> (hr)	T <sub>1/2</sub> (hr)
Rat	RDP	50 <sup>a</sup>	1	1100	359	0.25	N.R.
	OMP	50 <sup>b</sup>	1	1160	375	0.25	N.R.

Species	Formulation	Dose <sup>1</sup> (mg/kg)	No. of Doses	AUC <sub>0-∞</sub> (mcg*h/mL)	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> <sup>2</sup> (hr)	T <sub>1/2</sub> (hr)
Human <sup>3</sup>	OMP	6	14	632	93.9	N.R.	7.9

RDP = Reformulated Daptomycin Product (Cubicin® RF)

OMP = Original Marketed Product (Cubicin®)

N.R. = not reported

<sup>a</sup>NOAEL dose in the 14-day toxicology study in rats with the reformulated product (TT #15-1178)

<sup>b</sup>NOAEL dose in the 14-day toxicology study in rats with the marketed product (TT #15-1179)

<sup>1</sup>The doses of 15 mg/kg (dog), 50 mg/kg (rats), and 6 mg/kg (human) are nearly equivalent on a body surface area basis.

<sup>2</sup>T<sub>max</sub> values were the first timepoint collected in each study

<sup>3</sup>Human PK values taken from Table 7 of the Package Insert (PI) for Cubicin®.

Intravenous administration of daptomycin containing sucrose (Cubicin® RF) or the original marketed daptomycin product (Cubicin®) in two separate 14-day rat toxicology studies resulted in near identical pharmacokinetic and toxicity profiles between formulations. The daily amount of sucrose administered to rats in these studies was equivalent to the expected amount of sucrose to be administered to a 60 kg patient, when normalized to body surface area. Overall, there were no significant toxicity findings detected with either formulation at the NOAEL dose (50 mg/kg) in rats in either 14-day toxicity studies. At 100 mg/kg, neurodegeneration in the sciatic and ulnar nerves was observed with the reformulated product (no histopathology was conducted on rats administered the marketed product). Minimal proximal tubular degeneration observed in both sexes at 50 mg/kg with the reformulated product were of unknown etiology, lacked associated changes in serum chemistry and/or evidence of renal cell necrosis or degeneration/regeneration, and therefore were not considered toxicologically relevant. Increased serum glucose (25-29%) was also detected in rats administered either formulation at the NOAEL dose of 50 mg/kg and was considered to be of minimal toxicological significance and unrelated to sucrose.

Daptomycin with sucrose (b) (4) for hemolysis and flocculation potential and (b) (4) as the marketed product.

Pharmacology/Toxicology has no objection to the approval of NDA 21572 Supplement 52, to modify the formulation of the approved drug product Cubicin® (daptomycin for injection) 500 mg/vial to include the new (b) (4) Sucrose (b) (4) mg). Other than the product name from Cubicin® to Cubicin® RF, the Applicant recommended no changes to the pharmacology/toxicology relevant sections of the labeling. There are no additional nonclinical recommendations at this time.



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/s/  
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TERRY J MILLER  
05/11/2016

WENDELYN J SCHMIDT  
05/12/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21-572/S-052**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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<b>Date of This Review:</b>	July 6, 2016
<b>Requesting Office or Division:</b>	Division of Anti-Infective Products (DAIP)
<b>Application Type and Number:</b>	NDA 021572/S-052/S-053
<b>Product Name and Strength:</b>	Cubicin (daptomycin) for injection; Cubicin RF (daptomycin) for injection; 500 mg per vial
<b>Product Type:</b>	Single ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. and as agent for Cubist Pharmaceuticals LLC
<b>Submission Date:</b>	June 22, 2016 and July 5, 2016
<b>OSE RCM #:</b>	2016-435-3
<b>DMEPA Primary Reviewer:</b>	Sevan Kolejian, Pharm. D.
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD

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## **1 REASON FOR REVIEW**

The Division of Anti –Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Cubicin and Cubicin RF (See Appendix A) to determine if they are acceptable from a medication error perspective.

The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1,2,3</sup>

## **2 CONCLUSION**

The revised container labels and carton labeling for Cubicin and Cubicin RF are acceptable from a medication error perspective.

We have no further recommendations at this time.

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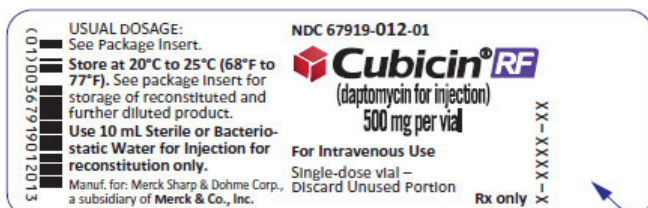
<sup>1</sup> Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 7. OSE RCM No.: 2016-435.

<sup>2</sup>Kolejian, S. Label and Labeling Memorandum for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 19. OSERCM No.: 2016-435-1

<sup>3</sup> Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 13. OSE RCM No.: 2016-435-2.

