PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PRCUBICIN®/CUBICIN® RF
(Daptomycin for Injection)

Lyophilized Powder for Solution, For Intravenous Use Only

10 mL vial, 500 mg/vial

Antibacterial Agent

Cubist Pharmaceuticals LLC
Weystrasse 20
6000 Lucerne 6
Lucerne, Switzerland

Imported and Distributed by:
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Mississauga ON
L5N 0E8

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Table of Contents

[PR]CUBICIN®/CUBICIN® RF

(Daptomycin for Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	Lyophilized Powder for Solution / 10 mL vial, 500 mg/vial	**CUBICIN®** Sodium hydroxide **CUBICIN® RF** Sodium hydroxide and sucrose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CUBICIN®/CUBICIN® RF (daptomycin for injection) is indicated for the following infections in adults:

Complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes* and *Streptococcus agalactiae*.

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative and/or anaerobic organisms. Skin and soft tissues infections are considered complicated when they involve deeper skin structures, such as fascia or muscle layers, require significant surgical intervention or arise in the presence of significant co-morbidity.

***Staphylococcus aureus* bloodstream infections (bacteremia) including those with right-sided *Staphylococcus aureus* infective endocarditis (native valve)** caused by methicillin-susceptible and methicillin-resistant strains.

Patients with prosthetic valves, meningitis, known osteomyelitis, polymicrobial bloodstream infections or with intravascular foreign material not planned for removal within 4 days of dosing (except vascular stents in place for > 6 months or permanent pacemakers) were **not** enrolled in clinical trials.

The efficacy of **CUBICIN®/CUBICIN® RF** in patients with left-sided infective endocarditis due to *Staphylococcus aureus* has **not** been demonstrated. The clinical trial of daptomycin in patients with *Staphylococcus aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor.

Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative and/or anaerobic organisms.

CUBICIN®/CUBICIN® RF is **not** indicated for the treatment of pneumonia.

Patients with persisting or relapsing *Staphylococcus aureus* infection or poor clinical response should have repeat blood cultures. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **CUBICIN®/CUBICIN® RF** and other antibacterial drugs, **CUBICIN®/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 are available, they 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.

Pediatrics (<18 years of age):

CUBICIN®/CUBICIN® RF is indicated for the following infections in pediatric patients (aged 1 to 17 years):

Complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes* and *Streptococcus agalactiae*.

***Staphylococcus aureus* bloodstream infections (bacteremia)** caused by methicillin-susceptible and methicillin-resistant strains.

The safety and effectiveness of **CUBICIN®/CUBICIN® RF** in the treatment of cSSSI and *S. aureus* bloodstream infections (bacteremia) have been established in the age groups 1 to 17 years of age. Use of **CUBICIN®/CUBICIN® RF** in these age groups is supported by evidence from adequate and well-controlled studies in adults, with additional data from pharmacokinetic (PK) studies in pediatric patients, and from safety, efficacy and PK studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections.

Safety and effectiveness in pediatric patients below the age of one year have not been established. **CUBICIN®/CUBICIN® RF** is not recommended in pediatric patients younger than one year of age due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) observed in neonatal dogs.

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

CUBICIN®/CUBICIN® RF has not been studied in pediatric patients with other bacterial infections.

CONTRAINDICATIONS

CUBICIN®/CUBICIN® RF (daptomycin for injection) is contraindicated in patients with known hypersensitivity to daptomycin.

WARNINGS AND PRECAUTIONS

General

There are differences in diluents recommended for reconstitution for **CUBICIN®** and **CUBICIN® RF**. **CUBICIN®** should be reconstituted with 0.9% sodium chloride for injection, USP (see **Reconstitution**). **CUBICIN® RF** must be reconstituted only with either Sterile Water for Injection or Bacteriostatic Water for Injection. (see **Reconstitution**)

CUBICIN®/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 (see **Reconstitution**).

CUBICIN®/CUBICIN® RF is inactive against Gram-negative bacteria.

Because daptomycin activity is inhibited in the presence of pulmonary surfactant, **CUBICIN®/CUBICIN® RF** is **not** indicated for use in pneumonia.

The safety and efficacy of **CUBICIN®/CUBICIN® RF** has **not** been established in patients with co-morbidities of meningitis, musculopathies, neuropathies or severe renal impairment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Tubulointerstitial Nephritis (TIN)

DRESS and TIN have been reported in post-marketing experience with daptomycin. Patients who develop fever, skin rash, peripheral eosinophilia and/or new or worsening renal impairment or other organ impairment while receiving **CUBICIN®/CUBICIN® RF** should undergo medical evaluation. If DRESS and/or TIN are suspected, **CUBICIN®/CUBICIN® RF** should be discontinued promptly and appropriate treatment instituted (see **Renal**).

Immune System

Hypersensitivity

Anaphylaxis and hypersensitivity reactions (including angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema and pulmonary eosinophilia) have been reported with **CUBICIN®** use. If an allergic reaction occurs, administration of **CUBICIN®/CUBICIN® RF** should be discontinued and appropriate therapy should be initiated.

Persisting or Relapsing *Staphylococcus aureus* Infection

Patients with persisting or relapsing *Staphylococcus aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *Staphylococcus aureus,* MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation 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 antibiotic regimen may be required.

In the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, failure of treatment due to persisting or relapsing *Staphylococcus aureus* infections was assessed in 19/120 (15.8%) **CUBICIN®**-treated patients [12 with methicillin-resistant *Staphylococcus aureus* (MRSA) and 7 with methicillin-susceptible *Staphylococcus aureus* (MSSA)] and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 **CUBICIN®**-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) on or following therapy. Most patients who failed due to persisting or relapsing *Staphylococcus aureus* infection had deep-seated infection and did not receive necessary surgical intervention.

Musculoskeletal

Myopathy and Creatine Phosphokinase (CPK)

Myopathy [muscular pains, weakness, and/or rhabdomyolysis (with or without acute renal failure)] associated with creatine phosphokinase (CPK) elevations has been observed with the use of daptomycin in human and animal studies and during post-marketing use (see **ADVERSE REACTIONS, DETAILED PHARMACOLOGY** and **TOXICOLOGY**).

Therefore, in patients receiving **CUBICIN®/CUBICIN® RF** it is recommended that:

- Patients should be monitored regularly for any signs and symptoms that might represent myopathy including muscle pain or weakness, particularly in the distal extremities.
- Any patient who develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days.
- Plasma CPK levels should be measured at baseline and at least once weekly during therapy in all patients.

- Patients who develop unexplained elevations in CPK should be monitored more frequently than once weekly.
- Consideration should be given prior to initiation of **CUBICIN®/CUBICIN® RF** therapy in patients with increased baseline CPK as these patients may be at increased risk of further increases of CPK during **CUBICIN®/CUBICIN® RF** therapy. If **CUBICIN®/CUBICIN® RF** is given, these patients should be monitored more frequently than once weekly.
- CPK should be measured more frequently than once weekly in patients who are at higher risk of developing myopathy. These patients include but are not limited to those with renal impairment, and those who recently received or are currently taking other medications known to be associated with myopathy (e.g., HMG-CoA reductase inhibitors).

CUBICIN®/CUBICIN® RF should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation > 1000 U/L (approximately 5 times ULN), or in patients without reported symptoms who have marked elevations in CPK (≥ 10 times ULN). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving **CUBICIN®/CUBICIN® RF**.

In adult Phase 3 complicated skin and skin structure infection trials (cSSSI) of **CUBICIN®,** at a dose of 4 mg/kg, elevations in serum CPK were reported as clinical adverse events in 15/534 (2.8%) **CUBICIN®**-treated patients, compared to 10/558 (1.8%) comparator-treated patients.

In the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, at a dose of 6 mg/kg, elevations in CPK were reported as clinical adverse events in 8/120 (6.7%) of **CUBICIN®**- treated patients, compared to 1/116 (< 1%) of the comparator-treated patients. There were a total of 11 patients who experienced CPK elevations to above 500 U/L (2.5 times ULN). Of these 11 patients, 5 had recent prior or concomitant treatment with an HMG-CoA reductase inhibitor. Three (2.6%) **CUBICIN®**-treated patients, including 1 with trauma associated with heroin overdose, 1 with spinal cord compression and 1 with concomitant HMG-CoA reductase inhibitor, had an elevation in CPK > 500 U/L with associated musculoskeletal symptoms. None of the patients in the comparator group had an elevation of CPK > 500 U/L with associated musculoskeletal symptoms.

In a Phase 1 study in adult healthy volunteers examining doses up to 12 mg/kg q24h of **CUBICIN®** for 14 days, no skeletal muscle effects or CPK elevations were observed.

Skeletal muscle effects associated with **CUBICIN®** were observed in animals (see **DETAILED PHARMACOLOGY, Animal Pharmacology and TOXICOLOGY**).

Neurologic

Neuropathy
Cases of peripheral neuropathy have been reported during post-marketing therapy with **CUBICIN®** (see **ADVERSE REACTIONS**).

Patients should be monitored for signs and symptoms of neuropathy during therapy with **CUBICIN®/CUBICIN® RF**.

Direct effects on the central nervous system have not been investigated.

In a small number of patients in adult Phase 1 and Phase 2 studies at doses up to 6 mg/kg, administration of **CUBICIN®** was associated with decreases in nerve conduction velocity and with adverse events (e.g., paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. In the *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, a total of 11/120 (9.2%) **CUBICIN®**-treated patients had treatment-emergent adverse events related to the peripheral nervous system. All of the events were classified as mild to moderate in severity; most were of short duration and resolved during continued treatment with **CUBICIN®** or were likely due to an alternative etiology.

In a Phase 1 study in adult healthy volunteers examining doses up to 12 mg/kg q24h of **CUBICIN®** for 14 days, no evidence of peripheral nerve conduction deficits or symptoms of peripheral neuropathy were observed.

In adult animals, effects of **CUBICIN®** on peripheral nerve were observed. In juvenile dogs, peripheral and spinal cord nerve effects were noted.

Pediatric patients younger than 12 months should not be given **CUBICIN®/CUBICIN® RF** due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs (see **INDICATIONS AND CLINICAL USE**, **Pediatrics**, **DETAILED PHARMACOLOGY, Animal Pharmacology** and **TOXICOLOGY**).

Renal

The safety and efficacy of **CUBICIN®/CUBICIN® RF** in patients with severe renal impairment (creatinine clearance < 30 mL/min) have not been established. **CUBICIN®/CUBICIN® RF** should only be considered for use in patients with severe renal impairment when the expected clinical benefit outweighs the potential risk and there are no further available therapeutic options. In these patients, a dose adjustment is required (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**). Response to treatment, renal function and creatine phosphokinase (CPK) should be closely monitored.

No dose adjustment is required in adult patients with mild to moderate renal impairment (creatinine clearance ≥30 mL/min). However, due to limited clinical experience, response to treatment, renal function and creatine phosphokinase (CPK) should be closely monitored in all patients with some degree of renal impairment (creatinine clearance < 80 mL/min).

Consideration should be given to monitoring renal function in adult patients treated with **CUBICIN®/CUBICIN® RF**. Renal impairment has been reported during treatment with **CUBICIN®** although the relationship to daptomycin remains unclear (see **ADVERSE REACTIONS**).

Caution is advised prior to commencing therapy with **CUBICIN®/CUBICIN® RF** in adult patients who already have some degree of renal impairment (creatinine clearance < 80 mL/min).

Regular monitoring of renal function is advised during the concomitant administration of potentially nephrotoxic agents, regardless of the patient's underlying renal function.

In the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, at a dose of **CUBICIN®** 6 mg/kg/day, a lower clinical success rate and an increase in serious adverse events were seen in patients with moderately impaired renal function (creatinine clearance 30 to < 50 mL/min).

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

If DRESS and/or TIN are suspected, **CUBICIN®/CUBICIN® RF** should be discontinued promptly and appropriate treatment instituted.

Carcinogenesis and Mutagenesis

Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was found in a battery of genotoxicity tests (see **TOXICOLOGY**).

Gastrointestinal

***Clostridium difficile*-Associated Disease**
Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including **CUBICIN®**. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Respiratory

Community-Acquired Pneumonia

In adult Phase 3 studies of community-acquired pneumonia, 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 community-acquired pneumonia in patients experiencing these adverse events (see **INDICATIONS AND CLINICAL USE**). Daptomycin's activity *in vitro* is inhibited by the presence of pulmonary surfactant.

Eosinophilic Pneumonia

Eosinophilic pneumonia has been reported in patients receiving **CUBICIN®**. In reported cases associated with **CUBICIN®**, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organizing pneumonia. 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®/CUBICIN® RF** should undergo prompt medical evaluation, and **CUBICIN®/CUBICIN® RF** should be discontinued immediately. Treatment with systemic steroids is recommended.

Susceptibility/Resistance

Development of Drug-Resistant Bacteria

The use of antibiotics may promote the overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

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

Special Populations

Pregnant Women: No clinical studies have been performed in pregnant women. **CUBICIN®/CUBICIN® RF** should not be used during pregnancy unless clearly necessary and the benefits to the mother outweigh the potential risks to the fetus. Animal studies have not demonstrated harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Nursing Women: Data from a single case indicated that daptomycin is present in human milk. Daptomycin is poorly bioavailable orally. Due to limited data, breastfeeding should be discontinued during treatment with **CUBICIN®/CUBICIN® RF**.

Pediatrics (<18 years of age): The safety and effectiveness of **CUBICIN®/CUBICIN® RF** in the treatment of cSSSI and *S. aureus* bloodstream infections (bacteremia) have been established

in the age groups 1 to 17 years of age. Use of **CUBICIN®/CUBICIN® RF** in these age groups is supported by evidence from adequate and well-controlled studies in adults, with additional data from pharmacokinetic (PK) studies in pediatric patients, and from safety, efficacy and PK studies in pediatric patients with cSSSI and *S. aureus* bloodstream infections.

Pediatric patients younger than 12 months should not be given **CUBICIN®/CUBICIN® RF** due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs (see **INDICATIONS AND CLINICAL USE, Pediatrics, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics, DETAILED PHARMACOLOGY, Animal Pharmacology**, and **TOXICOLOGY**).

Geriatrics (≥ 65 years of age): In the adult Phase 3 clinical studies, lower clinical success rates were seen in patients ≥ 65 years of age compared to those < 65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥ 65 years old than in patients < 65 years of age. Of the 534 patients treated with **CUBICIN®** in Phase 3 controlled clinical trials of complicated skin and skin structure infection (cSSSI), 27.0% were 65 years of age or older and 12.4% were 75 years or older. Of the 120 patients treated with **CUBICIN®** in the Phase 3 *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) controlled clinical trial, 25.0% were 65 years of age or older and 15.8% were 75 years or older.

Monitoring and Laboratory Tests

Creatine Phosphokinase (CPK)

Patients should be monitored regularly for any signs and symptoms that might represent myopathy including muscle pain or weakness, particularly in the distal extremities. Any patient who develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days.

Plasma CPK levels should be measured at baseline and at least once weekly during **CUBICIN®/CUBICIN® RF** therapy in all patients. Patients who develop unexplained elevations in CPK should be monitored more frequently than once weekly. Consideration should be given prior to initiation of **CUBICIN®/CUBICIN® RF** therapy in patients with increased baseline CPK as these patients may be at increased risk of further increases of CPK during **CUBICIN®/CUBICIN® RF** therapy. If **CUBICIN®/CUBICIN® RF** is given, these patients should be monitored more frequently than once weekly.

CPK should be measured more frequently than once weekly in patients who are at higher risk of developing myopathy. These patients include but are not limited to those with renal impairment, and those who recently received or are currently taking other medications known to be associated with myopathy (e.g., HMG-CoA reductase inhibitors) [see **WARNINGS AND PRECAUTIONS, Musculoskeletal, Myopathy and Creatine Phosphokinase (CPK)**].

Renal

Consideration should be given to monitoring renal function in patients treated with **CUBICIN®/CUBICIN® RF**.

In patients with renal impairment (creatinine clearance < 80 mL/min) response to treatment, renal function and creatine phosphokinase (CPK) should be closely monitored.

The safety and efficacy of **CUBICIN®/CUBICIN® RF** in patients with severe renal impairment (creatinine clearance < 30 mL/min) have not been established.

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

Neuropathy
Patients should be monitored for signs and symptoms of neuropathy during therapy with **CUBICIN®/CUBICIN® RF**.

Warfarin
As experience with the concomitant administration of **CUBICIN®/CUBICIN® RF** and warfarin is limited, anticoagulant activity in patients receiving **CUBICIN®/CUBICIN® RF** and warfarin should be monitored for the first several days after initiating therapy with **CUBICIN®/CUBICIN® RF**.

ADVERSE REACTIONS

CUBICIN® RF has not been studied in clinical trials. The treatment-emergent adverse event profile of **CUBICIN® RF** is expected to be similar to that of **CUBICIN®**. The active ingredient in **CUBICIN® RF** (daptomycin) is the same as that in **CUBICIN®**.

Adverse Drug Reaction Overview

Adults
Clinical studies enrolled 1,667 patients treated with **CUBICIN®** and 1,319 treated with comparator.

Overall, at least one adverse event was reported by 51.3% of **CUBICIN®**-treated subjects and by 52.5% of comparator-treated subjects in two adult Phase 3, double-blind, controlled complicated skin and skin structure infection (cSSSI) trials. In the randomized, comparative, open-label adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, the majority of patients experienced at least one treatment emergent adverse event during the study, including 95.8% and 94.8% of patients in the **CUBICIN®** and comparator groups, respectively. The majority of adverse events reported in the adult Phase 1, 2 and 3 clinical studies were described as mild or moderate in intensity.