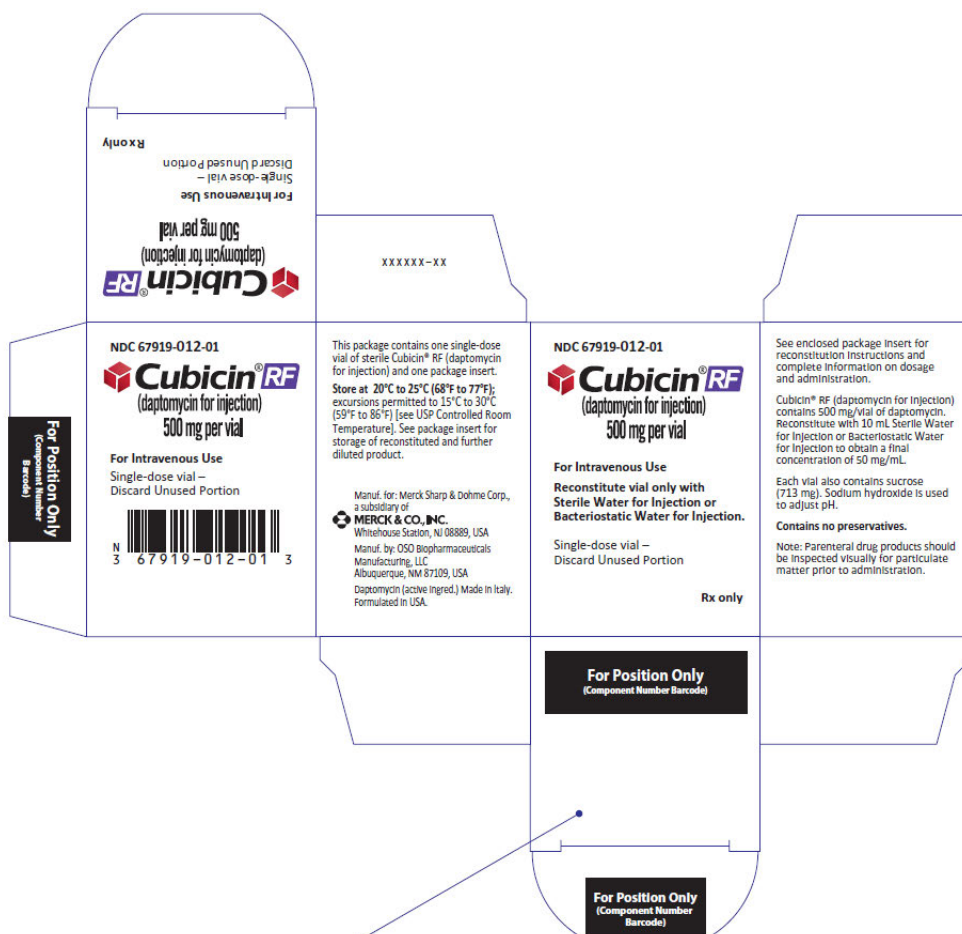
## APPENDIX A. LABEL AND LABELING SUBMITTED ON JUNE 22, 2016 AND JULY 5, 2016

### 1. Cubicin RF Container label Submitted on June 22, 2016



Lot and Expiry Area.  
Legends Printed Online.

### 2. Cubicin RF Carton labeling Submitted on June 22, 2016



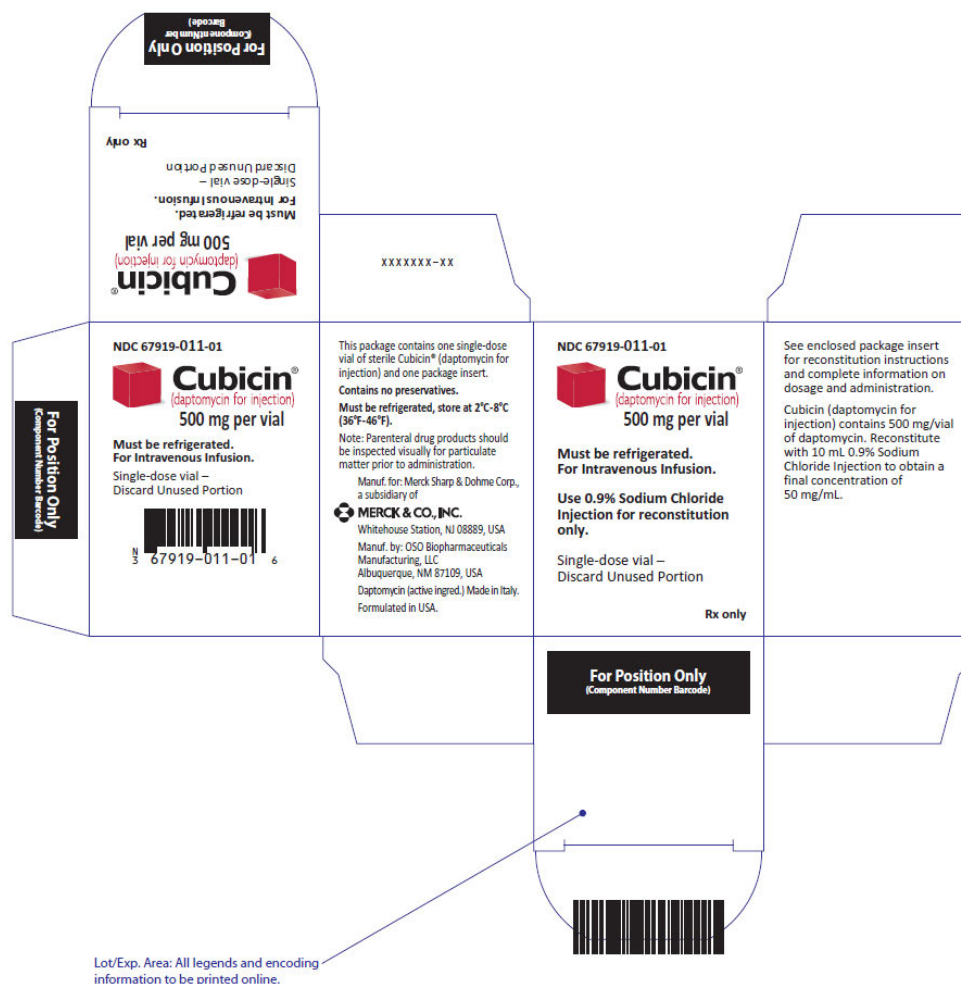
Lot/Exp. Area: All legends and encoding information to be printed online.

### 3. Cubicin Container label Submitted on July 5, 2016



Lot and Expiry Area.  
Legends Printed Online.

### 4. Cubicin RF Carton labeling Submitted on July 5, 2016



5.

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/s/  
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SEVAN H KOLEJIAN  
07/06/2016

BRENDA V BORDERS-HEMPHILL  
07/06/2016

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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<b>Date of This Review:</b>	June 17, 2016
<b>Requesting Office or Division:</b>	Division of Anti-Infective Products (DAIP)
<b>Application Type and Number:</b>	NDA 021572/S-052
<b>Product Name and Strength:</b>	Cubicin (daptomycin) for injection; Cubicin RF (daptomycin) for injection; 500 mg per vial
<b>Product Type:</b>	Single ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. and as agent for Cubist Pharmaceuticals LLC
<b>Submission Date:</b>	May 13, 2016
<b>OSE RCM #:</b>	2016-435-2
<b>DMEPA Primary Reviewer:</b>	Sevan Kolejian, Pharm. D.
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD
<b>Deputy Director:</b>	Lubna Merchant, Pharm.D., MS

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## 1 REASON FOR REVIEW

This memorandum serves as an addendum to our previous reviews<sup>1, 2</sup> in which we evaluated the label and labeling as well as considerations for the introduction of the proposed formulation of Cubicin RF intended to replace the current formulation of Cubicin. During an assessment of the previous review, we realized that our statement on the risk for medication error related to the introduction of this proposed product to the market as documented is not clearly conveyed. We determined that this proposed product can be introduced to the market but with label and labeling interventions that address the storage and reconstitution differences between these two products. This memorandum represents an amendment to the administrative record and provides additional recommendations to address the concerns identified by the review team to promote the safe use of both products and to address the risk of medication errors.

## 2 DISCUSSION

Merck has developed a new formulation of Cubicin RF (daptomycin for injection), intended to replace the current formulation of Cubicin (daptomycin for injection). However, both products may be on the market simultaneously (b) (4). The proposed formulation, Cubicin RF will be reconstituted with a different diluent (sterile water for injection) as compared to the currently marketed Cubicin which is reconstituted using 0.9 % sodium chloride. Additionally the two formulations differ in their storage requirements which depend upon the stage of preparation (b) (4)

We note that while the two formulations can be therapeutically interchanged, there is a potential that users may use the wrong diluent for reconstitution or improperly store the product. Therefore, to address these risks, we provide recommendations to the label and labeling of Cubicin RF that highlight the reconstitution directions as well as the storage requirements and are intended to mitigate the risk of wrong diluent used for reconstitution. Merck implemented these initial recommendations and submitted revised labeling on May 13, 2016, which we found acceptable. We also note that Merck plans to (b) (4)

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<sup>1</sup>Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 7. OSE RCM No.: 2016-435.

<sup>2</sup> Kolejian, S. Label and Labeling Memorandum for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 19. OSE RCM No.: 2016-435-1

Since both Cubicin and Cubicin RF may be available on the market simultaneously for a period of time, it is important that the labels and labeling for Cubicin are well differentiated from Cubicin RF labels and labeling and highlight the important storage and reconstitution instructions.

We provide additional recommendations from collaboration with the review team for both Cubicin and Cubicin RF in Section 3 to minimize the risk of use of wrong diluent or incorrect storage and promote safe use for Cubicin and Cubicin RF products.