In the adult cSSSI trials, **CUBICIN®** was discontinued in 15/534 (2.8%) patients due to an adverse event while comparator was discontinued in 17/558 (3.0%) patients. In the adult SAB/SAIE trial, **CUBICIN®** was discontinued in 20/120 (16.7%) patients due to an adverse event while comparator was discontinued in 21/116 (18.1%) patients.

The most frequent adverse events observed in the adult cSSSI trials were: constipation, nausea, injection site reactions, headache and diarrhea. In the SAB/SAIE trial, the most frequent adverse events were: diarrhea, vomiting, constipation and nausea.

The safety data for the administration of daptomycin via 2-minute intravenous injection are derived from two pharmacokinetic studies in adult healthy volunteers. Based on these study results, both methods of daptomycin administration, the 2-minute intravenous injection and the 30-minute intravenous infusion, had a similar safety and tolerability profile. There was no relevant difference in local tolerability or in the nature and frequency of adverse reactions.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Complicated Skin and Skin Structure Infection (cSSSI) Trials in Adults

Most Common Clinical Trial Adverse Drug Reactions in Two Adult Phase 3 cSSSI Studies

The rates of the most common treatment emergent adverse events irrespective of causality, organized by body system, observed in the cSSSI clinical trials are displayed in Table 1.

Table 1. Incidence (%) of Treatment Emergent Adverse Events Irrespective of Causality that Occurred in ≥ 2% of Patients in Either CUBICIN® or Comparator Treatment Groups in the Adult Phase 3 cSSSI Studies[1] (Population: Safety[2])

Adverse Event	CUBICIN® 4 mg/kg (N=534)	Comparator[3] (N=558)
Gastrointestinal Disorders		
Constipation	6.2%	6.8%
Nausea	5.8%	9.5%
Diarrhea	5.2%	4.3%
Vomiting	3.2%	3.8%
Dyspepsia	0.9%	2.5%
General Disorders		
Injection site reactions	5.8%	7.7%
Fever	1.9%	2.5%
Nervous System Disorders		
Headache	5.4%	5.4%
Insomnia	4.5%	5.4%
Dizziness	2.2%	2.0%
Skin/Subcutaneous Disorders		
Rash	4.3%	3.8%
Pruritus	2.8%	3.8%
Diagnostic Investigations		
Abnormal liver function tests	3.0%	1.6%
Elevated CPK	2.8%	1.8%
Infections		
Fungal infections	2.6%	3.2%
Urinary tract infections	2.4%	0.5%
Vascular Disorders		
Hypotension	2.4%	1.4%
Hypertension	1.1%	2.0%
Renal/Urinary Disorders		
Renal failure	2.2%	2.7%
Blood/Lymphatic Disorders		
Anemia	2.1%	2.3%
Respiratory Disorders		
Dyspnea	2.1%	1.6%
Musculoskeletal Disorders		
Limb pain	1.5%	2.0%
Arthralgia	0.9%	2.2%

[1] This table includes Adverse Events from both cSSSI Phase 3 trials. The first trial was conducted in the U.S. and South Africa, the second in Europe, South Africa, Australia and Israel

[2] Safety population includes all subjects who received at least one dose of **CUBICIN®** or comparator according to treatment actually received during the trials

[3] Comparators included vancomycin (1 g IV q12h), which was used in patients with known or suspected penicillin allergy or with methicillin-resistant *Staphylococcus aureus* infection, and anti-staphylococcal semi-synthetic penicillin (i.e. nafcillin, oxacillin, cloxacillin, flucloxacillin 4-12 g/day IV), which were selected based on the standard therapy in each country.

Additional adverse events that occurred in < 1 to 2% of patients in either **CUBICIN®** (4 mg/kg) or comparator treatment groups in the adult cSSSI studies are as follows: edema, cellulitis, hypoglycemia, elevated alkaline phosphatase, cough, back pain, abdominal pain, hypokalemia, hyperglycemia, decreased appetite, anxiety, chest pain, sore throat, cardiac failure, confusion and *Candida* infections. These events occurred at rates ranging from 0.2 to 1.7% in **CUBICIN®**-treated patients and at rates of 0.4 to 1.8% in comparator-treated patients.

The most common possibly or probably drug-related treatment emergent adverse events organized by body system, observed in the adult cSSSI trials are displayed in Table 2.

Table 2. Incidence (%) of Possibly or Probably Drug-Related Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients in Either CUBICIN® or Comparator Treatment Groups in the Adult Phase 3 cSSSI Studies (Population: Safety)

Adverse Event	CUBICIN® 4 mg/kg (N=534)	Comparator (N=558)
Gastrointestinal Disorders		
Nausea	2.2%	3.4%
Investigations		
Blood creatine phosphokinase increased	2.1%	1.4%

Less Common Clinical Trial Adverse Drug Reactions (<1%) in Two Adult Phase 3 cSSSI Studies

Additional drug-related adverse events (possibly or probably related) that occurred in < 1% of patients receiving **CUBICIN®** in the complicated skin and skin structure infection (cSSSI) trials are as follows:

Body as a Whole: fatigue, weakness, rigors, discomfort, tremor, 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, flatulence, stomatitis, jaundice, increased serum lactate dehydrogenase
Metabolic/Nutritional System: hypomagnesemia, increased serum bicarbonate, electrolyte disturbance
Musculoskeletal System: myalgia, muscle cramps, muscle weakness, osteomyelitis
Nervous System: vertigo, mental status change, paraesthesia
Special Senses: taste disturbance, eye irritation
Reproductive System and Breast Disorders: vaginitis

Abnormal Hematologic and Clinical Chemistry Findings in Two Adult Phase 3 cSSSI Studies

In the two adult Phase 3 comparator-controlled complicated skin and skin structure (cSSSI) studies, there was no clinically or statistically significant difference ($p<0.05$) in the incidence of

creatine phosphokinase (CPK) elevations between patients treated with **CUBICIN®** and those treated with comparator. CPK elevations in both groups were generally related to medical conditions, for example, skin and skin structure infection, surgical procedures, or intramuscular injections; and were not associated with muscle symptoms.

Table 3 summarizes the CPK shifts from Baseline through End of Treatment in the adult cSSSI trials.

Table 3. Incidence (%) of Creatine Phosphokinase (CPK) Elevations From Baseline Through End of Treatment in either CUBICIN® or Comparator Treatment Groups in Adult Phase 3 cSSSI Studies

Change	All Patients				Patients with Normal CPK at Baseline			
	CUBICIN® (N=430)		Comparator (N=459)		CUBICIN® (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 >1x ULN*	9.3%	40	8.9%	41	8.8%	33	8.9%	35
>2x ULN	4.9%	21	4.8%	22	3.7%	14	3.1%	12
>4x ULN	1.4%	6	1.5%	7	1.1%	4	1.0%	4
>5x ULN	1.4%	6	0.4%	2	1.1%	4	0.0%	0
>10x ULN	0.5%	2	0.2%	1	0.2%	1	0.0%	0

* ULN (Upper Limit of Normal) is defined as 200 U/L.

In the adult cSSSI studies, 0.2% of patients treated with **CUBICIN®** had symptoms of muscle pain or weakness associated with CPK elevations to greater than 4 times the upper limit of normal. The symptoms resolved within 3 days and CPK returned to normal within 7 to 10 days after discontinuing treatment [see **WARNINGS AND PRECAUTIONS, Musculoskeletal, Myopathy and Creatine Phosphokinase (CPK)**].

***Staphylococcus aureus* Bacteremia/*Staphylococcus aureus* Infective Endocarditis (SAB/SAIE) Trial in Adults**

Most Common Clinical Trial Adverse Drug Reactions in the Adult SAB/SAIE Trial

The rates of the most common treatment emergent adverse events irrespective of causality and organized by body system observed in the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial are displayed in Table 4.

Table 4. Incidence (%) of Treatment Emergent Adverse Events Irrespective of Causality that Occurred in ≥ 5% of Patients in CUBICIN® or Comparator Treatment Groups in the Adult SAB/SAIE Study (Population: Safety[a])

Adverse Events	CUBICIN® 6 mg/kg (N=120)	Comparator[b] (N=116)
Infections and Infestations	**54.2%**	**48.3%**
Urinary tract infection NOS[c]	6.7%	9.5%
Osteomyelitis NOS	5.8%	6.0%
Sepsis NOS	5.0%	2.6%
Bacteremia	5.0%	0%
Pneumonia NOS	3.3%	7.8%
Gastrointestinal Disorders	**50.0%**	**58.6%**
Diarrhea NOS	11.7%	18.1%
Vomiting NOS	11.7%	12.9%
Constipation	10.8%	12.1%
Nausea	10.0%	19.8%
Abdominal pain NOS	5.8%	3.4%
Dyspepsia	4.2%	6.9%
Loose stools	4.2%	5.2%
Gastrointestinal hemorrhage NOS	1.7%	5.2%
General Disorders and Administration Site Conditions	**44.2%**	**59.5%**
Edema peripheral	6.7%	13.8%
Pyrexia	6.7%	8.6%
Chest pain	6.7%	6.0%
Edema NOS	6.7%	4.3%
Asthenia	5.0%	5.2%
Injection site erythema	2.5%	6.0%
Respiratory, Thoracic and Mediastinal Disorders	**31.7%**	**37.1%**
Pharyngolaryngeal pain	8.3%	1.7%
Pleural effusion	5.8%	6.9%
Cough	3.3%	6.0%
Dyspnea	3.3%	5.2%
Skin and Subcutaneous Tissue Disorders	**30.0%**	**34.5%**
Rash NOS	6.7%	8.6%
Pruritus	5.8%	5.2%
Erythema	5.0%	5.2%
Sweating increased	5.0%	0%
Musculoskeletal and Connective Tissue Disorders	**29.2%**	**36.2%**
Pain in extremity	9.2%	9.5%
Back pain	6.7%	8.6%
Arthralgia	3.3%	11.2%
Psychiatric Disorders	**29.2%**	**24.1%**
Insomnia	9.2%	6.9%
Anxiety	5.0%	5.2%
Nervous System Disorders	**26.7%**	**27.6%**
Headache	6.7%	10.3%
Dizziness	5.8%	6.0%
Investigations	**25.0%**	**28.4%**
Blood creatine phosphokinase increased	6.7%	<1%
Blood and Lymphatic System Disorders	**24.2%**	**20.7%**

Adverse Events	CUBICIN® 6 mg/kg (N=120)	Comparator[b] (N=116)
Anemia NOS	12.5%	15.5%
Metabolism and Nutrition Disorders	**21.7%**	**32.8%**
Hypokalemia	9.2%	12.9%
Hyperkalemia	5.0%	8.6%
Vascular Disorders	**17.5%**	**17.2%**
Hypertension NOS	5.8%	2.6%
Hypotension NOS	5.0%	7.8%
Injury, Poisoning and Procedural Complications	**15.8%**	**15.5%**
Renal and Urinary Disorders	**15.0%**	**22.4%**
Renal failure NOS	3.3%	9.5%
Renal failure acute	3.3%	6.0%
Cardiac Disorders	**11.7%**	**15.5%**
Reproductive System and Breast Disorders	**5.0%**	**6.9%**
Eye Disorders	**4.2%**	**8.6%**

[a] Safety population includes all subjects who received at least one dose of **CUBICIN**® or comparator according to treatment actually received during the trials

[b] Comparator: vancomycin (1 g IV q12h), which was used in patients with known or suspected penicillin allergy or with methicillin-resistant *Staphylococcus aureus,* or anti-staphylococcal semi-synthetic penicillins (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), which were selected based on the standard therapy in each country, each with initial synergistic gentamicin.

[c] NOS: Not Otherwise Specified

Note: p-values by body system were as follows: infections p=0.435; gastrointestinal p=0.194; general and administration site p=0.020; respiratory, thoracic, mediastinal p=0.412; skin and subcutaneous tissue p=0.488; musculoskeletal and connective tissue p=0.269; psychiatric p=0.462; nervous system p=0.885; investigations p=0.560; blood and lymphatic system p=0.537; metabolism and nutrition p=0.059; vascular p>0.999; injury, poisoning p>0.999; renal and urinary p=0.181; cardiac disorders p=0.449; reproductive system p=0.591; eye disorders p=0.189

The most common possibly or probably drug-related treatment emergent adverse events, organized by body system, observed in the adult SAB/SAIE trial are displayed in Table 5.

Table 5. Incidence (%) of Possibly or Probably Drug-Related Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients in Either CUBICIN® or Comparator Treatment Groups in the Adult Phase 3 SAB/SAIE Study (Population: Safety)

Adverse Events	CUBICIN® 6 mg/kg (N=120)	Comparator (N=116)
Investigations		
Blood creatine phosphokinase (CPK) increased	5.0%	0%
Blood phosphorus increased	2.5%	<1%
Blood alkaline phosphatase increased	1.7%	0%
International normalized ratio increased	1.7%	0%
Liver function test abnormal	1.7%	<1%
Blood creatinine increased	0%	2.6%
Gastrointestinal Disorders		
Loose stools	3.3%	1.7%
Dyspepsia	2.5%	<1%
Diarrhea NOS	1.7%	9.5%
Nausea	1.7%	5.2%
Vomiting	<1%	1.7%
Skin and Subcutaneous Tissue Disorders		
Rash NOS	2.5%	2.6%
Renal and Urinary Disorders		
Renal failure NOS	1.7%	6.0%
Renal impairment NOS	<1%	1.7%
Renal failure acute	0%	2.6%
Infections and Infestations		
Candidal infection NOS	1.7%	0%
Vaginal candidiasis	1.7%	0%
General Disorders and Administration Site Conditions		
Chest pain	1.7%	0%
Pyrexia	0%	2.6%
Blood and Lymphatic System Disorders		
Eosinophilia	1.7%	0%
Nervous System Disorders		
Dysgeusia	0%	2.6%
Vascular Disorders		
Hypotension NOS	0%	2.6%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	0%	1.7%
Weakness in extremity	1.7%	0%

Less Common Clinical Trial Adverse Drug Reactions in the Adult SAB/SAIE Trial (< 1%)

The following events, not included above in Table 5, were reported as possibly or probably drug-related in the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) **CUBICIN®**-treated group:

Blood and Lymphatic System Disorders: lymphadenopathy, thrombocythemia, 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: fungemia, oral candidiasis, urinary tract infection fungal
Investigations: 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: heat rash, pruritus generalized, rash vesicular

Abnormal Hematologic and Clinical Chemistry Findings in the Adult SAB/SAIE Trial

In the adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial, a total of 11 **CUBICIN®** patients (9.2%) had treatment-emergent elevations in creatine phosphokinase (CPK) to > 500 U/L, including 4 patients with elevations > 10X ULN. Three of these 11 patients had CPK levels return to the normal range during continued **CUBICIN®** treatment, 6 had values return to the normal range during follow-up, 1 had values returning toward baseline at the last assessment, and 1 did not have follow-up values reported. Six of the 11 patients with treatment-emergent CPK elevations > 500 U/L had medical or surgical reasons for the elevated CPK. Three patients discontinued **CUBICIN®** due to CPK elevation. Table 6 presents the incidence of CPK elevations from baseline in all patients and in patients with normal CPK levels through the end of treatment with **CUBICIN®** and comparator in the adult SAB/SAIE trial.

Table 6. Incidence (%) of Creatine Phosphokinase (CPK) Elevations from Baseline through End of Treatment in either CUBICIN® or Comparator Treatment Groups in the Adult SAB/SAIE Study

Change	All Patients				Patients with Normal CPK at Baseline			
	CUBICIN® (N=116)		Comparator (N=111)		CUBICIN® (N=92)		Comparator (N=96)	
	%	N	%	N	%	N	%	N
No Increase	75.9	88	87.4	97	75.0	69	87.5	84
Maximum Value > 1X ULN*	24.1	28	12.6	14	25.0	23	12.5	12
> 2X ULN	13.8	16	6.3	7	12.0	11	5.2	5
> 4X ULN	8.6	10	0.9	1	7.6	7	0.0	0
> 5X ULN	6.9	8	0.9	1	5.4	5	0.0	0
> 10X ULN	3.4	4	0.9	1	2.2	2	0.0	0

* ULN (Upper Limit of Normal) is laboratory specific.
Note: CPK evaluations through 3 days post-treatment are included in the analysis.

There was more renal dysfunction in comparator-treated patients than in **CUBICIN®**-treated patients. The incidence of decreased renal function, defined as the proportion of patients with a

creatinine clearance level < 50 mL/min if baseline clearance was ≥ 50 mL/min or with a decrease of ≥ 10 mL/min if baseline clearance was < 50 mL/min, is shown in Table 7.

Table 7. Incidence of Decreased Renal Function Based on Creatinine Clearance Levels

Study Interval	CUBICIN® 6 mg/kg (N=120) n/N (%)	Comparator[a] (N=116) n/N (%)
Days 2 to 4	2/96 (2.1%)	6/90 (6.7%)
Days 2 to 7	6/115 (5.2%)	16/113 (14.2%)
Days 2 to End of Study	13/118 (11.0%)	30/114 (26.3%)

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

Complicated Skin and Skin Structure Infection (cSSSI) Trial in Pediatric Patients

The safety of **CUBICIN®** was evaluated in one cSSSI clinical trial which included 256 pediatric patients (1 to 17 years of age) treated with intravenous **CUBICIN®** and 133 patients treated with comparator agents. Patients were given age-dependent doses once daily for a treatment period of up to 14 days (median treatment period was 3 days). The doses given by age group were as follows: 10 mg/kg for 1 to <2 years, 9 mg/kg for 2 to 6 years, 7 mg/kg for 7 to 11 years and 5 mg/kg for 12 to 17 years of age. Patients treated with **CUBICIN®** were 51% male, 49% female and 46% Caucasian and 32% Asian.