### **3 CONCLUSION**

DMEPA concludes that the proposed product can be introduced to the market with revisions to the labels and labeling for both Cubicin RF and Cubicin to increase clarity and prominence of reconstitution directions and the storage requirements to promote safe use of these products (See section 4).

If you have further questions or need clarifications, please contact Janet Higgins, OSE Project Manager, at 240-402-0330.

### **4 RECOMMENDATIONS FOR MERCK**

We recommend the following be implemented prior to approval of this NDA 021572/S-052:

#### **A. Proposed Cubicin RF Container label:**

1. Delete (b) (4) statement from the principal display panel for consistency with Cubicin labels which will allow space for the Cubicin labels to convey important storage information.
2. Revise the side panel reconstitution information to read “Use 10 ml Sterile or Bacteriostatic Water for Injection for reconstitution only” for clarity of the amount used for reconstitution.

#### **B. Proposed Cubicin RF Carton labeling:**

1. Delete (b) (4) statement from all panels for consistency with Cubicin labels which will allow space for the Cubicin labels to convey important storage information.
2. Revise the side panel reconstitution information to read “Reconstitute with 10 mL Sterile Water for Injection or Bacteriostatic Water for Injection to obtain a final concentration of 50 mg/mL.” for clarity of the amount used for reconstitution.

#### **C. Cubicin Container label:**

1. Replace “Must be reconstituted” with “Must be refrigerated” on the principal display panel to highlight the key storage message.

2. Add the statement: “Use 10 mL 0.9% Sodium Chloride Injection for reconstitution only.” on side panel for clarity of the diluent and amount that is used for reconstitution.

B. Cubicin Carton labeling:

1. Replace “Must be reconstituted” with “Must be refrigerated” on all panels to highlight the key storage message.
2. Add the statement: “Use 0.9% Sodium Chloride Injection for reconstitution only.” to the principal display panel to highlight the important diluent information.
3. Revise the reconstitution information on the side panel to read: “Reconstitute with 10 mL 0.9% sodium chloride injection to obtain a final concentration of 50 mg/mL.” for clarity of the amount used for reconstitution

## **APPENDIX A. LABEL AND LABELING**

### **I. CUBICIN RF LABELS AND LABELING SUBMITTED ON MAY 13, 2016**

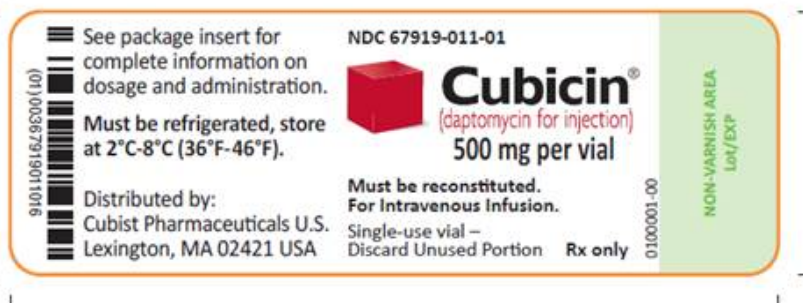
#### **1. Container label**



#### **2. Carton labeling**



II. CUBICIN Labels and Labeling ( in use labels)  
1. Container label



2. Carton Labeling



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/s/  
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SEVAN H KOLEJIAN  
06/17/2016

BRENDA V BORDERS-HEMPHILL  
06/17/2016

LUBNA A MERCHANT  
06/17/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** June 2, 2016

**To:** Christopher Davi, MS  
Senior Regulatory Project Manager  
Division of Anti-Infective Products (DAIP)

**From:** Adam George, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Amy Toscano, Pharm.D, RAC, CPA  
Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **Supplement 52 and 53 for NDA 021572 Cubicin (daptomycin for injection) for intravenous use**

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This consult review is in response to DAIP's February 9, 2016, request for OPDP's review of the proposed (b) (4) draft package insert (PI) for supplements 52 and 53 for NDA 021572 Cubicin (daptomycin for injection) for intravenous use (Cubicin). On February 9, 2016, Merck Sharp & Dohme Corp submitted CMC prior approval supplement 52 to NDA 021572 for Cubicin. The purpose of this supplement is for the proposed re-formulated Cubicin<sup>®</sup> product (Cubicin<sup>®</sup> RF) and provides for changes in the Dosage and Administration, and How Supplied sections of the PI. According to the pharmacology/toxicology review of supplement 52, the proposed reformulated drug product is intended to be (b) (4) to the currently marketed product with (b) (4), concentration, dosage form, route, and indication. The addition of sucrose is (b) (4) to the formulation. In section 1.16 of the supplement submission the Applicant included (b) (4). Supplement 53 proposed revisions to the Dosage and Administration section of the PI. These changes were implemented in Supplement 52.

Per the consult request, we have reviewed the Applicant's proposed (b) (4)

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**Conclusion:** From our perspective the Applicants

(b) (4)

(b) (4)

(b) (4)

I have read the clinical review of supplement 52

(b) (4)

Additionally, the DMEPA review of supplement 52 notes that “the introduction of Cubicin RF (daptomycin for injection) to the market

(b) (4)

From a

(b) (4)

, OPDP has

(b) (4)

This position was discussed with DAIP at the May 10 Supplement Status meeting for supplement 52.

OPDP contacted the Applicant on May 25, 2016, to

(b) (4)

Based upon the May 25 telephone conversation the Applicant is

(b) (4)

(This approach is acceptable since for this NDA there is currently

(b) (4)

The Applicant stated they

(b) (4)

From OPDP’s perspective the proposed

(b) (4)

When the

(b) (4)

OPDP

(b) (4)

Supplement 53 proposed

(b) (4)

OPDP reviewed the substantially complete titled “CubicinRFs052Label.docx” accessed via SharePoint on May 23, 2016. This version of the PI

(b) (4)

We have no comments on



the PI at this time. A copy of the reviewed PI is attached to this consult response for your reference.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or [adam.george@fda.hhs.gov](mailto:adam.george@fda.hhs.gov).

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/s/  
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ADAM N GEORGE  
06/02/2016

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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<b>Date of This Review:</b>	May 19, 2016
<b>Requesting Office or Division:</b>	Division of Anti-Infective Products (DAIP)
<b>Application Type and Number:</b>	NDA 021572/S-052
<b>Product Name and Strength:</b>	Cubicin RF (daptomycin) for injection; 500 mg per vial
<b>Product Type:</b>	Single ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. and as agent for Cubist Pharmaceuticals LLC
<b>Submission Date:</b>	May 13, 2016
<b>OSE RCM #:</b>	2016-435-1
<b>DMEPA Primary Reviewer:</b>	Sevan Kolejian, Pharm. D.
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD

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## **1 REASON FOR REVIEW**

The Division of Anti –Infective Products (DAIP) requested that we review the revised container labels and carton labeling for Cubicin RF (See Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

## **2 CONCLUSION**

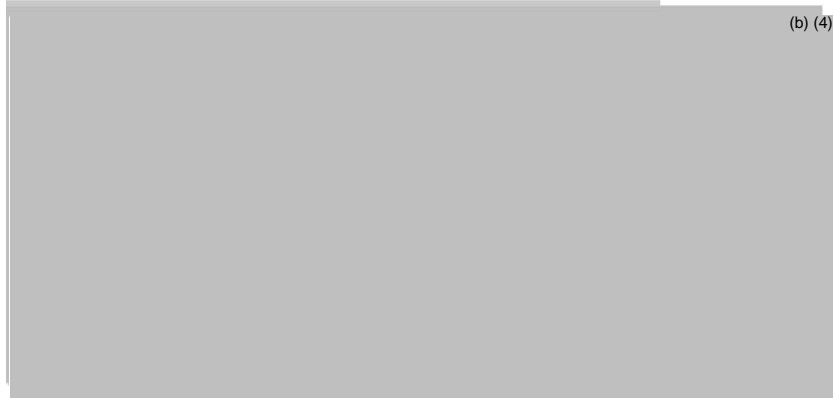
The revised container labels and carton labeling for Cubicin RF are acceptable from a medication error perspective. We note that the word (b) (4) appears next to the established name for this product and we defer to OPQ to determine the appropriateness of the word reformulation that appears next to the established name.

We have no further recommendations at this time.

## **APPENDIX A. LABEL AND LABELING SUBMITTED ON MAY 13, 2016**

<sup>1</sup>Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 7. OSE RCM No.: 2016-435.

1. Container label



(b) (4)

2. Carton labeling



(b) (4)

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/s/  
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SEVAN H KOLEJIAN

05/19/2016

BRENDA V BORDERS-HEMPHILL

05/19/2016

### Clinical Memo

<b>NDA</b>	021572 SUPPL-52 and 53
<b>Product</b>	Daptomycin
<b>Tradename</b>	Cubicin®/Cubicin®RF
<b>Sponsor</b>	Merck Sharp &Dohme as agent for Cubist Pharmaceuticals
<b>Dates Received</b>	February 9, 2016 (SUPPL-52) and April 12, 2016 (SUPPL-53)
<b>Reviewer</b>	Hala Shamsuddin MD

On February 9, 2016, the Sponsor submitted a CMC Prior Approval Supplement (Supplement 52) for the proposed re-formulated Cubicin® product (Cubicin® RF) that provided for changes in the Dosing and Administration section and How Supplied sections in Cubicin approved labeling.