In the pediatric cSSSI study, **CUBICIN®** was discontinued in 7/256 (2.7%) patients due to an adverse reaction, while comparator was discontinued in 7/133 (5.3%) patients.

Most Common Clinical Trial Adverse Drug Reactions in the Pediatric cSSSI Trial

The rates of the most common adverse events, organized by body system, observed in pediatric patients with cSSSI are displayed in Table 8.

Table 8. Incidence (%) of Adverse Events that Occurred in ≥2% of Pediatric Patients in the CUBICIN® Treatment-Arm and Greater Than or Equal to the Comparator Treatment-Arm in the Pediatric cSSSI Trial

Adverse Events	CUBICIN® (N=256)	Comparator* (N=133)
Gastrointestinal Disorders		
Diarrhea	7.0%	5.3%
Vomiting	2.7%	0.8%
Abdominal Pain	2.0%	0%
General Disorders and Administration Site Conditions		
Pyrexia	3.9%	3.0%
Investigations		
Blood creatine phosphokinase (CPK) increased	5.5%	5.3%
Nervous System Disorders		
Headache	2.7%	2.3%
Skin and Subcutaneous Tissue Disorders		
Pruritus	3.1%	1.5%

*Comparators included intravenous therapy with either vancomycin, clindamycin, or an anti-staphylococcal semi-synthetic penicillin (nafcillin, oxacillin, or cloxacillin)

The safety profile in the clinical trial of cSSSI pediatric patients was similar to that observed in the cSSSI adult trials.

Staphylococcus aureus Bacteremia Trial in Pediatric Patients

The safety of **CUBICIN®** was evaluated in one *S. aureus* bacteremia clinical trial which treated 55 pediatric patients with intravenous **CUBICIN®** and 26 patients with comparator agents. Patients were given age-dependent doses once daily for a treatment period of up to 42 days (mean duration of IV treatment was 12 days). The doses by age group were as follows: 12 mg/kg for 1 to <6 years, 9 mg/kg for 7 to 11 years and 7 mg/kg for 12 to 17 years of age. Patients treated with **CUBICIN®** were 69% male and 31% female. No patients 1 to <2 years of age were enrolled.

In the bacteremia study, **CUBICIN®** was discontinued in 3/55 (5.5%) patients due to an adverse reaction, while comparator was discontinued in 2/26 (7.7%) patients.

Most Common Clinical Trial Adverse Drug Reactions in the Pediatric Bacteremia Trial

The rates of the most common adverse events, organized by body system, observed in pediatric patients with bacteremia are displayed in Table 9.

Table 9. Incidence (%) of Adverse Events that Occurred in ≥5% of Pediatric Patients in the CUBICIN® Treatment-Arm and Greater Than or Equal to the Comparator Treatment-Arm in the Pediatric Bacteremia Trial

Adverse Events	CUBICIN® (N=55)	Comparator* (N=26)
Gastrointestinal Disorders		
Vomiting	10.9%	7.7%
Investigations		
Blood creatine phosphokinase (CPK) increased	7.3%	0%

*Comparators included intravenous therapy with either vancomycin, cefazolin, or an anti-staphylococcal semi-synthetic penicillin (nafcillin, oxacillin, or cloxacillin)

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported with **CUBICIN®** in worldwide post-marketing experience. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established.

Immune System Disorders: anaphylaxis; hypersensitivity reactions, including angioedema, drug reaction with eosinophilia and systemic symptoms (DRESS), pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema and pulmonary eosinophilia.
Infections and Infestations: Clostridium difficile-associated diarrhea.
Investigations: platelet count decreased.
Musculoskeletal Disorders: myoglobin increased; rhabdomyolysis (some reports involved patients treated concurrently with **CUBICIN®** and HMG-CoA reductase inhibitors).
Neurologic Disorders: one case of coma post-anaesthesia/surgery; peripheral neuropathy.
Renal and Urinary Disorders: acute kidney injury; renal failure; renal insufficiency; tubulointerstitial nephritis (TIN).
Respiratory, Thoracic, and Mediastinal Disorders: cough; eosinophilic pneumonia (see **WARNINGS AND PRECAUTIONS, Respiratory, Eosinophilic Pneumonia**); organizing pneumonia.
Skin and Subcutaneous Tissue Disorders: acute generalized exanthematous pustulosis; serious skin reactions, including Stevens-Johnson syndrome and vesiculobullous rash (with or without mucous membrane involvement).

DRUG INTERACTIONS

Overview

There is limited experience regarding concomitant administration of **CUBICIN®/CUBICIN® RF** (daptomycin for injection) with other medicinal products that may trigger myopathy (e.g., HMG-CoA reductase inhibitors). However, some cases of marked rises in creatine phosphokinase (CPK) levels and cases of rhabdomyolysis occurred in adult patients taking one of these medications at the same time as **CUBICIN®**. It is recommended that other medications

associated with myopathy should, if possible, be temporarily discontinued during treatment with **CUBICIN®/CUBICIN® RF** unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CPK levels should be measured more frequently than once weekly and patients should be closely monitored for any signs or symptoms that might represent myopathy.

Daptomycin is primarily cleared by renal filtration and, therefore, plasma levels may be increased during co-administration with medicinal products that reduce renal filtration (e.g., NSAIDs and COX-2 inhibitors). In addition, there is a potential for a pharmacodynamic interaction to occur during co-administration due to additive renal effects. Therefore, caution is advised when **CUBICIN®/CUBICIN® RF** is co-administered with any other medicinal product known to reduce renal filtration.

Drug-Drug Interactions

CUBICIN® RF has not been studied in drug-drug interaction studies. The active ingredient in **CUBICIN® RF** (daptomycin) is the same as that in **CUBICIN®**. Therefore, differences in drug-drug interactions between **CUBICIN®** and **CUBICIN® RF** are not expected.

Drug-drug interaction studies were performed in adults with **CUBICIN®** and other drugs that are likely to either be co-administered or associated with overlapping toxicity as shown in Table 10 .

Table 10. Established or Potential Drug-Drug Interactions with CUBICIN®

Drug Name	Ref	Effect	Clinical comment
Aztreonam	CT	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, the C_{max} and $AUC_{0-\infty}$ of daptomycin were not significantly altered by aztreonam.	No dosage adjustment of **CUBICIN®/CUBICIN® RF** is warranted when **CUBICIN®/CUBICIN® RF** is co-administered with aztreonam.
HMG-CoA Reductase Inhibitors	CT	In 20 healthy adult subjects on a stable daily dose of oral simvastatin 40 mg, administration of **CUBICIN®** 4 mg/kg IV q24h for 14 days (N=10) was not associated with a higher incidence of adverse events than subjects receiving placebo once daily (N=10).	Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. Experience with co-administration of HMG-CoA reductase inhibitors and **CUBICIN®** in patients is limited, therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving **CUBICIN®/ CUBICIN® RF** (see **WARNINGS AND PRECAUTIONS, Musculoskeletal)**.
Probenecid	CT	Concomitant administration of oral probenecid (500 mg four times daily) and a single dose of **CUBICIN®** 4 mg/kg IV did not significantly alter the C_{max} and $AUC_{0-\infty}$ of daptomycin.	No dosage adjustment of **CUBICIN®/CUBICIN® RF** is warranted when **CUBICIN®/ CUBICIN® RF** is co-administered with probenecid.

Drug Name	Ref	Effect	Clinical comment
Tobramycin	CT	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, the mean C_{max} and $AUC_{0-\infty}$ of daptomycin increased 12.7% and 8.7%, respectively, when administered with tobramycin. The mean C_{max} and $AUC_{0-\infty}$ of tobramycin decreased 10.7% and 6.6%, respectively, when administered with **CUBICIN®**. These differences were not statistically significant.	The interaction between **CUBICIN®** and tobramycin with a clinical dose of **CUBICIN®** is unknown. Caution is warranted when **CUBICIN®/ CUBICIN® RF** is co-administered with tobramycin.
	Non-clinical	In rats, mild skeletal muscle degeneration and/or regeneration was observed with 20 mg/kg IV **CUBICIN®** when administered alone. During concurrent administration with tobramycin 10 mg/kg SC b.i.d., mild skeletal muscle changes were observed with 5 mg/kg IV **CUBICIN®**. Tobramycin may have a weak potentiating effect on muscle damage caused by **CUBICIN®**.	
Warfarin	CT	In 16 healthy adult subjects, concomitant administration of **CUBICIN®** 6 mg/kg IV q24h for 5 days followed by a single oral dose of warfarin (25 mg) had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio).	As experience with the concomitant administration of **CUBICIN®** and warfarin is limited, anticoagulant activity in patients receiving **CUBICIN®/CUBICIN® RF** and warfarin should be monitored for the first several days after initiating therapy with **CUBICIN®/CUBICIN® RF**.
Gentamicin	Non-Clinical	An increase in nephrotoxicity was apparent upon combination treatment with daptomycin 30 mg/kg/day IV and a high dose of gentamicin (30 mg/kg/day IM) in dogs. No meaningful difference in nephrotoxicity was observed in animals receiving daptomycin in combination with a more clinically relevant dose of gentamicin (9 mg/kg/day IM).	Concurrent administration of daptomycin and clinical levels of gentamicin is unlikely to alter the nephrotoxic potential of gentamicin in humans. However, caution should be used when administering the combination to renally impaired patients.

CT: Clinical Trial

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Clinically relevant plasma levels 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 levels may be present at trough to cause interaction.

If confronted with an abnormally high PT/INR result in a patient being treated with **CUBICIN®/ 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®/CUBICIN® RF** dose (i.e., at trough concentration). If the PT/INR value drawn at trough remains substantially elevated over what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

DOSAGE AND ADMINISTRATION

For CUBICIN®/CUBICIN® RF:

Adults

Complicated Skin and Skin Structure Infections: CUBICIN®/CUBICIN® RF (daptomycin for injection) 4 mg/kg should be administered intravenously once every 24 hours for 7 to 14 days, either by injection over a 2-minute period or by infusion over a 30-minute period.

***Staphylococcus aureus* Bloodstream Infections (Bacteremia) including those with Right-Sided *Staphylococcus aureus* Infective Endocarditis (Native Valve)**: **CUBICIN®/CUBICIN® RF** 6 mg/kg should be administered intravenously once every 24 hours, either by injection over a 2-minute period or by infusion over a 30-minute period. Duration of treatment should be based on the treating physician's working diagnosis. In the clinical trial, duration ranged from 10 days to 42 days with an option for an additional 14 days.

There are limited safety data for the use of **CUBICIN®** for more than 28 days.

Clinical studies in adult patients employed infusion of daptomycin over 30 minutes. There is no clinical experience in patients with the administration of daptomycin as an injection over 2 minutes. This mode of administration was only studied in healthy subjects. However, when compared with the same doses given as intravenous infusions over 30 minutes, there were no clinically important differences in the pharmacokinetics and safety profile of daptomycin (see

also **ADVERSE REACTIONS, Adverse Drug Reaction Overview** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Clinical studies have not been conducted with **CUBICIN® RF**.

Dosing and Administration Considerations

General

- **CUBICIN®/CUBICIN® RF** should not be dosed more frequently than once a day. In Phase 1 and 2 clinical studies with **CUBICIN®**, creatine phosphokinase (CPK) elevations appeared to be more frequent when **CUBICIN®** was dosed more frequently than once daily.
- Clinical studies with **CUBICIN®** have shown that dosing adjustments based on age alone, gender, race or obesity are not required (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).
- **CUBICIN®/CUBICIN® RF** should be reconstituted with a 21 gauge or smaller needle to prevent contamination of broken rubber in the reconstituted solution.

The recommended dosing schedule for adult patients including those with creatinine clearance ≥30 mL/min is presented in Table 11.

Table 11. Recommended Dosage of CUBICIN®/CUBICIN® RF in Adult Patients including those with Creatinine Clearance ≥ 30 mL/min

Creatinine Clearance	Indication	Dosage Regimen	Duration
≥ 30 mL/min	Complicated Skin and Skin Structure Infections	4 mg/kg once every 24 hours	7 to 14 days
	Staphylococcus aureus Bloodstream Infections (Bacteremia) including those with Right-Sided *Staphylococcus aureus* Infective Endocarditis (Native Valve)	6 mg/kg once every 24 hours	10 to 42 days with an option for an additional 14 days

Patients with Renal Impairment

Daptomycin is eliminated primarily by the kidney.

No dose adjustment is required in patients whose creatinine clearance is ≥30 mL/min (see Table 11).

Patients with Creatinine Clearance < 30 mL/min

CUBICIN®/CUBICIN® RF should only be used in patients whose creatinine clearance is < 30 mL/min when it is considered that the expected clinical benefit outweighs the potential risk and for whom there are no further therapeutic options.

Clinical efficacy and safety of **CUBICIN®/CUBICIN® RF** have not been established in patients with severe renal impairment (creatinine clearance < 30 mL/min).

The dose interval adjustment guidance presented below in Table 12 is based on pharmacokinetic modeling data.

Response to treatment, renal function and creatine phosphokinase (CPK) should be closely monitored in these patients.

Whenever possible, **CUBICIN®/CUBICIN® RF** should be administered following the completion of dialysis on dialysis days. The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with low-flux membranes.

Table 12. Dosage Adjustment of CUBICIN®/CUBICIN® RF in Adult* Patients with Severe Renal Impairment (creatinine clearance < 30 mL/min)

Creatinine Clearance	Indication	Dosage Regimen	Duration
< 30 mL/min	Complicated Skin and Skin Structure Infections	4 mg/kg once every 48 hours	7 to 14 days
	Staphylococcus aureus Bloodstream Infections (Bacteremia) including those with Right-Sided *Staphylococcus aureus* Infective Endocarditis (Native Valve)	6 mg/kg once every 48 hours	10 to 42 days with an option for an additional 14 days

*The dosage regimen for CUBICIN®/CUBICIN® RF in pediatric patients with renal impairment has not been established

Patients with Hepatic Insufficiency

No dose adjustment is necessary when administering **CUBICIN®/CUBICIN® RF** to patients with mild or moderate hepatic insufficiency (Child-Pugh Class B). No data are available in patients with severe hepatic insufficiency (Child-Pugh Class C).

Pediatrics

Complicated Skin and Skin Structure Infections:

Table 13. Recommended Dosage of CUBICIN®/CUBICIN® RF in Pediatric Patients (aged 1 to 17 years) with cSSSI, based on Age

Age Group	Dosage*	Duration of Therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to less than 2 years	10 mg/kg once every 24 hours infused over 60 minutes	

*Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

***Staphylococcus aureus* Bloodstream Infections (Bacteremia):**

Table 14. Recommended Dosage of CUBICIN®/CUBICIN® RF in Pediatric Patients (aged 1 to 17 years) with *S. aureus* Bacteremia based on Age

Age Group	Dosage*	Duration of Therapy
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	

*Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

Dosing and Administration Considerations

- **Unlike in adults, do NOT administer CUBICIN®/CUBICIN® RF by injection over a two (2) minute period to pediatric patients.**
- Administer **CUBICIN®/CUBICIN® RF** to pediatric patients intravenously by infusion over a 30- or 60-minute period, based on age:
    - Pediatric Patients 7 to 17 years of age: Administer **CUBICIN®/CUBICIN® RF** intravenously by infusion over a 30-min period. The appropriate volume of reconstituted **CUBICIN®/CUBICIN® RF** (concentration of 50 mg/mL) should be further diluted into a 50 mL intravenous infusion bag containing 0.9% sodium chloride injection. The infusion rate should be maintained at 1.67 mL/minute over the 30-minute period.
    - Pediatric Patients 1 to 6 years of age: Administer **CUBICIN®/CUBICIN® RF** intravenously by infusion over a 60-minute period. The appropriate volume of

reconstituted **CUBICIN®/CUBICIN® RF** (concentration of 50 mg/mL) should be further diluted into an intravenous infusion bag containing 25 mL of 0.9% sodium chloride injection. The infusion rate should be maintained at 0.42 mL/minute over the 60-minute period.

Reconstitution

CUBICIN® and **CUBICIN® RF** are two different formulations of daptomycin that have differences concerning storage and reconstitution. Carefully follow the reconstitution and storage procedures for each formulation.

CUBICIN® should be reconstituted with 0.9% sodium chloride for injection, USP (see **Reconstitution**).

CUBICIN® RF must be reconstituted **ONLY** with either Sterile Water for Injection or Bacteriostatic Water for Injection (see **Reconstitution**).

For CUBICIN®:

CUBICIN® is supplied in single-dose vials containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a **CUBICIN®** 500 mg vial should be reconstituted with 10 mL of 0.9% sodium chloride for injection to 50 mg/mL. Since no preservative or bacteriostatic agent is present in the product, aseptic technique must be used in preparation of the product.