The Sponsor claimed (and was granted) a waiver from providing the in vivo bioavailability/bioequivalence data, and supplied non clinical studies to ensure that the addition of sucrose would not alter the safety or efficacy profile of Cubicin® RF. Additionally, the Sponsor provided data demonstrating that the free drug concentration as measured by protein binding and microbiological potency was similar between the two formulations and that pH and osmolality post-reconstitution of Cubicin® RF were similar for compatibility with blood for injection site tolerability. The Sponsor also provided a (b) (4)

Supplement 52 was reviewed by CMC and by OPQ, DMEPA and OPDP. The proposed new name and reformulation were agreed on, (b) (4). OPDP determined that there was no need to require the Sponsor to (b) (4)

***The Medical Officer concurs with the reviewers from the other disciplines and recommends approval of labeling supplement 52.***

On April 12, 2016, the Sponsor submitted labeling supplement 53 proposing revisions to the Dosage and Administration section to change “single use” to “single dose”, and to recommend the use of a 21-gauge needle for reconstitutions to address postmarketing reports of particulates that were later determined to be pieces of the vial stopper material caused by needle insertion during reconstitution of the lyophilized powder. These changes were already implemented in Supplement 52.

Additionally, the Sponsor proposed adding the terms “acute generalized exanthematous pustulosis” (or AGEP), “acute kidney injury”, “renal insufficiency”, “renal failure”, “anemia” and “pyrexia” to the postmarketing section. The term AGEP was proposed based upon a review of postmarketing cases for daptomycin received by Merck & Co., Inc., and entered into the Merck Adverse Event Reporting and Review System (MARRS) database and also based on identification of this safety signal by the EMA Pharmacovigilance Risk Assessment Committee.

The terms anemia, pyrexia, renal insufficiency, renal failure and acute kidney injury were proposed because these terms were noted in the Company Core Data Sheet (CCDS).

***The Sponsor submitted literature reports to support adding the term AGEF, but did not submit literature reports to support the addition of the other terms and a Pubmed search did not identify any such reports.***

***The reviewer agrees with the Sponsor to update the Adverse Reactions/Postmarketing section of the label and recommends approval of Supplement 53.***



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/s/  
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HALA H SHAMSUDDIN  
05/17/2016

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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<b>Date of This Review:</b>	April 7, 2016
<b>Requesting Office or Division:</b>	Division of Anti-Infective Products (DAIP)
<b>Application Type and Number:</b>	NDA 021572/S- 052
<b>Product Name and Strength:</b>	Cubicin RF (daptomycin) for injection; 500 mg per vial
<b>Product Type:</b>	Single ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. and as agent for Cubist Pharmaceuticals LLC
<b>Submission Date:</b>	February 9, 2016
<b>OSE RCM #:</b>	2016-435
<b>DMEPA Primary Reviewer:</b>	Sevan Kolejian, Pharm. D.
<b>DMEPA Team Leader:</b>	Vicky Borders-Hemphill, PharmD

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## 1 REASON FOR REVIEW

Merck has developed a new formulation of Cubicin RF (daptomycin for injection), intended to overcome limitations and to replace the current formulation of Cubicin (daptomycin for injection). Merck proposes that the new formulation, Cubicin RF, (b) (4)

The Division of Anti-Infective Products (DAIP) requested that we review the container label, carton labeling (see Appendix G), and prescribing information for proposed reformulation for Cubicin RF (daptomycin for injection) to determine if they are acceptable from a medication error perspective.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	N/A
(b) (4) for Cubicin® RF	F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed container labels and carton labeling submitted by Merck on February 9, 2016 are different from the previously marketed labels and labeling. The proposed labels and labeling were revised to reflect the proposed proprietary name, Cubicin RF, reviewed and found acceptable (RCM No: 2015-2312210<sup>1</sup>), and the changes related to reconstituting with sterile water for injection (instead of (b) (4)), room temperature storage of vials, and longer stability post reconstitution both at room temperature and refrigeration.

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<sup>1</sup> Kolejian, S. Proprietary Name Review for Cubicin RF (daptomycin for injection) NDA 021572. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 March 15. OSE RCM No.: 2015-2312210.

Merck plans to replace the currently marketed formulation once the sNDA is approved, but acknowledged that overlap of the two formulations will occur due to the necessity of continuity in supply to customers. Merck has proposed (b) (4)

(b) (4) DMEPA determined that the introduction of Cubicin RF (daptomycin for injection) to the market does not possess safety risk from a medication error perspective.

We performed a risk assessment of the proposed container label, carton labeling, prescribing information and to identify deficiencies that may lead to medication errors and areas for improvement.

Our review of the full prescribing information and proposed (b) (4) In section 4.1, we provide additional recommendations to mitigate confusion and promote the safe use of this product.

Our review of the container label and carton labeling identified areas of improvement to increase clarity, prominence, and readability of important information (see section 4.2).

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the introduction of Cubicin RF (daptomycin for injection) to the market does not possess safety concern from a medication error perspective. However, the proposed labels and labeling can be improved to increase clarity and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

DMEPA concludes that the proposed labeling is vulnerable to confusion which can lead to medication errors. We have revised the *Dosage and Administration* section of the Full Prescribing Information and have provided a detailed summary below for review and consideration by DAIP. We advise the following recommendations be implemented prior to approval:

###### **A. General Comment**

1. Update all labels and labeling to reflect the OPQ determined established name presentation, and package type term where appropriate for consistency.