Procedure:

1. Prior to reconstitution, remove the **CUBICIN®** vials from refrigeration and allow the product to sit at room temperature for a few minutes. **CUBICIN®** vials do not need to be warmed to room temperature prior to reconstitution.
2. Remove the polypropylene flip-off cap from the **CUBICIN®** vial to expose the central portions of the rubber stoppers. Gently tap vial twice on counter to settle/loosen the lyophilized powder cake.
3. Using a syringe, slowly transfer the diluent through the center of the rubber stopper into the **CUBICIN®** vial, pointing the transfer needle toward the wall of the vial to prevent excessive foaming. Ensure that the complete daptomycin product is wetted by gently rotating the vial.
4. Allow the product to sit undisturbed for approximately 10 minutes at room temperature.
5. Gently swirl the **CUBICIN®** vial until a clear, fully reconstituted solution is obtained. This typically takes from 5 to 15 minutes.
6. AVOID VIGOROUS SHAKING TO PREVENT FOAMING OF THE PRODUCT DURING RECONSTITUTION.

The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Freshly reconstituted solutions of **CUBICIN®** range in colour from pale yellow to light brown.

For IV injection over a period of 2 minutes:
Reconstitute **CUBICIN®**, as directed above, to a concentration of 50 mg/mL with 0.9% sodium chloride for injection.

For IV infusion over a period of 30 minutes:
Reconstitute **CUBICIN®**, as directed above, to a concentration of 50 mg/mL with 0.9% sodium chloride for injection. Further dilute using aseptic technique with additional 0.9% sodium chloride for injection to a final concentration in the range of 2.5 to 20 mg/mL (typically 10 mg/mL).

Vial Size	Nominal Concentration of Reconstituted Solution	Approximate Available Volume of Reconstituted Solution	Volume of Additional Diluent	Total Volume of Solution for Infusion	Nominal Concentration of Solution for Infusion
500 mg	50 mg/mL	10 mL	15 mL	25 mL	20 mg/mL
500 mg	50 mg/mL	10 mL	40 mL	50 mL	10 mg/mL
500 mg	50 mg/mL	10 mL	190 mL	200 mL	2.5 mg/mL

Because **CUBICIN®** does not contain any preservative or bacteriostatic agent, aseptic technique must be used during preparation for administration and the product should be used promptly. If reconstituted **CUBICIN®** within the vial or infusion bag is not used immediately, it must be refrigerated at 2 to 8°C. It is recommended that the solution be used within 72 hours due to the possibility of microbial contamination during reconstitution (see also **STORAGE AND STABILITY**).

CUBICIN® 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.

CUBICIN® vials are for single-use only.

For CUBICIN® RF:

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 containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a **CUBICIN® RF** 500 mg vial should be reconstituted with 10 mL of either Sterile Water for Injection or Bacteriostatic Water for Injection to 50 mg/mL. Since no preservative or bacteriostatic agent is present in the product, aseptic technique must be used in preparation of the product.

Procedure

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 it to dry. After cleaning, the rubber stopper should not be touched or allowed 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 to dissolve the contents for a few minutes, as needed, to obtain a completely reconstituted solution.
5. Slowly remove the reconstituted liquid containing daptomycin (50 mg/mL) from the vial using a beveled sterile needle that is 21 gauge or smaller in diameter.

The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Freshly reconstituted solutions of **CUBICIN® RF** range in colour from pale yellow to light brown.

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.

CUBICIN® RF vials are for single-use only.

For IV injection over a period of 2 minutes:
Reconstitute **CUBICIN® RF**, as directed above, to a concentration of 50 mg/mL with 10 mL of either Sterile Water for Injection or Bacteriostatic Water for Injection.

For IV infusion over a period of 30 minutes:
Reconstitute **CUBICIN® RF**, as directed above, with 10 mL of either Sterile Water for Injection or Bacteriostatic Water for Injection to a concentration of 50 mg/mL. Further dilute into a 50 mL IV infusion bag containing 0.9% sodium chloride for injection to a final concentration in the range of 1 to 14 mg/mL (typically 10 mg/mL). Refer to Table 15 for allowable in-use storage following reconstitution.

Examples of CUBICIN® RF Concentrations for Sample Dose to be Delivered

Vial Size	Nominal Concentration of Reconstituted Solution	Volume of Reconstituted Solution to Transfer for Infusion	Volume of IV Bag*	Volume of IV Bag after Addition of Reconstituted Solution	Nominal Concentration of Solution for Infusion	Dose to be Delivered†
500 mg	50 mg/mL	20 mL (2 vials)	50 mL	70 mL	14 mg/mL	1000 mg
500 mg	50 mg/mL	10 mL	50 mL	60 mL	8 mg/mL	500 mg
500 mg	50 mg/mL	3 mL	50 mL	53 mL	3 mg/mL	150 mg

*Typical IV bag volume.
†Daptomycin is dosed by mg/kg

Because **CUBICIN® RF** does not contain any preservative or bacteriostatic agent, aseptic technique must be used during preparation for administration. Table 15 below provides in-use storage conditions for **CUBICIN® RF** in acceptable IV diluents. The listed shelf-life of reconstituted and diluted solutions of **CUBICIN® RF** should not be exceeded. Unused portions of **CUBICIN® RF** should be discarded.

Table 15 In-Use Storage Conditions for CUBICIN® RF Once Reconstituted in Acceptable IV Diluents

Container	Diluent	In-Use[3] Shelf-Life	
		Room Temperature (20°C–25°C)	Refrigerated (2°C–8°C)
Glass Vial	Sterile Water for Injection	1 Day	3 Days
	Bacteriostatic Water for Injection	2 Days[1]	3 Days
Sterile Polypropylene Syringe	Sterile Water for Injection	1 Day	3 Days
	Bacteriostatic Water for Injection	2 Days[1]	5 Days[2]
Polyvinyl Chloride IV Bag	Reconstitution: Sterile Water for Injection for immediate dilution with 0.9% sodium chloride for injection	19 Hours	3 Days
	Reconstitution: Bacteriostatic Water for Injection for immediate dilution with 0.9% sodium chloride for injection	2 Days[1]	5 Days[2]

[1]It is recommended that the solution be used within 1 day due to the possibility of microbial contamination during reconstitution.
[2]It is recommended that the solution be used within 3 days due to the possibility of microbial contamination during reconstitution.
[3]In-use periods are not cumulative, reconstituted solution may be stored for the given time period in the vial **or** for the given time period in the syringe **or** for the given time period in the IV bag.

Compatible Intravenous Solutions

For CUBICIN®:

CUBICIN® is compatible with 0.9% sodium chloride injection and lactated Ringer's injection. The following are compatible at room temperature when co-administered with **CUBICIN®** in

0.9% sodium chloride through the same IV line from separate infusion bags: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin, and lidocaine.

CUBICIN® is **NOT** compatible with glucose (dextrose) containing diluents. Other than the nine drugs listed above, additives and other medications should not be infused simultaneously with **CUBICIN®** through the same IV line because only limited data are available on compatibility. If the same IV line is used for sequential infusion of several different drugs, the line should be flushed with a compatible infusion solution before and after infusion with **CUBICIN®**. No other product than the approved diluent should be added to the **CUBICIN®** vial or infusion bag.

For CUBICIN® RF:

CUBICIN® RF is chemically and physically compatible with Sterile Water for Injection, Bacteriostatic Water for Injection and 0.9% sodium chloride injection for injection. See **DOSAGE AND ADMINISTRATION, Reconstitution** section above for information on solutions recommended for use in the reconstitution or dilution of **CUBICIN® RF.**

CUBICIN® RF is **NOT** compatible with glucose (dextrose) containing diluents.

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**. No other product than the approved diluent should be added to the **CUBICIN® RF** vial or infusion bag.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered over 4 hours) or peritoneal dialysis (approximately 11% recovered over 48 hours). The use of high-flux membranes during 4 hours of hemodialysis may increase the percentage of dose removed, as evidenced by the larger decrease in the pre- to post-dose concentrations (41%) compared with low-flux membranes (5 to 7%).

A 58-year old male with a history of multiple sclerosis, diabetes and hypertension was administered an accidental single dose of **CUBICIN®** 3 g (43 mg/kg). Twenty-four hours later

symptoms of orofacial movements, lip smacking and shoulder shrugging were observed and diagnosed as dyskinesia. **CUBICIN®** was discontinued and the patient was treated with benztropine and lorazepam. The events resolved and therapy was restarted without further incident.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Daptomycin is a cyclic lipopeptide antibacterial agent. Daptomycin binds to Gram-positive bacterial membranes in a calcium-dependant manner and causes a rapid depolarization of membrane potential. This loss of membrane potential causes inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death. Activity of daptomycin is dependant on the presence of physiological levels of free calcium ions (50 μg/mL) (see **MICROBIOLOGY**).

Resistance

Cases of daptomycin resistance have been reported in staphylococci in clinical trials and during post-marketing use.

Pharmacokinetics

The mean pharmacokinetic parameters of daptomycin at steady-state following IV administration of **CUBICIN®** over a 30-minute period at 4 to 12 mg/kg q24h to healthy young adults are summarized in Table 16.

Table 16. Mean Daptomycin Pharmacokinetic Parameters in Healthy Adult Volunteers at Steady-State

Dose[b] (mg/kg)	N	Pharmacokinetic Parameters[a] Mean (Standard Deviation)					
		[c]AUC_{0-24} (μg*h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (mL/h/kg)	[c]C_{max} (μg/mL)	[c]C_{min} (μg/mL)
4	6	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)	5.9 (1.6)
6	6	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)	6.7 (1.6)
8	6	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)	10.3 (5.5)
10	9	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)	12.9 (2.9)
12	9	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)	13.7 (5.2)

[a] AUC_{0-24}: area under the concentration-time curve from 0 to 24 hours; $t_{½}$: terminal elimination half-life ; V_{ss}: volume of distribution at steady-state; CL_T: plasma clearance; C_{max}: maximum plasma concentration (total drug)

[b] Doses of **CUBICIN®** in excess of 6 mg/kg have not been approved

[c] Values relate to total drug in plasma (free + protein bound)

Absorption: Daptomycin pharmacokinetics were generally linear and time-independent at doses of 4 to 12 mg/kg q24h. Steady-state trough concentrations were achieved by the third daily dose. The mean (standard deviation) steady-state trough concentrations attained following 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) μg/mL, respectively. The mean AUC and C_{min} (minimum plasma concentration) of daptomycin during once-daily dosing with 6, 8, 10 and 12 mg/kg were dose proportional; however, the mean C_{max} (maximum plasma concentration) was slightly less than dose proportional. Total clearance was unchanged across 4 to 12 mg/kg q24h.

Daptomycin administered as a 2-minute intravenous injection also exhibited dose proportional pharmacokinetics in the approved therapeutic dose range of 4 to 6 mg/kg. Comparable exposure (AUC and C_{max}) was demonstrated in healthy adult subjects following administration of daptomycin as a 30-minute intravenous infusion or as a 2-minute intravenous injection.

Following IV administration of **CUBICIN®** to healthy adult volunteers over a 2-minute period at doses of 4 and 6 mg/kg, the mean (SD) daptomycin steady-state $AUC_{0\text{-}tau}$ values were 475 (71) and 701 (82) μg*h/mL, respectively. The mean (SD) steady-state C_{max} values were 63 (11) and 92 (18) μg/mL, respectively.

Distribution: Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding at doses from 4 to 12 mg/kg ranged from 90 to 93%. The apparent volume of distribution (V_d) of daptomycin at steady-state in healthy adult subjects was low, approximately 0.1 L/kg at doses of 4 to 12 mg/kg, consistent with distribution primarily within the extracellular space.

Daptomycin penetrates into skin blister fluid and reaches a mean C_{max} of 27.6 μg/mL (mean $t_{½}$= 17.3 hrs).

In clinical studies, mean serum protein binding in adult subjects with creatinine clearance (CL_{CR}) ≥ 30 mL/min was comparable to that observed in healthy adult subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among subjects with CL_{CR} < 30 mL/min (87.6%), including hemodialysis patients (85.9%) and continuous ambulatory peritoneal dialysis patients (83.5%). The protein binding of daptomycin in subjects with moderate hepatic impairment (Child-Pugh B) was similar to healthy adult subjects.

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

In a separate study, no metabolites were observed in plasma on Day 1 following administration of daptomycin at 6 mg/kg to healthy adult subjects. Inactive metabolites have been detected in urine, as determined by the difference in total radioactivity concentrations and microbiologically active concentrations. Minor amounts of 3 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 kidney. In a mass balance study of 5 healthy adult subjects using radiolabelled 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 dose was recovered from feces (collected for up to nine days) based on total radioactivity.

Due to limited clinical experience, response to treatment, renal function and creatine phosphokinase (CPK) should be closely monitored in all patients with some degree of renal impairment (CL_{CR} < 80 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Pharmacokinetic studies with **CUBICIN® RF** have not been conducted. The active ingredient in **CUBICIN® RF** (daptomycin) is the same as that in **CUBICIN®**. Pharmacokinetic parameters of **CUBICIN® RF** are expected to be similar to those of **CUBICIN®**.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of daptomycin in pediatric subjects was evaluated in 3 single-dose pharmacokinetic studies. In general, body weight-normalized total body clearance in pediatric patients was higher than in adults and increased with a decrease of age, whereas elimination half-life tends to decrease with a decrease of age. Body weight-normalized total body clearance and elimination half-life of daptomycin in children 2 to 6 years of age were similar at different doses.

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in pediatric patients (1 to 17 years old, inclusive) with cSSSI caused by Gram-positive pathogens. Patients were enrolled into 4 age groups and intravenous **CUBICIN®** doses of 5 to 10 mg/kg once daily were administered. Following administration of multiple doses, daptomycin exposure (AUC_{ss} and $C_{max,ss}$) was similar across different age groups after dose adjustment based on body weight and age (Table 17).

Table 17. Mean (SD) Daptomycin Population Pharmacokinetic Parameters in cSSSI Pediatric Populations

Age	Pharmacokinetic Parameters						
	Dose (mg/kg	Infusion Duration (min)	AUC_{ss} (µg·h/mL)	$t_{1/2}$ (h)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (µg/mL)
12 to 17 years (N=6)	5	30	434 (67.9)	7.1 (0.9)	8200 (3250)	11.8 (2.15)	76.4 (6.75)
7 to 11 years (N=2)	7	30	543*	6.8*	4470*	13.2*	92.4*
2 to 6 years (N=7)	9	60	452 (93.1)	4.6 (0.8)	2750 (832)	20.8 (4.29)	90.3 (14.0)
1 to <2 years (N=27)	10	60	462 (138)	4.8 (0.6)	1670 (446)	23.1 (5.43)	81.6 (20.7)

AUCss: area under the concentration-time curve at steady-state; $t_{½}$: terminal elimination half-life ; V_{ss}: volume of distribution at steady-state; CL_T: plasma clearance; C_{max}: maximum plasma concentration at steady-state (total drug).
*Mean is calculated from N=2

A study was conducted to assess the safety, efficacy and pharmacokinetics of daptomycin in pediatric patients with *S. aureus* bacteremia. Patients were enrolled into 3 age groups and intravenous doses of 7 to 12 mg/kg once daily were administered. Following administration of multiple doses, daptomycin exposure (AUC_{ss} and $C_{max,ss}$) was similar across different age groups after dose adjustment based on body weight and age (Table 18).

Table 18. Mean (SD) of Daptomycin Pharmacokinetics in Bacteremia Pediatric Patients

Age	Pharmacokinetic Parameters						
	Dose (mg/kg	Infusion Duration (min)	AUC_{ss} (µg·h/mL)	$t_{1/2}$ (h)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (µg/mL)
12 to 17 years (N=13)	7	30	656 (334)	7.5 (2.3)	6420 (1980)	12.4 (3.9)	104 (35.5)
7 to 11 years (N=19)	9	30	579 (116)	6.0 (0.8)	4510 (1470)	15.9 (2.8)	104 (14.5)
2 to 6 years (N=19)	12	60	620 (109)	5.1 (0.6)	2200 (570)	19.9 (3.4)	106 (12.8)

AUCss: area under the concentration-time curve at steady-state; $t_{½}$: terminal elimination half-life ; V_{ss}: volume of distribution at steady-state; CL_T: plasma clearance; C_{max}: maximum plasma concentration at steady-state (total drug).
No patients 1 to <2 years of age were enrolled in the study. Simulation using a population pharmacokinetic model demonstrated that the AUC_{ss} of daptomycin in pediatric patients 1 to <2 years of age receiving daptomycin 12 mg/kg once daily would be comparable to adult patients receiving 6 mg/kg once daily.

Pharmacokinetic studies with **CUBICIN® RF** have not been conducted. The active ingredient in **CUBICIN® RF** (daptomycin) is the same as that in **CUBICIN®**. Pharmacokinetic parameters of **CUBICIN® RF** are expected to be similar to those of **CUBICIN®**.

Geriatrics: The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥ 75 years of age) and 11 healthy young matched controls (18 to 30 years of age). Following administration of a single 4 mg/kg IV dose of **CUBICIN®**, the mean total clearance of daptomycin was reduced approximately 35% and the mean $AUC_{0-\infty}$ increased approximately 58% in elderly subjects compared to young healthy subjects. There were no differences in C_{max}. No dosage adjustment is warranted for elderly patients with normal renal function based on age alone.

Gender: No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when administering **CUBICIN®/CUBICIN® RF**.

Hepatic Insufficiency: The pharmacokinetics of daptomycin were evaluated in 10 adult subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with healthy adult 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 administering **CUBICIN®/CUBICIN® RF** to patients with mild to moderate hepatic impairment. The pharmacokinetics of **CUBICIN®/CUBICIN® RF** in patients with severe hepatic insufficiency have not been evaluated.

Renal Impairment in Adult Complicated Skin and Skin Structure Infections (cSSSI): Population derived pharmacokinetic parameters were determined for adult patients with cSSSI and healthy non-infected adult subjects with varying degrees of renal function (N=282). Following the administration of a single 4 mg/kg IV dose of **CUBICIN®**, the plasma clearance (CL_T) was reduced and the systemic exposure ($AUC_{0-\infty}$) was increased with decreasing renal function (see Table 19). The mean $AUC_{0-\infty}$ was not markedly different for subjects and patients with creatinine clearance (CL_{CR}) 30-80 mL/min as compared to those with normal renal function (CL_{CR} > 80 mL/min). The mean $AUC_{0-\infty}$ for subjects and patients with CL_{CR} < 30 mL/min was approximately 2-times higher than that observed in individuals with normal renal function. For subjects on hemodialysis (dosed post-dialysis)/continuous ambulatory peritoneal dialysis, the mean $AUC_{0-\infty}$ was 3-times higher than that observed in individuals with normal renal function. The mean C_{max} ranged from 59.6 to 69.6 µg/mL in subjects with $CL_{CR} \geq 30$ mL/min, while those with CL_{CR} < 30 mL/min ranged from 41.1 to 57.7 µg/mL. In non-infected adult subjects undergoing dialysis, approximately 15% and 11% of the administered dose was removed by 4 hours of hemodialysis and 48 hours of continuous ambulatory peritoneal dialysis, respectively. In patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently. **CUBICIN®/CUBICIN® RF** should be administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE AND ADMINISTRATION**).

Table 19. Daptomycin Population Pharmacokinetic Parameters Following a Single 30-Minute IV Infusion of 4 mg/kg of CUBICIN® to Adult Patients with Complicated Skin and Skin Structure Infections (cSSSI) and Healthy Volunteers with Varying Degrees of Renal Function

Renal Function	N	Pharmacokinetic Parameters Mean (Standard Deviation)			
		$AUC_{0-\infty}$ (μg*h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	CL_T (mL/h/kg)
Normal (CL_{CR}>80 mL/min)	165	417 (155)	9.39 (4.74)	0.13 (0.05)	10.9 (4.0)
Mild Renal Impairment (CL_{CR} 50-80 mL/min)	64	466 (177)	10.75 (8.36)	0.12 (0.05)	9.9 (4.0)
Moderate Renal Impairment (CL_{CR} 30-<50 mL/min)	24	560 (258)	14.70 (10.50)	0.15 (0.06)	8.5 (3.4)
Severe Renal Impairment (CL_{CR} <30 mL/min)	8	925 (467)	27.83 (14.85)	0.20 (0.15)	5.9 (3.9)
Hemodialysis and CAPD	21	1244 (374)	29.81 (6.13)	0.15 (0.04)	3.7 (1.9)

CL_{CR}: creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight; V_{ss}: volume of distribution at steady-state; CAPD: continuous ambulatory peritoneal dialysis

Renal Impairment in the Adult *Staphylococcus aureus* bacteremia/*Staphylococcus aureus* infective endocarditis (SAB/SAIE) Trial: A second population analysis was conducted to determine pharmacokinetic parameters at steady-state in adult SAB/SAIE patients (Table 20). Patients (N=108) received 6 mg/kg q24h of **CUBICIN®** and were stratified by varying degrees of renal function. Plasma clearance (CL_T) decreased with decreasing renal function, whereas AUC and C_{min} increased with decreasing renal function. Mean AUC increased 1.6-fold while mean C_{min} increased 2.8-fold in patients with moderate renal impairment compared to those with CL_{CR} > 80 mL/min. In the two patients with CL_{CR} < 30 mL/min, pharmacokinetic parameters were similar to those with moderate renal impairment. Mean C_{max} values ranged from 80 to 114 μg/mL in patients with moderate to mild renal impairment and were similar to those of normal subjects. In SAB/SAIE patients, the overall mean volume of distribution at steady-state (V_{ss}) was 0.16 L/kg and was greater than that in non-infected subjects (0.1 L/kg), but similar to cSSSI patients. In non-infected adult subjects undergoing dialysis, approximately 15% and 11% of the administered dose was removed by 4 hours of hemodialysis (N=6) and 48 hours of continuous ambulatory peritoneal dialysis [CAPD (N=5)], respectively. In patients with renal impairment, both renal function and CPK should be monitored more frequently. **CUBICIN®/CUBICIN® RF** should be administered following the completion of hemodialysis on hemodialysis days (see **DOSAGE AND ADMINISTRATION**).

Table 20. Daptomycin Population Pharmacokinetic Parameters at Steady-State in Adult SAB/SAIE Patients Dosed with 6 mg/kg of CUBICIN® with Varying Degrees of Renal Function

Renal Function	N	Pharmacokinetic Parameters Mean (Standard Deviation)[1]					
		AUC_{0-24} [µg*h/mL]	$t_{1/2}$ [h]	V_{ss} [L/kg]	CL_T [mL/h/kg]	C_{max} [µg/mL]	C_{min} [µg/mL]
Normal CL_{CR}[2] >80 L/min	62	545 (296)	9.0 (2.86)	0.15 (0.07)	13.2 (5.0)	108 (143)	6.9 (3.5)
Mild Impairment CL_{CR} 50-80 mL/min	29	637 (215)	12.0 (2.26)	0.17 (0.04)	10.5 (3.5)	80 (41)	12.4 (5.6)
Moderate Impairment CL_{CR} 30-<50 mL/min	15	868 (349)	16.1 (3.62)	0.17 (0.05)	8.2 (3.6)	114 (124)	19.0 (9.0)
Severe Impairment CL_{CR} <30 mL/min	2	1050, 892	25.8, 16.0	0.20, 0.15	5.7, 6.7	97, 83	25.4, 21.4

[1] Mean (SD) values are presented except Severe Impairment where N=2;
[2] Creatinine clearance was estimated using the Cockcroft-Gault equation with actual body weight.

A 41% reduction in daptomycin plasma concentration was achieved using high-flux dialysis membranes, and a 5 to 7% reduction was achieved using low-flux dialysis membranes.

Obesity: The pharmacokinetics of daptomycin were evaluated in 6 moderately obese [Body Mass Index (BMI) 25 to 39.9 kg/m^2] and 6 extremely obese (BMI ≥ 40 kg/m^2) adult subjects and controls matched for age, sex, and renal function. Following administration of a single 4 mg/kg IV dose of **CUBICIN®** based on total body weight, the plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in moderately obese adult subjects and 23% lower in extremely obese adult subjects compared with non-obese controls. The $AUC_{0-\infty}$ of daptomycin increased approximately 30% in moderately obese and 31% in extremely obese adult subjects compared with non-obese controls. In the adult complicated skin and skin structure infection trials (cSSSI), 8 adult patients > 150 kg received daptomycin 4 mg/kg. The highest total dose exposure occurred in one patient weighing 238.6 kg (total exposure 20 900 mg daptomycin over 21 days). No dosage adjustment of **CUBICIN®/CUBICIN® RF** is warranted in obese patients based solely on weight.

STORAGE AND STABILITY

For CUBICIN®:

Store vials containing lyophilized powder at 2 to 8ºC.

Chemical and physical in-use stability of the reconstituted solution in the vial, or infusion solutions, has been demonstrated for 12 hours at 25°C and up to 10 days if stored under refrigeration (2 to 8°C), under normal lighting conditions. However, because **CUBICIN®** (daptomycin for injection) does not contain any preservative or bacteriostatic agent, aseptic technique must be used during preparation for administration and the product should be used promptly. If the reconstituted product is not used immediately, it must be refrigerated at 2 to 8°C. It is recommended that the solution be used within 72 hours due to the possibility of microbial contamination during reconstitution. Avoid excessive heat.

The combined time (vial and infusion bag) at room temperature, up to 25°C, should not exceed 12 hours. The combined time (vial and infusion bag) at 2-8°C should not exceed 10 days.

For CUBICIN® RF:

Store vials containing lyophilized powder at 15°C to 30°C.

For the in-use shelf life of reconstituted and diluted solutions of **CUBICIN® RF**, see **DOSAGE AND ADMINISTRATION, Reconstitution** above.

SPECIAL HANDLING INSTRUCTIONS

For information on reconstitution, see **DOSAGE AND ADMINISTRATION** above.

DOSAGE FORMS, COMPOSITION AND PACKAGING

For CUBICIN®:

CUBICIN® (daptomycin for injection) is supplied as a pale yellow to light brown lyophilized cake in a single-use vial (500 mg/10 mL vial). Available in packages of 10 vials. **CUBICIN®** may also contain sodium hydroxide used to adjust pH in trace amounts.

For CUBICIN® RF:

CUBICIN® RF (daptomycin for injection) is supplied as a pale yellow to light brown lyophilized powder in a single-dose vial (500 mg/10 mL vial). Available in packages of 1 vial. **CUBICIN® RF** also contains sodium hydroxide and approximately 713 mg of sucrose. The pH of the solution upon reconstitution is approximately 6.8.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: daptomycin

Chemical name: *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 ε_1-lactone

Molecular formula: $C_{72}H_{101}N_{17}O_{26}$

Molecular mass: 1620.67

Structural formula:

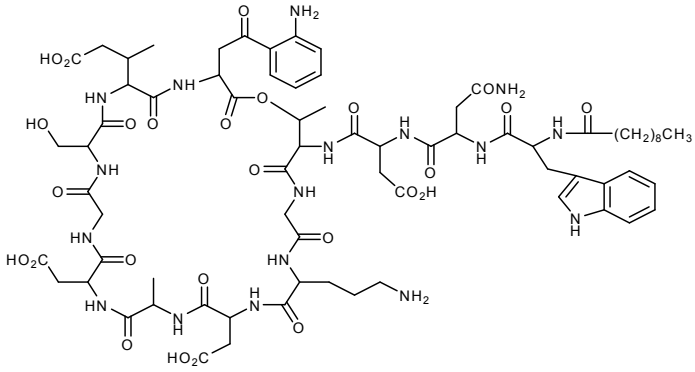

Table 21. Physicochemical properties

Attribute	Description
Appearance	Clear, dark yellow to light brown solution (bulk drug substance; frozen concentrate). Pale yellow to light brown lyophilized powder (lyophilized drug product).
Solubility (at 25°C)	
Water	> 1000 mg/mL
Acetonitrile	< 0.05 mg/mL
Methanol	34.9 mg/mL
Ethanol	1.20 mg/mL
Isopropyl alcohol	0.11 mg/mL
Partition Coefficient	
1-octanol/water	-1.32
1-octanol/tris-buffer, pH 7.4	-3.26
pKa (aqueous)	2.9, 3.5, 4.3, 4.7, 10.5
Melting Point	215°C
Specific Rotation (at 25°C)	
Water	+17.8°
Methanol	+11.2°

CLINICAL TRIALS

Complicated Skin and Skin Structure Infections (cSSSI) in Adults

Study demographics and trial design

The patient demographics and basic trial design for the two pivotal adult cSSSI studies are summarized in Table 22. Adult patients were included for skin and skin structure infections complicated by factors implicating deeper soft tissue, significant surgical intervention, co-morbidities, hospitalization and/or other factors. The main diagnoses were wound infections, major abscesses and ulcer infections, 57% of which were considered severe in accordance with the SIRS rating scale. Children, pregnant or lactating women and, among others, patients such as those with bacteremia, pneumonia, osteomyelitis, primary muscle disorders or CPK > 50% Upper Limit Normal, third degree burns, shock/hypotension, and severe renal impairment (calculated creatinine clearance < 30 mL/min) were excluded. In the majority of patients with Gram-positive cSSSI, the infections were polymicrobial either due to Gram-positive bacteria, Gram-negative bacteria or anaerobes and 30% of patients received adjunctive surgery. Microbiological analyses were restricted to Gram-positive organisms.

For purposes of the comparator arm, overall analyses, and the grouping of clinically similar patients, all patients were pre-randomized to either vancomycin or anti-staphylococcal semi-synthetic penicillins. Vancomycin was chosen in cases of known or suspected MRSA or patient intolerance to penicillins. The anti-staphylococcal semi-synthetic penicillin chosen was dependent upon availability and standard of care in the study country. All patients were then randomized 1:1 to either daptomycin or the comparator arm. Patients could be switched to oral therapies after a minimum of four days of IV treatment if clinical improvement was demonstrated and if a switch was required for other relevant reasons. Patients initially treated with penicillins could be switched to vancomycin if MRSA was cultured after randomization had occurred. Aztreonam and metronidazole could be concurrently administered for the treatment of Gram-negative and anaerobic bacteria respectively.

Overall, the daptomycin and comparator arms were comparable. In study 9801 the large majority of patients were from the US whereas in study 9901 the majority was from South Africa. In the former relative to the latter, study patients tended to be slightly older and included slightly more Caucasians, diabetics, surgical interventions, and vancomycin usage.

Table 22. Summary of Trial Design and Demographics

Study Number (location)	Basic Design	Primary Efficacy Parameter	Antibiotic Treatments Compared (dose and duration)	Number of Patients Treated (ITT)*	Mean Age in Years (range)	Gender (%M/F)	Race (% caucasian/ black/other)
DAP-SST-9801 (US and South Africa)	Multicentre, randomized, parallel group, investigator blinded	Clinical outcome in MITT* and CE* patient populations with cSSSI 7-12 days after treatment cessation	Daptomycin (4mg/kg/q24h IV x 7-14 days) versus Comparator: vancomycin (1g q12h IV x 7-14 days) or semi-synthetic penicillins** (4-12 g/d IV in divided doses x 7-14 days)	264 266	55.2 (18-91) 55.5 (19-94)	54.2/45.8 55.6/44.4	67.0/18.9/14.4 62.8/22.6/14.9
DAP-SST-9901 (South Africa, Europe, Australia and Israel)	Multicentre, randomized, parallel group, investigator blinded	Clinical outcome in MITT* and CE* patient populations with cSSSI 7-12 days after treatment cessation	Daptomycin (4mg/kg/q24h iv x7-14days) versus Comparator: vancomycin (1g q12h iv x 7-14days) or semi-synthetic penicillins*** (4-12 g/d iv in divided doses x 7-14 days)	270 292	47.9 (18-87) 48.6 (17-85)	55.6/44.4 54.8/45.2	50.4/35.2/14.4 50.0/31.2/18.8

* analytical subpopulations included: ITT: intent to treat population (patients with cSSSI who received at least one dose); MITT: modified intent to treat population (ITT patients with proved Gram-positive bacterial cSSSI at baseline); CE: clinically evaluable population (all ITT patients in whom clinical outcome could be inferred to reflect the effect of the study drug, met clinical criteria for study infection, received correct study drug as randomized for appropriate duration and intensity, had required clinical evaluations and did not receive confounding non-study medications); ME: microbiologically evaluable population (CE patients with a Gram-positive bacterium at baseline); about 82% of ITT patients met MITT criteria and 81% of ITT patients met CE criteria; 84% of CE patients met ME criteria for microbiological evaluability at Test of Cure visit

** anti-staphylococcal semi-synthetic penicillin: nafcicillin, cloxacillin or oxacillin

*** anti-staphylococcal penicillin: flucloxacillin, cloxacillin or oxacillin

Study results

Overall clinical efficacy results are provided in Tables 23 and 24 in terms of the sponsor-defined primary clinical efficacy parameters at the Test Of Cure visit (7-12 days after cessation of antibiotic treatment) for MITT and CE populations.

Table 23. Clinical efficacy outcome (MITT population)

Clinical Response	DAP-SST-9801		DAP-SST-9901		Pooled Results	
	CUBICIN® (N=215) n (%)	Comparator[a] (N=216) n (%)	CUBICIN® (N=213) n (%)	Comparator[a] (N=255) n (%)	CUBICIN® (N=428) n (%)	Comparator[a] (N=471) n (%)
Clinical Success	140 (65.1)	140 (64.8)	179 (84.0)	212 (83.1)	319 (74.5)	352 (74.7)
Cure	90 (41.9)	84 (38.9)	82 (38.5)	109 (42.7)	172 (40.2)	193 (41.0)
Clinical Improvement	50 (23.3)	56 (25.9)	97 (45.5)	103 (40.4)	147 (34.3)	159 (33.8)
Clinical Failure	75 (34.9)	76 (35.2)	34 (16.0)	43 (16.9)	109 (25.5)	119 (25.3)

[a] Vancomycin or anti-staphylococcal semi-synthetic penicillins

Table 24. Clinical efficacy outcome (CE population)

Clinical Response	DAP-SST-9801		DAP-SST-9901		Pooled Results	
	CUBICIN® (N=208) n (%)	Comparator[a] (N=206) n (%)	CUBICIN® (N=238) n (%)	Comparator[a] (N=250) n (%)	CUBICIN® (N=446) n (%)	Comparator[a] (N=456) n (%)
Clinical Success	158 (76.0)	158 (76.7)	214 (89.9)	226 (90.4)	372 (83.4)	384 (84.2)
Cure	105 (50.5)	96 (46.6)	103 (43.3)	117 (46.8)	208 (46.6)	213 (46.7)
Clinical Improvement	53 (25.5)	62 (30.1)	111(46.6)	109 (43.6)	164(36.8)	171 (37.5)
Clinical Failure	50 (24.0)	48 (23.3)	24 (10.1)	24 (9.6)	74 (16.6)	72 (15.8)

[a] Vancomycin or anti-staphylococcal semi-synthetic penicillins

The pooled clinical efficacy results, based on sponsor-defined clinical efficacy outcome parameters for the MITT population in studies DAP-SST-9801 and DAP-SST 9901, are provided in Table 25 in terms of infecting bacteria and patient pre-randomization to either anti-staphylococcal semi-synthetic penicillins or vancomycin. These two clinical groupings were based upon the likelihood of patients having MRSA or penicillin intolerance and the patients of both groupings received either **CUBICIN®** or the appropriate comparator drug (vancomycin or an anti-staphylococcal semi-synthetic penicillin).