###### **B. Full Prescribing Information (see Appendix F)**

###### **a. Dosage and Administration Section**

1. In section 2.5, Preparation of CUBICIN RF for Administration, to improve readability, consider adding subheadings 2.6 as follows:

## 2.6 Administration Instructions

### 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 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.

2. in Table 2,

a. Consider further clarifying container type. For example, “Cubicin vial”, “Injection administration syringe”, 50 mL 0.9% sodium chloride IV infusion bag.

b. Revise the statement “Reconstitution: Sterile Water for Injection for immediate dilution with 0.9% sodium chloride (b) (4) injection” to read (b) (4) for clarity.

c. Revise the statement “Reconstitution: Bacteriostatic Water for Injection for immediate dilution with 0.9% sodium chloride (b) (4) injection” to read (b) (4) for clarity.

3. In section 2.6, to prevent reconstitution with 0.9% sodium chloride for injection, consider revising the section to read as follows:

## 2.6 COMPATIBLE INTRAVENOUS SOLUTIONS

(b) (4)

C. (b) (4) (b) (4)

## 4.2 RECOMMENDATIONS FOR THE MERCK

We recommend the following be implemented prior to approval of this supplement NDA 021572- S052:

### A. Container Label

1. Add clarifying statement similar to (b) (4) highlighted on the container label to promote the correct diluent use during the preparation of the product..
2. On the side panel, revise the statement (b) (4) to read “see package insert for storage of reconstituted and further diluted product”.

### B. Carton labeling

1. Relocate and highlight the statement “Reconstitute vial only with sterile water for injection or bacteriostatic water for injection” to the front display panel.
2. See A.2 above.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Cubicin RF that Merck submitted on February 9, 2016.

(b) (4)



## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On March 22 2016, we searched the L: drive and AIMS using the terms, Cubicin to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified two previous reviews<sup>2,3</sup> RCM # 2012-1561 submitted by Hospira for Daptomycin, NDA 203797 and completed on February 21, 2013 and RCM # 2014-2635 for Cubicin (daptomycin) for injection, NDA21572, submitted by Cubist Pharmaceuticals. However, the recommendation in previous review was not relevant to current review.

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<sup>2</sup> Kolejian S. Review of Revised Label and Labeling Memorandum for Cubicin (daptomycin) for injection(NDA 21572; S-048). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 FEB 5. OSE RCM No.: 2014-2635.

<sup>3</sup> Winiarski, A. Label and Labeling Review for daptomycin for injection (NDA 203797). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 FEB 21. OSE RCM No.: 2012-1561.



## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On March 28, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing, ISMP Medication Safety Alert
Search Strategy and Terms	Match Exact Word or Phrase: Cubicin

### D.2 Results

Our search of ISMP newsletters resulted in the following newsletter articles on Cubicin for injection.

ISMP Medication Safety Alert, Vol. 8, No. 22 October 30, 2003, Page 1  
ISMP Medication Safety Alert, Vol. 8, No. 25 December 18, 2003, Page 2  
ISMP Medication Safety Alert, Vol. 9, No. 2 January 29, 2004, Page 4  
ISMP Medication Safety Alert, Vol. 10, No 24 December 1, 2005, Page 2  
ISMP Medication Safety Alert Vol. 14, No. 1 January 15, 2009, Page 2  
ISMP Medication Safety Alert, Vol. 11, No 2 January 26, 2006, page 5

These articles have been identified and assessed previously in our OSE review # 2014-2635<sup>4</sup>. We note that the look-alike /sound-alike potential between daptomycin and dactinomycin has already been identified and the names are on the ISMP List of Confused Names<sup>5</sup>. In addition, mix up between Daptomycin and Dactinomycin have been reviewed previously as a potential signal in OSE review # 2009-586, dated May 26, 2009 and concluded to continue to monitor these wrong drug errors between Daptomycin and Dactinomycin to determine if any additional action is warranted. Our review did not identify any new cases.

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<sup>4</sup> Kolejian S. Label and Labeling Review for Cubicin (NDA 21572; S-048). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 15. 3 p. OSE RCM No.: 2014-2635.

<sup>5</sup> ISMP's List of Confused Names Available at: [https:// http://www.ismp.org/tools/confuseddrugnames.pdf](https://http://www.ismp.org/tools/confuseddrugnames.pdf). Accessed: December 30, 2015.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>6</sup> along with postmarket medication error data, we reviewed the following Cubicin RF labels and labeling submitted by Merck on February 9, 2016.