Table 25. Pooled clinical success rates by infecting pathogen and patient pre-randomization (MITT population)

Pathogen	Pre-randomized to Semi-synthetic Penicillins		Pre-randomized to Vancomycin	
	Drug Received		Drug Received	
	CUBICIN® n/N(%)	Semi-synthetic Penicillins n/N (%)	CUBICIN® n/N (%)	Vancomycin n/N (%)
Staphylococcus aureus (MSSA)	130/161 (80.7)	128/160 (80.0)	38/50 (76.0)	56/79 (70.9)
Staphylococcus aureus (MRSA)	3/7 (42.9)	6/9 (66.7)	15/29 (51.7)	20/38 (52.6)
Streptococcus pyogenes	70/79 (88.6)	74/88 (84.1)	9/9 (100.0)	8/15 (53.3)
Streptococcus agalactiae	13/15 (86.7)	15/27 (55.6)	7/9 (77.8)	7/14 (50.0)

Similarly, the pooled microbiological efficacy results (eradication or presumed eradication in the ME population) for studies DAP–SST-9801 and DAP-SST 9901, are provided in Table 26.

Table 26. Pooled microbiological success rates (eradication or presumed eradication) by infecting pathogen and patient pre-randomization (ME population)

Pathogen	Pre-randomization to Semi-synthetic Penicillins		Pre-randomization to Vancomycin	
	Drug Received		Drug Received	
	CUBICIN® n/N (%)	Semi-synthetic penicillins n/N (%)	CUBICIN® n/N (%)	Vancomycin n/N (%)
Staphylococcus aureus (MSSA)	108/144 (75.0)	108/139 (77.7)	31/41 (75.6)	49/68 (72.1)
Staphylococcus aureus (MRSA)	2/4 (50.0)	3/6 (50.0)	12/21 (57.1)	18/30 (60.0)
Streptococcus pyogenes	66/72 (91.7)	65/79 (82.3)	9/9 (100.0)	7/9 (77.8)
Streptococcus agalactiae	12/14 (85.7)	12/18 (66.7)	6/7 (85.7)	7/11 (63.6)

Complicated Skin and Skin Structure Infections (cSSSI) in Pediatric Patients (1 to 17 years of Age)

The cSSSI pediatric trial was a single prospective multi-center, randomized, comparative trial. A total of 396 pediatric patients aged 1 to 17 years with cSSSI caused by Gram-positive pathogens were enrolled into the study. Patients known to have bacteremia, osteomyelitis, endocarditis, and pneumonia at baseline were excluded. Patients were enrolled in a stepwise approach into four age groups and given age-dependent doses of **CUBICIN®** once daily for up to 14 days. The different age groups and doses evaluated were as follows: Adolescents (12 to 17 years) treated with 5 mg/kg of **CUBICIN®** (n=113), Children (7 to 11 years) treated with 7 mg/kg of **CUBICIN®** (n=113), Children (2 to 6 years) treated with 9 mg/kg of **CUBICIN®** (n=125) and Infants (1 to <2) treated with 10 mg/kg of **CUBICIN®** (n=45).

Patients were randomized 2:1 to receive **CUBICIN®** or a standard of care (SOC) comparator, which included intravenous therapy with either vancomycin, clindamycin, or an anti-staphylococcal semi-synthetic penicillin (nafcillin, oxacillin, or cloxacillin). Patients could switch to oral therapy after clinical improvement was demonstrated (no minimum IV dosing was required).

The primary objective of this study was to evaluate the safety of **CUBICIN®**. The clinical outcome was determined by resolution or improvement of symptoms at the End-of-Treatment (EOT), 3 days after the last dose, and at Test-of-Cure (TOC), 7 – 14 days after the last dose. Investigator observed outcomes were verified in blinded fashion. Of the 396 subjects randomized in the study, 389 subjects were treated with **CUBICIN®** or comparator and included in the ITT population. Of these, 257 subjects were randomized to the **CUBICIN®** group and 132 subjects were randomized to the comparator group. Approximately 95% of subjects switched to oral therapy. The mean day of switch was day 4, and ranged from day 1 to day 14. The clinical success rates determined at 7 – 14 days after last dose of therapy (IV and oral) (TOC visit) were 88% (227/257) for **CUBICIN®** and 86% (114/132) for comparator.

***Staphylococcus aureus* Bacteremia/*Staphylococcus aureus* Infective Endocarditis (SAB/SAIE) Trial in Adults**

Study Demographics and Trial Design

The trial design and patient demographics for the adult *Staphylococcus aureus* bacteremia/ *Staphylococcus aureus* infective endocarditis (SAB/SAIE) trial are summarized in Table 27 and Table 28.

Adult patients ≥ 18 years of age with clinically documented *Staphylococcus aureus* bacteremia determined by at least one positive blood culture for *Staphylococcus aureus* obtained within 2 calendar days prior to the first dose of study drug and irrespective of source were enrolled. The major exclusion criteria were patients with a prosthetic heart valve, cardiac decompensation and/or valve damage, shock or hypotension, severe renal disease, increased AST or ALT, severe neutropenia, or known osteomyelitis. Patients who developed osteomyelitis during treatment were permitted to remain on study. In addition, patients with meningitis, pneumonia, polymicrobial bloodstream infections or with intravascular foreign material not planned for removal within 4 days of dosing (except vascular stents in place > 6 months or permanent pacemakers) were not to be enrolled.

Baseline characteristics in the Intent-to-Treat (ITT) population were well balanced between the two treatment arms. Patients were generally seriously ill and included the elderly, those with systemic inflammatory response syndrome (SIRS), diabetes mellitus, injection drug use, extravascular foreign materials, intravascular foreign materials, percutaneous intravascular devices, presence of a catheter at first positive culture, prior endocarditis, pre-existing valvular heart disease, abnormal chest x-ray, HIV positive, prior endocarditis and surgery, infection and/or trauma within 30 days of onset of the *Staphylococcus aureus* bacteremia. Eighty-nine patients (38%) had bacteremia caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Vancomycin was used if the patient had methicillin-resistant *Staphylococcus aureus*. Vancomycin was used unless or until susceptibility results proved to be methicillin-susceptible whereupon therapy was changed to an anti-staphylococcal semi-synthetic penicillin (SSP) unless contraindicated. The choice of anti-staphylococcal semi-synthetic penicillin was based on the standard therapy in each country.

Table 27. Trial design in the pivotal SAB/SAIE Study

Study Number/ Country	Design	Primary Efficacy Parameter	Treatment Regimen	Number of Patients Treated
DAP-IE-01-02 United States (40 sites) Europe (8 sites)	Multi-centre, randomized, open-label, comparative (non-inferiority)	Co-primary composite efficacy endpoint was clinical and microbiological success at test-of-cure visit (6 weeks after last treatment dose), based on an Independent External Adjudication Committee outcome, in the ITT and PP populations*	<u>Dose</u> Daptomycin (6 mg/kg IV q24h) versus vancomycin† (1 g IV q12h) or semi-synthetic penicillin** (2 g IV q4h) Gentamicin† (1 mg/kg IV q8h): given to all patients in comparator group and those with left-sided infective endocarditis in daptomycin group for the first 4 days (or until blood cultures were negative for 48 hours) <u>Duration</u> 10-42 days with an option to extend for 14 days. The duration of treatment was to be based on the patient's diagnosis as determined by the Investigator and the susceptibility of the *S. aureus* isolate.	120 115

* ITT population included all patients who were randomized and received at least one dose of study medication; PP population included those in the ITT population with documented adherence to the protocol

** Anti-staphylococcal semi-synthetic penicillins included nafcillin, oxacillin, cloxacillin or flucloxacillin based on standard therapy in each country

† Vancomycin and gentamicin were to be adjusted based on renal function and plasma level according to Investigator's standard practice and manufacturer's guidelines

Table 28. Summary of Demographic Characteristics for the SAB/SAIE Study (ITT Population)

Characteristic	CUBICIN® (N=120)	Comparator (N=115)	Total (N=235)
Median Age (years) (range)	50.5 (21, 87)	55.0 (25, 91)	53.0 (21, 91)
Age, years [N (%)]			
≥65	30 (25.0%)	37 (32.2%)	67 (28.5%)
≥75[a]	19 (15.8%)	15 (13.0%)	34 (14.5%)
Gender, N (%) Male	70 (58.3%)	71 (61.7%)	141 (60.0%)
Female	50 (41.7%)	44 (38.3%)	94 (40.0%)
Race, N (%) Caucasian	75 (62.5%)	81 (70.4%)	156 (66.4%)
BMI, kg/m^2 Median (range)	26.90 (17.6, 49.7)	25.67 (17.0, 44.0)	26.47 (17.0, 49.7)
CLcr, mL/min[b], Median (range)	86.44 (28.0, 246.9)	83.61 (17.9, 277.0)	84.56 (17.9, 277.0)
CLcr, N (%) <50 mL/min[b]	19 (15.8%)	22 (19.1%)	41 (17.4%)

[a] Age category ≥75 years is a subset of the category ≥65 years.

[b] Calculated by the Sponsor using the Cockcroft-Gault equation.

Upon entry, adult patients were classified for likelihood of endocarditis using the modified Duke criteria (Possible, Definite, or Not Endocarditis). Echocardiography, including transesophageal echocardiogram (TEE), was performed within 5 days following study enrollment. Final diagnoses and outcome assessments at Test of Cure were made by a treatment-blinded Independent External Adjudication Committee (IEAC), using protocol-specified clinical definitions.

Of the 37 patients with an entry diagnosis of Definite Endocarditis, all (100%) had a final diagnosis of infective endocarditis; of the 144 patients with an entry diagnosis of Possible Endocarditis, 15 (10%) had a final diagnosis of infective endocarditis; and, of the 54 patients with an entry diagnosis of Not Endocarditis, 1 (2%) had a final diagnosis of infective endocarditis. There were 182 patients with bacteremia including 121 with complicated and 61 with uncomplicated *Staphylococcus aureus* bacteremia; and, there were 53 patients with infective endocarditis, including 35 with right-sided and 18 with left-sided endocarditis. A summary of the entry and final diagnostic subgroups (defined below) in the ITT population are presented in Table 29.

Complicated bacteremia was defined as *Staphylococcus 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 *Staphylococcus 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.

Right-sided infective endocarditis (RIE) 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. Patients with a final diagnosis of RIE based on these criteria were further classified as either complicated or uncomplicated RIE as described below:

Complicated RIE included patients who met **any** of the following criteria: were not intravenous drug users; had a positive blood culture for MRSA; had a serum creatinine ≥2.5 mg/dL; **or** had evidence of extrapulmonary sites of infection.

Uncomplicated RIE included patients who met **all** of the following criteria: were intravenous drug users; had a positive blood culture for MSSA; had a serum creatinine <2.5 mg/dL; **and** were without evidence of extrapulmonary sites of infection.

Left-sided infective endocarditis (LIE) was definite or possible endocarditis according to modified Duke criteria and echocardiographic evidence of involvement or predisposing pathology of the mitral or aortic valve.

Table 29. Summary of Entry and Final Diagnostic Subgroups in the SAB/SAIE Trial (ITT Population)

Diagnostic Subgroup	CUBICIN® (N=120)	Comparator (N=115)	Total (N=235)
IEAC Entry Diagnostic Subgroup [N (%)]			
N	120	115	235
Definite IE	17 (14.2%)	20 (17.4%)	37 (15.7%)
Possible IE	73 (60.8%)	71 (61.7%)	144 (61.3%)
Not IE	30 (25.0%)	24 (20.9%)	54 (23.0%)
IEAC Final Diagnostic Subgroup [N (%)]			
N	120	115	235
Complicated RIE	13 (10.8%)	12 (10.4%)	25 (10.6%)
Uncomplicated RIE	6 (5.0%)	4 (3.5%)	10 (4.3%)
Complicated bacteremia	60 (50.0%)	61 (53.0%)	121 (51.5%)
Uncomplicated bacteremia	32 (26.7%)	29 (25.2%)	61 (26.0%)
LIE	9 (7.5%)	9 (7.8%)	18 (7.7%)

Study Results

The overall success rates at Test of Cure in the ITT population were 44.2% (53/120) in patients treated with **CUBICIN®** and 41.7% (48/115) in patients treated with comparator [95% CI 2.4% (-10.2, 15.1)]. The success rates at Test of Cure in the Per Protocol Population were 54.4% (43/79) in patients treated with **CUBICIN®** and 53.3% (32/60) with comparator [95% CI 1.1% (-15.6, 17.8)].

The success rates in the ITT population are shown in Table 30.

Table 30. Success Rates* at Test of Cure in the pivotal SAB/SAIE Trial (ITT Population)

Population	CUBICIN® 6 mg/kg n/N (%)	Comparator[a] n/N (%)	Difference: CUBICIN® − Comparator (Confidence Interval)
Overall	53/120 (44.2%)	48/115 (41.7%)	2.4% (−10.2, 15.1)[c]
Baseline Pathogen			
MSSA	33/74 (44.6%)	34/70 (48.6%)	−4.0% (−22.6, 14.6)[d]
MRSA	20/45 (44.4%)	14/44 (31.8%)	12.6% (−10.2, 35.5)[d]
Entry Diagnosis[b]			
Definite or Possible Infective Endocarditis	41/90 (45.6%)	37/91 (40.7%)	4.9% (−11.6, 21.4)[d]
Not Infective Endocarditis	12/30 (40.0%)	11/24 (45.8%)	−5.8% (−36.2, 24.5)[d]
Final Diagnosis[f]			
Complicated Bacteremia	26/60 (43.3%)	23/61 (37.7%)	5.6% (−17.3, 28.6)[e]
Uncomplicated Bacteremia	18/32 (56.3%)	16/29 (55.2%)	1.1% (−31.7, 33.9)[e]
Right-Sided Infective Endocarditis (RIE)	8/19 (42.1%)	7/16 (43.8%)	−1.6% (−44.9, 41.6)[e]
Complicated RIE	5/13 (38.5%)	6/12 (50.0%)	−11.5% (−62.4, 39.4)[e]
Uncomplicated RIE	3/6 (50.0%)	1/4 (25.0%)	25.0% (−51.6, 100.0)[e]
Left-Sided Infective Endocarditis	1/9 (11.1%)	2/9 (22.2%)	−11.1% (−55.9, 33.6)[e]

* Success: if patient was judged as cured or improved by IEAC, had a negative blood culture, did not receive potentially effective non-study antibiotic that could have altered outcome, and received at least the minimum amount of study medication

[a] Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin According to the modified Duke criteria

[b] According to the modified Duke criteria

[c] 95% Confidence Interval

[d] 97.5% Confidence Interval (adjusted for multiplicity)

[e] 99% Confidence Interval (adjusted for multiplicity)

[f] See definitions above.

Table 31 presents a summary of success rates at Test of Cure by duration of study treatment in the ITT population. Across all patients in the ITT population, success rates increased with increasing duration of treatment in both the **CUBICIN®** and comparator groups.

Table 31. Summary of Success Rates at Test of Cure in the SAB/SAIE Trial by Duration of Treatment and Final Diagnosis (ITT Population)

Group	CUBICIN® 6 mg/kg q24h n/N (%)				Comparator n/N (%)			
	1-14 days	15-28 days	29-42 days	>42 days	1-14 days	15-28 days	29-42 days	>42 days
Overall ITT	29/77 (37.7%)	15/29 (51.7%)	7/11 (63.6%)	2/3 (66.7%)	14/52 (26.9%)	21/41 (51.2%)	11/18 (61.1%)	2/4 (50.0%)
Complicated bacteremia	14/36 (38.9%)	6/14 (42.9%)	4/7 (57.1%)	2/3 (66.7%)	5/30 (16.7%)	10/18 (55.6%)	7/11 (63.6%)	1/2 (50.0%)
Uncomplicated bacteremia	12/25 (48.0%)	6/7 (85.7%)	0/0 (0%)	0/0 (0%)	9/16 (56.2%)	5/11 (45.5%)	1/1 (100%)	1/1 (100%)
Right-sided endocarditis	3/9 (33.3%)	3/7 (42.9%)	2/3 (66.7%)	0/0 (0%)	0/4 (0%)	4/6 (66.7%)	3/5 (60.0%)	0/1 (0%)
Left-sided endocarditis	0/7 (0%)	0/1 (0%)	1/1 (100%)	0/0 (0%)	0/2 (0%)	2/6 (33.3%)	0/1 (0%)	0/0 (0%)

Note: anti-staphylococcal semi-synthetic penicillin (SSP) included nafcillin, oxacillin, cloxacillin, and flucloxacillin.

In the overall ITT population, there was no statistically significant difference in time to clearance of *Staphylococcus 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 *Staphylococcus aureus* infections was assessed in 19/120 (15.8%) adult **CUBICIN®**-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 **CUBICIN®**-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility on or following therapy). Most patients who failed due to persisting or relapsing *Staphylococcus aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see **WARNINGS AND PRECAUTIONS**).

***Staphylococcus aureus* Bacteremia (SAB) Trial in Pediatric Patients (1 to 17 years of Age)**

The pediatric *S. aureus* bacteremia study was designed as a prospective multi-center, randomized comparative trial to treat pediatric patients aged 1 to 17 years with bacteremia. Patients known to have endocarditis or pneumonia at baseline were excluded. Patients were enrolled in a stepwise approach into three age groups and given age-dependent doses of **CUBICIN®** once daily for up to 42 days. The different age groups and doses evaluated were as follows: Adolescents (12 to 17 years) treated with **CUBICIN®** dosed at 7 mg/kg (n=14) once daily, Children (7 to 11 years) treated with **CUBICIN®** dosed at 9 mg/kg once daily (n=19) and Children (2 to 6 years) treated with **CUBICIN®** dosed at 12 mg/kg once daily (n=22). No patients 1 to <2 years were enrolled.

Patients were randomized 2 :1 to receive **CUBICIN®** or a standard of care comparator, which included intravenous therapy with vancomycin, semi-synthetic penicillin, first generation cephalosporin or clindamycin. Patients could switch to oral therapy after clinical improvement was demonstrated (no minimum IV dosing was required).

The primary objective of this study was to assess the safety of **CUBICIN®**. The clinical outcome was determined by resolution or improvement of symptoms at the Test-of-Cure (TOC) visit, 7 to 14 days after the last dose, which was assessed by the site level Blinded Evaluator.

Of the 82 subjects randomized in the study, 81 subjects were treated with **CUBICIN®** or comparator and included in the safety population, and 73 had a proven *S. aureus* bacteremia at Baseline. Of these, 51 subjects were randomized to the **CUBICIN®** group and 22 subjects were randomized to the comparator group. The mean duration of IV therapy was 12 days, with a range of 1 to 44 days. Forty-eight subjects switched to oral therapy, and the mean duration of oral therapy was 21 days. The clinical success rates determined at 7 to 14 days after last dose of therapy (IV and oral) (TOC visit) were 88% (45/51) for **CUBICIN®** and 77% (17/22) for comparator.

DETAILED PHARMACOLOGY

Animal Pharmacology

Adult Animals

In animals, daptomycin administration has been associated with effects on skeletal muscle with no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by 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 IV) and dogs (100 mg/kg/day IV). 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 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 doses higher than those associated with skeletal myopathy. Deficits in the dogs' patellar reflexes were seen within 2 weeks of the start of treatment at 40 mg/kg IV (9 times the human C_{max} at the 6 mg/kg IV q24h dose), with some clinical improvement noted within 2 weeks of the cessation of dosing. However, at 75 mg/kg/day IV for 1 month, 7/8 dogs failed to regain full patellar reflex responses within the duration of a 3-month recovery period. In a separate study in dogs receiving doses of 75 and 100 mg/kg/day IV for 2 weeks, minimal residual histological changes were noted at 6 months after cessation of dosing. However, recovery of peripheral nerve function was evident.

Acute IV administration of daptomycin to male mice was associated with dose-related effects on the central nervous system that were minimal at dose levels below 100 mg/kg but significant at 200 mg/kg. These effects included decreased motor activity, leg weakness, tremors, grasping loss, decreased abdominal tone, piloerection, decreased frequency of acetic acid-induced writhing, and increased hexobarbital-induced sleep time. Animal model studies have

demonstrated that there is an increased penetration of daptomycin into the cerebrospinal fluid through inflamed meninges.

Daptomycin has been shown to penetrate into rabbit meninges (non-inflamed, 2%; inflamed 6%).

In another study of general pharmacological properties at doses up to 150 mg/kg IV, daptomycin caused no changes in gross behavior of rats at 15 mg/kg. Slight hypoactivity and abnormal posture were observed at 50 mg/kg. At 150 mg/kg, changes included hypoactivity, abnormal posture and gait, ptosis, decreased limb tone, increased defecation, and decreased food consumption and body weight. Most effects were transient and reversed within 24 hours post-dose. After pre-treatment at this dose, daptomycin also potentiated thiopental-Na anesthesia by 4 to 8-fold and inhibited motor coordination.

Tissue distribution studies in rats have shown that daptomycin is retained in the kidney.

The effect of concurrent administration of daptomycin and simvastatin on skeletal muscle was studied in a repeat dose study in CD rats. A total of four groups of male rats (15 rats per group) were treated as follows: Group 1: vehicle, days 0-27; Group 2: daptomycin 20 mg/kg/day IV, days 14-27; Group 3: Simvastatin 10 mg/kg/day Oral, days 0-27; and Group 4: Simvastatin 10 mg/kg/day Oral, days 0-27 and daptomycin 20mg/kg/day IV, days 14-27. Blood for serum chemistry was obtained on days 13 (prior to the initiation of daptomycin treatment) and 27. Following 14 days of treatment with 10 mg/kg/day of simvastatin in combination with 20 mg/kg/day of daptomycin, a slight, statistically significant increase was detected in the levels of aspartate aminotransferase but not creatine phosphokinase (Table 32). However, it is noteworthy that following thirteen days of treatment with simvastatin alone (prior to the administration of daptomycin), slight, statistically significant elevations in mean serum levels of creatine phosphokinase and aspartate aminotransferase were detected in Group 4 animals as compared to Group 3 animals (see Table 32). Because the magnitude of the difference in CPK and AST between Group 4 and Group 3 (10/20 and 10/0 mg/kg/day simvastatin/daptomycin, respectively) on day 27 (1.4 and 1.4-fold respectively) was comparable to that noted on day 13, the difference is most likely related to the pre-existing (day 13) elevation and not due to the addition of daptomycin administration to simvastatin.

The microscopic examination of skeletal muscle at the end of study revealed minimal degenerative and/or regenerative changes in animals from all groups. Although the incidence was slightly higher for daptomycin (with or without simvastatin) as compared to vehicle or simvastatin alone treated groups, there was no increase in the incidence or severity of muscle effects in the daptomycin alone group as compared to daptomycin in combination with simvastatin.

Together, these data support the conclusion that no effect of drug interaction on skeletal muscle was observed upon co-administration of daptomycin and simvastatin to rats at clinically relevant doses.

Table 32. Summary of Creatine Phosphokinase (CPK) and Aspartate Aminotransferase (AST) Levels in Rats Following Administration of Oral Simvastatin With and Without Intravenous Daptomycin

Daily Dose[a]	Control Vehicle + Vehicle Group 1	Daptomycin 20mg/kg/day + Vehicle Group 2	Simvastatin 10 mg/kg/day +Vehicle Group 3	Simvastatin 10mg/kg/day + Daptomycin 20 mg/kg/day Group 4
CPK (IU/L)				
Day 13[b]	331.4	435.7	352.5	590.2[c]
Day 27	509.1(54%)[e]	568.5 (30%)[e]	777.0 (121%)[e]	1083 (84%)[e]
AST (U/L)				
Day 13 [b]	99.2	99.3	97.7	121.7[d]
Day 27	104.5 (5%)[e]	107.1 (8%)[e]	121.3 (24%)[e]	169.5[d] (39%)[e]

[a] Dose administration of simvastatin was initiated 14 days prior to addition of daptomycin treatment. Simvastatin was administered from Treatment Days 0 to 27; Daptomycin was administered from Treatment Days 14-27.

[b] Values for Day 13 preceded initiation of daptomycin treatment.

[c] Significantly different from Groups 1 and 3 but not Group 2 by Duncan's test ($p<0.05$)

[d] Significantly different from Groups 1, 2 and 3 by Duncan's test ($p<0.05$)

[e] Numbers in parentheses represent the percentage increase in CPK or AST values from Day 13 to 27

The effect of concurrent administration of daptomycin and tobramycin with respect to nephrotoxicity and neuromuscular toxicity was studied in rats. Daptomycin dose levels were 1, 5, and 20 mg/kg IV q24h. The tobramycin dose was 10 mg/kg SC b.i.d. Tobramycin treatment alone was associated with mild nephropathy. In comparison to the control group, absolute and relative kidney weights were increased in all groups receiving tobramycin. In addition, an increased incidence and severity of cortical tubular regeneration was observed in all tobramycin-treated groups. Concurrent administration of daptomycin had no effect on the tobramycin-induced nephropathy. Mild skeletal muscle degeneration and/or regeneration were observed in the high dose daptomycin group when given alone. When daptomycin was administered concurrently with tobramycin, skeletal muscle degeneration and/or regeneration were observed at dose levels of daptomycin ≥ 5 mg/kg. An increase in the incidence of the muscle damage in relation to tobramycin dose suggests that daptomycin-induced myopathy may be potentiated by co-administration of tobramycin. This increase is most likely related to the nephrotoxic effects of tobramycin, which may have resulted in reduced renal clearance of daptomycin and higher systemic exposure. No microscopic damage to the sciatic nerve was apparent.

The effect of concurrent administration of daptomycin and gentamicin with respect to nephrotoxicity was investigated in dogs. Gentamicin dose levels were 9 or 30 mg/kg/day IM (3 or 10 mg/kg q8h). The daptomycin dose was 30 mg/kg/day IV (10 mg/kg.q8h). When daptomycin was administered with high dose gentamicin, blood urea nitrogen and creatinine levels were 2-fold greater and potassium levels were slightly decreased (approximately 17%) as compared to the values observed with gentamicin alone. High dose gentamicin alone produced slight to minimal renal tubular necrosis and tubular epithelial regeneration. In animals receiving high dose gentamicin in combination with daptomycin, the severity of these lesions was graded as minimal to moderate. Thus, when a high dose of gentamicin was given in combination with daptomycin, the severity of the nephrotoxic lesions was increased and changes in clinical chemistry parameters indicative of renal effects were observed. In contrast, the administration of daptomycin with a low dose of gentamicin did not produce a functionally meaningful difference

in the severity of nephrotoxicity. Daptomycin, given alone at 30 mg/kg/day did not induce nephrotoxicity.

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 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. 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 apparent 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 (see **TOXICOLOGY**).

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 µg/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 µg/mL).

Neonatal Animals
Administration of daptomycin to postnatal day (PND) 4 neonatal dogs at 50 and 75 mg/kg/day (C_{max} and AUC_{inf} values of ≥321 µg/mL and ≥1470 µg•h/mL, respectively) produced marked clinical signs of twitching, muscle rigidity in the limbs, impaired use of limbs, and a decrease in body weights and overall body condition necessitating early discontinuation by PND 19. A dose of 25 mg/kg/day from PND 4 to PND 31 (C_{max} and AUC_{inf} values of 147 µg/mL and 717 µg•h/mL, respectively) produced mild reversible clinical signs of twitching and one incidence of muscle rigidity with no effects on body weight. No histopathological effect related to daptomycin was observed (including peripheral and central nervous system and skeletal muscle) at any dose. No effects were observed in dogs administered daptomycin at 10 mg/kg/day, the NOAEL, following 28 days of treatment with associated C_{max} and AUC_{inf} values of 62 µg/mL and 247 µg•h/mL, respectively.

Human Pharmacology

Pharmacodynamics
In a placebo-controlled study in healthy adult volunteers, there was no evidence that exposure to **CUBICIN®** at 6 mg/kg IV q24h x 14d caused any meaningful changes in cardiac repolarization as measured by QTcB. In nerve motor function studies in adults, **CUBICIN®** administration did not cause any significant changes in the set of objective measures indicative of neuropathy or myopathy. **CUBICIN®** administration was associated with a significant increase in the number

of affirmative responses to the neurological questionnaire designed to assess symptoms and deficits associated with small fiber sensory function. During the 14-day follow-up period more subjects in the **CUBICIN®** group (8) compared to the normal saline group (5) reported symptoms of tingling, numbness and weakness.

In an ascending dose study in adults, **CUBICIN®** was well-tolerated at doses up to 12 mg/kg for up to 14 days. No significant adverse effects, including effects on skeletal muscle and peripheral nerves, were observed during the study period in any dose group.

Pharmacokinetics

The pharmacokinetic profile of **CUBICIN®** in humans is highly predictable following intravenous administration. Single and multiple doses of **CUBICIN®**, up to 12 mg/kg/day for up to 14 consecutive days have been studied in healthy adult subjects (see Table 16, **ACTION AND CLINICAL PHARMACOLOGY**).

The pharmacokinetics and concentrations of daptomycin in cantharides-induced skin blisters and in plasma were determined over a 24-hour period following a single IV infusion of 4 mg/kg of **CUBICIN®** in healthy adult volunteers. Daptomycin penetrated the inflammatory exudate moderately rapidly, with mean 1- and 2- hour concentrations of 9.4 µg/mL and 14.5 µg/mL, respectively. T_{max} in the inflammatory fluid occurred approximately 3 hours later than in plasma (3.7 hours vs. 0.5 hours) with a C_{max} of 27.6 µg/mL. The mean C_{max} in the plasma was 77.5 µg/mL. The elimination half-life of daptomycin from the inflammatory exudate was highly variable, ranging from 6.3 hours to 30.9 hours, with a mean of 17.3 hours. The mean $AUC_{0\text{-}24h}$ in the inflammatory exudate was 318.2 µg·hr/mL. Mean plasma elimination half-life was 7.74 hours with mean plasma $AUC_{0\text{-}24h}$ of 468.0 µg·hr/mL, representing approximately 88% of the mean $AUC_{0\text{-}\infty}$ (529.7 µg·hr/mL). The penetration of daptomycin into inflammatory exudate, calculated as $AUC_{0\text{-}24h}$ exudate/$AUC_{0\text{-}24h}$ plasma, was 68.4%.

A study was conducted to evaluate the pharmacokinetics of daptomycin over a period of 3 weeks in adult subjects with End Stage Renal Disease (ESRD) on hemodialysis three times weekly using both high-flux (Baxter CT190G) and low-flux (Fresenius F8) dialysis membranes. **CUBICIN®** was administered as an 8 mg/kg loading dose followed by 6 mg/kg 3 times per week.

The AUC values on Day 17 appear higher in the low-flux group at 2586 µg x h/mL compared with the high-flux group at 1716 µg x h/mL (Table 33). However, examination of the individual AUC's of the 4 adult subjects in the low-flux group and 3 adult subjects in the high-flux group indicated that the low flux cohort's AUCs were consistently higher across all time points than those of the subjects in the high-flux cohort. Thus, there was little evidence of excessive accumulation in the low flux group compared with the high flux group.

Due to high variability in daptomycin pharmacokinetics between adult subjects under hemodialysis using low-flux and high-flux membranes, no statistically significant differences were detectable. However, the pre- to post-dialysis decrease in daptomycin levels was greater on the high-flux membrane (41%) compared to the low-flux membrane (5 to 7%).

Table 33. Pharmacokinetic Parameters of Daptomycin Following Single (Day 1) and Repeat (3 times/week) Dosing of CUBICIN® in Adult Subjects with ESRD

Membrane Type	Day	N	Pharmacokinetic Parameters Mean (CV%)					
			C_{max} (µg/mL)	C_{min} (µg/mL)	AUC[a] (µg x h/mL)	$T_{1/2}$ (h)	CL (mL/h/kg)	Vss L/kg
Low-Flux	1	6	91 (31)	--	1697 (33)	38.5 (21.3)	2.8 (40.7)	0.14 (17.8)
	8	5	86 (33)	17 (9)	1916 (45)	42.3 (26.9)	3.5 (54.4)	0.18 (28.3)
	17	4	103 (26)	29 (11)	2586 (35)	55.9 (36.1)	2.2 (35.4)	0.16 (21.0)
High - Flux	1	7	107 (39)	--	1945 (34)	35.7 (11.3)	2.8 (51.6)	0.14 (54.2)
	8	6	81 (38)	14 (6)	1672 (36)	38.1 (16.6)	3.7 (50.0)	0.19 (54.6)
	17	3	94 (17)	22 (3)	1716 (27)	45.3 (37.8)	3.6 (44.1)	0.27 (85.1)

Subjects received 8 mg/kg on Day 1, followed by 6 mg/kg 3 times per week.

[a] AUC (0-t): Area under the concentration versus time curve from 0 to end of dosing interval

MICROBIOLOGY

Daptomycin has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria only. Daptomycin inserts directly into the cytoplasmic membrane of both growing and stationary phase Gram-positive bacteria resulting in dissipation of the membrane potential and efflux of potassium ions, which causes inhibition of protein, DNA and RNA synthesis and bacterial cell death with negligible lysis. The antibacterial activity of daptomycin requires the presence of free calcium, therefore, the determination of *in vitro* susceptibility of bacteria to daptomycin requires that broth media be supplemented with physiological levels of free (ionized) calcium at a concentration of 50 µg/mL. Daptomycin retains activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (see **INDICATIONS AND CLINICAL USE**). Daptomycin is not active against Gram-negative bacteria.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology.

Daptomycin's activity *in vitro* is inhibited in the presence of pulmonary surfactant. In mouse and hamster models of broncho-alveolar pneumonia (BAP), daptomycin lacked efficacy.
In vitro studies have investigated daptomycin interactions with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions of daptomycin occurred with aminoglycosides, β-lactam antibiotics and rifampin against some isolates of staphylococci including some methicillin-resistant isolates.

Daptomycin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections.