- Container label
- Carton labeling

### **G.2 Label and Labeling Images**

#### **I. Container label**



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<sup>6</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

II. Carton labeling

(b) (4)



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/s/  
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SEVAN H KOLEJIAN

04/07/2016

BRENDA V BORDERS-HEMPHILL

04/07/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 21-572/S-052**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## **Davi, Christopher**

---

**From:** Davi, Christopher  
**Sent:** Friday, April 22, 2016 8:40 AM  
**To:** Wood, Sandra Lynn (sandra\_wood2@merck.com)  
**Subject:** NDA 21-572/S-052 - Information Request (Pharm/Tox)

Hi Sandi,

Please see the following information request from the Pharm/tox review team as it relates to the above referenced supplement:

### **Questions for the Applicant**

Please confirm the actual Study Day in Week 2 that blood was collected under anesthesia for hematology and clinical chemistry for both repeat-dose, 14-day toxicity studies in rats (Study No: TT #15-1178 and TT #15-1179) that you submitted in your NDA manufacturing supplement. Also, please clarify why the final blood samples for hematology and clinical chemistry analysis were collected under anesthesia during Study Week 2, instead of at time of necropsy?

When you've had a chance to review this on your end, please let me know when we might anticipate a response.

Thank you,

Chris

**J. Christopher Davi, MS**  
**Senior Regulatory Project Manager**  
**Food & Drug Administration (FDA)**  
**Division of Anti-Infective Products**  
**Office of Antimicrobial Products**  
**(301) 796-0702**  
[christopher.davi@fda.hhs.gov](mailto:christopher.davi@fda.hhs.gov)

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/s/  
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JOSEPH C DAVI  
04/22/2016

**Davi, Christopher**

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**From:** Davi, Christopher  
**Sent:** Wednesday, April 20, 2016 11:06 AM  
**To:** Wood, Sandra Lynn (sandra\_wood2@merck.com)  
**Subject:** NDA 21-572/S-052 - Product Quality Information Requests

Hi Sandi,

We continue with our review of the above referenced supplement and have the following product quality information requests at this time:

***A. Microbiology Deficiencies:***

(b) (4)

***For future submissions, for a microbiological in-use study, provide a) actual enumeration data for the quantity of microorganisms spiked into the diluted samples, b) actual concentration of microorganisms recovered at each storage time point and temperature for each diluent, and c) results of a positive control that demonstrates the viability of the organisms over the duration of the test period.***

The Product quality team has requested a response by COB on Wednesday, May 4, 2016. If you have questions, please let me know.



Best regards,

Chris Davi

**J. Christopher Davi, MS**  
**Senior Regulatory Project Manager**  
**Food & Drug Administration (FDA)**  
**Division of Anti-Infective Products**  
**Office of Antimicrobial Products**  
**(301) 796-0702**  
**[christopher.davi@fda.hhs.gov](mailto:christopher.davi@fda.hhs.gov)**

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JOSEPH C DAVI  
04/20/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): <b>Mail: OPDP</b>			FROM: J. Christopher Davi, MS, Senior RPM, DAIP and Alma Davidson, MD, Medical Officer, DAIP	
DATE: February 23, 2016	IND NO.: N/A	NDA NO. 21-572/S-052	TYPE OF DOCUMENT: Prior Approval CMC Supplement	DATE OF DOCUMENT: February 9, 2016
NAME OF DRUG: Cubicin (daptomycin for injection)	PRIORITY CONSIDERATION: N/A		CLASSIFICATION OF DRUG: Parenteral Antibiotic	DESIRED COMPLETION DATE: April 15, 2016
NAME OF FIRM: Merck Sharpe & Dohme, Inc., (agent for Cubist Pharmaceuticals, L.L.C.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): (b) (4)				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Merck Sharp & Dohme Corp. (b) (4)				
SIGNATURE OF REQUESTER: J. Christopher Davi, MS, Senior RPM, DAIP			METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

06/18/2013

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JOSEPH C DAVI  
02/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): <b>Mail: OSE</b>			FROM: J. Christopher Davi, MS, Senior Regulatory Project Manager, DAIP and Alma Davidson, MD, Clinical Reviewer, DAIP	
DATE: February 23, 2016	IND NO.: N/A	NDA NO. 21-572/S-052	TYPE OF DOCUMENT: CMC Manufacturing Supplement (Prior Approval)	DATE OF DOCUMENT: February 9, 2016
NAME OF DRUG: Cubicin (daptomycin for injection)	PRIORITY CONSIDERATION: N/A		CLASSIFICATION OF DRUG: Parenteral Antibiotic	DESIRED COMPLETION DATE: April 15, 2016
NAME OF FIRM: Merck Sharp and Dohme, Inc., (Agent for Cubist Pharmaceuticals, L.L.C.)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
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IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proposed carton/container labels for this CMC supplement. A new modifier "RF" is being added to the Cubicin name to denote a new formulation. Is this sufficient to differentiate between the 2 formulations and/or are there any other concerns? The proposed carton and containers can be accessed in DARRTS under NDA 21-572/S-052 as SDN 625.				
SIGNATURE OF REQUESTER: J. Christopher Davi, MS, Senior Regulatory Project Manager (301) 796-0702			METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

06/18/2013

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JOSEPH C DAVI  
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