Table 34. Daptomycin MIC_{50} and MIC_{90} for Susceptible Aerobic and Facultative Gram-Positive Bacteria *in vitro* and in Clinical Infections

Microorganism	# of clinical isolates	MIC (µg/mL)		
		MIC_{50}	MIC_{90}	Range
Staphylococcus aureus (including methicillin-resistant strains)	3848	0.25	0.5	≤0.06 – 2
Streptococcus agalactiae	187	0.12	0.25	≤0.06 - 0.5
Streptococcus pyogenes	170	≤0.06	≤0.06	≤0.06 - 0.12

The following *in vitro* data are available (Table 35), but their clinical significance is unknown. Greater than 90% of the following microorganisms demonstrate an *in vitro* MIC less than or equal to the susceptible breakpoint for daptomycin versus the bacterial genus. The efficacy of daptomycin in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Table 35. Daptomycin MIC_{50} and MIC_{90} for Susceptible Aerobic and Facultative Gram-Positive Microorganisms *in vitro*

Microorganism	# of clinical isolates	MIC (µg/mL)		
		MIC_{50}	MIC_{90}	Range
Corynebacterium jeikeium	68	0.25	0.5	0.06 – 1
Enterococcus faecalis (vancomycin-resistant strains)	34	0.5	2	0.25 – 2
Enterococcus faecalis (vancomycin-susceptible strains)	917	0.5	1	≤0.06 - 4
Enterococcus faecium (including vancomycin-resistant strains)	398	2	4	0.25 - 4
Staphylococcus epidermidis (including methicillin-resistant strains)	164	0.5	0.5	0.12 - 1
Staphylococcus haemolyticus	102	0.25	0.5	0.03 - 1
Streptococcus dysgalactiae subsp. equisimilis	102	≤0.03	0.06	≤0.03 - 0.12

Resistance

At this time, no mechanism of resistance to daptomycin has been identified. There have been reports of *Staphylococcus aureus* isolates exhibiting decreased or intermediate vancomycin susceptibility demonstrating decreased daptomycin susceptibility.

Non-susceptible isolates of *Staphylococcus aureus* have been recovered from patients in clinical trials. These include one patient enrolled in a Phase 2 study, one who received **CUBICIN®** in a compassionate use study, and seven from the SAB/SAIE trial.

Cases of daptomycin resistance have been reported in staphylococci during post-marketing.

Susceptibility Testing Methods

Susceptibility testing by dilution methods requires the use of daptomycin susceptibility powder. The testing also requires the presence of physiological levels of free calcium ions (50 µg/mL of calcium, using calcium chloride) in Mueller-Hinton broth.

Dilution Technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure based on a broth dilution method or equivalent using standardized inoculum and concentrations of daptomycin. The use of the agar dilution method is not recommended with daptomycin. The MICs should be interpreted according to the criteria in Table 36.

Table 36. Susceptibility Interpretive Criteria for Daptomycin

Pathogen	Broth Dilution MIC (µg/mL)[a]		
	S	I	R
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant)	≤ 1	(b)	(b)
Streptococcus pyogenes and *Streptococcus agalactiae*	≤ 1	(b)	(b)

[a] The MIC interpretive criteria for *S. aureus* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 µg/mL; 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 µg/mL, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.

[b] Limited data on daptomycin resistant strains precludes defining any categories other than "Susceptible". Strains 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 confirmation of results using CLSI reference broth microdilution method.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Diffusion Technique

Quantitative methods that require measurements of zone diameters have not been shown to provide reproducible estimates of the susceptibility of bacteria to daptomycin. The use of a disk diffusion method is not recommended with daptomycin.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the procedures. Standard daptomycin powder should provide the range of values noted in Table 37. Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 37. Acceptable Quality Control Ranges for Daptomycin to be used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges
	Broth Dilution MIC (µg/mL)[a]
Staphylococcus aureus ATCC 29213	0.12-1
Streptococcus pneumoniae ATCC 49619[b]	0.06-0.5

[a] The quality control ranges for *S. aureus* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 µg/mL; the quality control ranges for *S. pneumoniae* are applicable only to tests performed by broth dilution using Mueller-Hinton broth adjusted to a calcium content of 50 µg/mL, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35ºC for 20 to 24 hours.

[b] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

TOXICOLOGY

Single-Dose Toxicity Studies

Acute toxicity testing identified the neuromuscular system (nervous system and/or skeletal muscle) as the target organ of daptomycin toxicity, and uncovered potential differences in sensitivity among the species tested (i.e., mouse, rat, dog, and monkey). Studies performed are listed in Table 38 below.

Table 38. Results of Single-Dose Toxicity Studies

Species/ Strains	Route	Dose Levels (mg/kg)	Max. Non-Lethal Dose (mg/kg)	Noteworthy Findings
Mouse/ ICR	IV	0, 700, 900, 1100, 1400	<700	0: Transient generalized leg weakness 700: 1M and 5F died ≥700: Generalized leg weakness, hypoactivity, ataxia, tremors, ptosis, and death
Rat/ Fischer	IV	0, 110, 140, 180, 225	110	0: Transient generalized leg weakness 110: Transient generalized leg weakness, hypoactivity 140: 4M and 1F died ≥140: Leg weakness, ataxia, hindlimb paralysis, tremors, clonic convulsions, and death
Dog/ Beagle	IV	25, 200	200	≥25: Slight (2-3X) increases in serum creatine phosphokinase (CPK) within 24 h post-dose and generally returned to normal within 48 h after dosing 200: 10% decrease in body weight in 1 of 4 dogs, and slight reduction in appetite in 2 of 4 dogs
Monkey/ Rhesus	IV	25, 200	25	25: Slight, transient lethargy and paleness of the facial skin in 2 of 4 animals; CPK increased >10-fold at 3 h post-dose and returned to normal within 48 h 200: 1M and 2F died. Death preceded by extreme lethargy, ataxia, and severe muscle weakness; slight axonal degeneration of the sciatic nerve in one of the deaths; CPK increased >10-fold at 3 h post-dose and did not return to normal until Day 7 after dosing
Rat/ Fischer	SC	0, 350, 700	700	0: Transient generalized leg weakness ≥ 350: Transient generalized leg weakness; sores/scabs at injection sites

IV: intravenous; SC: subcutaneous; M: male; F: female; h: hour.

Repeat-Dose Toxicity Studies

The results of repeat-dose and investigative studies consistently demonstrated daptomycin's primary target organ to be skeletal muscle in adult rats and dogs, with effects observed in peripheral nerve at higher dose levels in both species (Table 39). Skeletal myopathy was usually accompanied by serum creatine phosphokinase (CPK) elevations in adult dogs, which preceded clinical effects and correlated with the severity of microscopic lesions. Nephrotoxicity and gastrointestinal effects observed in rats appear to be species-specific because these effects were not evident in either dogs or monkeys up to the highest doses tested (75 mg/kg/day and 10 mg/kg/day in dogs and monkeys, respectively). Recovery from skeletal myopathy was more rapid than recovery from daptomycin-related peripheral neuropathy. Recovery of peripheral nerve function was evident within 3 to 6 months post-dosing, although very minimal histological changes were observed 6 months after dosing cessation.

In contrast to adult dogs, juvenile dogs showed evidence of effects in nerves of the spinal cord as well as peripheral nerves after 28 days of dosing (Table 39 and see **DETAILED PHARMACOLOGY, Animal Pharmacology, Juvenile Animals**). The effects were noted at lower daptomycin doses and at lower daptomycin blood concentrations than in adult dogs. The data suggests that as compared to adult populations, juvenile populations may be more sensitive to daptomycin-related nerve effects.

Table 39. Summary of Findings on Repeat-Dose Toxicity and Investigative Studies*

Species / Strain	Study Duration	Dose Range (mg/kg/day)	Noteworthy Findings (Dose levels affected)
Rat/ Fischer	2 weeks; 1, 3, and 6 months	1 to 150	▪ Skeletal Muscle (≥ 5 mg/kg): Mild myofiber degeneration/regeneration (e.g., diaphragm, quadriceps, pectoral, biceps femoris); electron microscopy revealed intracellular edema of endothelial cells and infiltration of macrophages and monocytes. Both Type I and Type II fibers affected. Effects were reversible within 30 days following cessation of dosing. ▪ Nervous System (≥ 100 mg/kg): Peripheral neuropathy such as slight axonal degeneration of the sciatic nerve. ▪ Kidney (≥ 10 mg/kg): Increased kidney weight; vacuolar degeneration/ regeneration of renal cortical tubular epithelium; cytoplasmic bodies observed upon electron microscopy. Effects were reversible. ▪ GI Tract (≥ 20 mg/kg): Cecal changes (dilatation and increased weight) attributable to changes in enterobacterial flora typical of prolonged antibiotic treatment. Effects were reversible after an 8-week recovery phase.
Dog/ Beagle	2 weeks; 1, 3, and 6 months	1 to 100	▪ Skeletal Muscle (≥ 10 mg/kg): Reversible myofiber degeneration/ regeneration (degenerative effects limited to ≤ 0.1% of fibers). CPK/AST/ALT elevations. Skeletal muscle effects are independent of C_{max} and appear primarily related to dosing frequency (time between doses) and/or AUC. ▪ Nervous System (≥ 40 mg/kg; based upon 6 months of dosing): Abnormal patellar reflex, decreased sensory and motor nerve conduction velocities, minimal microscopic axonal degeneration observed following 6 months of dosing (at 40 mg/kg/day). In shorter term studies (14 days to 3 months duration), nerve effects were observed at doses ≥ 75 mg/kg. Moderate to severe clinical signs (abnormal posture/gait, impaired coordination, inability to stand, sternal recumbency) and functional (electrophysiology) deficits were evident. Microscopic effects were detected in peripheral nerves, dorsal ganglia, nerve roots (including left and right ventral and dorsal roots) and spinal nerves. C_{max} appeared the key determinant for peripheral nerve effects. Recovery of peripheral nerve function was evident within 3 to 6 months post-dosing (consistent with the lack of effect upon the neuronal cell body), although histological changes (dorsal roots, ventral roots and spinal nerves) were evident 6 months after dosing. In all but one case, the axonal degeneration observed in these tissues was graded as very minimal and described as rare, scattered vacuoles.
Juvenile Dog/ Beagle	2 weeks and 1 month	1 to 150	▪ Skeletal Muscle (≥ 150 mg/kg): Reversible degeneration of skeletal muscle. In contrast to adult dogs, CPK levels were not increased in juvenile dogs. ▪ Nervous System (≥ 50 mg/kg): Minimal to slight axonal degeneration of peripheral nerve fiber (sciatic, ulnar) and spinal cord (cervical, thoracic, lumbar, dorsal nerve root) observed. Peripheral nerve (sciatic) and spinal cord (cervical, thoracic, lumbar) effects were not reversed following a 4-week recovery phase.
Monkey/ Rhesus	1 month	1 to 10	No effects were observed up to 10 mg/kg, the highest dose tested.

* Daptomycin was administered by bolus IV injection in all studies; one study also investigated administration via 30-minute IV infusion. For most studies, daptomycin was administered once daily (q24h), except for select investigative studies in which it was also administered on a three times daily (q8h) regimen.

GI: gastrointestinal; CPK: creatine phosphokinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; C_{max}: maximum serum concentration following dosing.

Genotoxicity

Daptomycin was not mutagenic or clastogenic 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.

Carcinogenicity

Carcinogenicity studies have not been conducted.

Reproduction and Development Toxicity

Reproductive and developmental toxicity studies of daptomycin were conducted in rats (up to 150 mg/kg) and rabbits (up to 75 mg/kg) by once-daily bolus IV injection. Studies were conducted at daptomycin dose levels up to and including those that caused parental toxicity (see **Repeat-Dose Toxicity Studies**).

Daptomycin administration to the F_0 generation was not associated with any reproductive toxicity, such as adverse effects on mating, fertility, parturition, and lactation. Further, there were no findings to suggest that daptomycin treatment of the F_0 generation resulted in any developmental toxicities in the F_1 generation. No test article-related mortality, teratogenic potential, alterations in growth, or functional toxicities was noted in any of the studies. Effects on progeny were limited to a slight (~10%), transient decrease in body weight at a dose level of 150 mg/kg in rats; this effect was reversible within 14 days postpartum. No other effects on the growth, behavior, or reproductive performance of the offspring were noted.

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Tenth Edition*. CLSI document M07-A10, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-seventh Informational Supplement*, CLSI document M100-S27, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2017.
3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Twelfth Edition. CLSI document M02-A12, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrCUBICIN®/CUBICIN® RF
Daptomycin for Injection

Read this carefully before you start taking **CUBICIN®/CUBICIN® RF** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CUBICIN®/CUBICIN® RF**.

What is CUBICIN®/CUBICIN® RF used for?
CUBICIN®/CUBICIN® RF is used to treat bacterial infections:

- of the skin and soft tissues (patients 1 year and older)
- in the blood (patients 1 year and older)
- certain heart valve infections (patients 18 years and older)

Antibacterial drugs like **CUBICIN®/CUBICIN® RF** treat only infections caused by bacteria. They do not treat viral infections. Although you may feel better early in treatment, **CUBICIN®/CUBICIN® RF** should be used exactly as directed. Misuse or overuse of **CUBICIN®/CUBICIN® RF** could lead to growth of bacteria that will not be killed by **CUBICIN®/CUBICIN® RF** (resistance). This means that **CUBICIN®/CUBICIN® RF** may not work for you in the future.

How does CUBICIN®/CUBICIN® RF work?
CUBICIN®/CUBICIN® RF are antibiotics. They work by killing certain bacteria that cause your infection.

What are the ingredients in CUBICIN®?
Medicinal ingredients: Daptomycin
Non-medicinal ingredients: Sodium hydroxide

What are the ingredients in CUBICIN® RF?
Medicinal ingredients: Daptomycin
Non-medicinal ingredients: Sodium hydroxide and sucrose

CUBICIN®/CUBICIN® RF comes in the following dosage forms:
Lyophilized powder for solution available as 500 mg/10 mL vial

Do not use CUBICIN®/CUBICIN® RF if:

- you are allergic to daptomycin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CUBICIN®/CUBICIN® RF. Talk about any health conditions or problems you may have, including if you:

- have kidney or severe liver problems.
- have high blood levels of creatine phosphokinase (CPK).
- are pregnant, or planning on becoming pregnant.
- are breastfeeding or plan to breastfeed. Breastfeeding should be stopped during treatment

with **CUBICIN®/CUBICIN® RF**.
- are allergic to any antibiotics or other drugs.
- are taking other medications (see **The following may interact with CUBICIN®/CUBICIN® RF**).
- have any questions about your treatment, both before and during treatment.

Other warnings you should know about:

Stop taking **CUBICIN®/CUBICIN® RF** and contact your doctor right away if you:
- have severe or lasting diarrhea (bloody or watery) with or without
  - fever.
  - stomach pain or tenderness.

You may have Clostridium difficile colitis (bowel inflammation).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CUBICIN®/CUBICIN® RF:
- Drugs that lower cholesterol (HMG-CoA reductase inhibitors also known as “statins” such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin)
- Tobramycin (another antibiotic)
- Blood thinners (warfarin)

How to take CUBICIN®/CUBICIN® RF:
CUBICIN®/CUBICIN® RF will be given intravenously (injected into a vein) by a doctor or nurse in a hospital or clinical setting.

Usual dose:
Adults:

Serious skin infections: The usual adult dose is 4 mg for every kg of body weight. Your dose will be given either as an injection over a 2-minute period or by infusion over a 30-minute period every 24 hours for 7 to 14 days.

Bacterial infections in the blood, including certain heart valve infections: The usual adult dose is 6 mg for every kg of body weight. Your dose will be given either as an injection over a 2-minute period or by infusion over a 30-minute period every 24 hours for 10 to 56 days.

Children:

Your doctor will decide how much CUBICIN® / CUBICIN® RF to give your child based on their age, weight and type of infection.

Serious skin infections:

Age Group	Dosage*	Duration of Therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to less than 2 years	10 mg/kg once every 24 hours infused over 60 minutes	

Bacterial infections in the blood:

Age Group	Dosage	Duration of Therapy
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	

Overdose:

If you think you have taken too much **CUBICIN®/CUBICIN® RF**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using CUBICIN®/CUBICIN® RF?

These are not all the possible side effects you may feel when taking **CUBICIN®/CUBICIN® RF**. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- headache or dizziness.
- diarrhea or constipation.
- nausea or vomiting.
- rash or itching.
- difficulty sleeping.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON A serious allergic reaction with symptoms such as: • shortness of breath, difficulty swallowing. • hives, itching, drug rash, blister-like sores. • swelling of the mouth, throat, lips and limbs (angioedema).		X	

Pain in the hands and feet with symptoms such as: • burning, "pins and needles", numbness. • muscle pain, weakness or tiredness (myopathy).		X	
Irregular heartbeat		X	
Kidney problems with symptoms such as: • reduced kidney function, kidney failure. • increased urination, bloody urine. • lower back pain, pressure in the bladder. • fatigue and nausea. • Fever or rash		X	
VERY RARE Respiratory problems with symptoms such as: • fever, cough, shortness of breath or difficulty breathing (eosinophilic pneumonia). • Inflammation of the lungs (organizing pneumonia)		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting: **https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html**
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
CUBICIN® vials containing lyophilized powder should be stored at 2ºC to 8ºC.

CUBICIN® RF vials containing lyophilized powder should be stored at 15ºC to 30ºC.

Reconstituted solutions are to be used immediately or refrigerated (2ºC to 8ºC) and used within 72 hours, then discarded. Health Care professionals should refer to the Product Monograph for more details.

Keep out of reach and sight of children.

If you want more information about CUBICIN®/CUBICIN® RF:

- Talk to your healthcare professional
- Find this document plus the full product monograph, prepared for health professionals at: http://www.sunovion.ca or by contacting the sponsor, Sunovion Pharmaceuticals Canada Inc., at: 1-866-260-6291 or by visiting the Health Canada website at: https://www.canada.ca/en/health-canada.html.

This leaflet was prepared by Sunovion Pharmaceuticals Canada Inc.

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