PRODUCT DESCRIPTION

Name of Pharmaceutical Product

CUBICIN® (daptomycin for injection) 500mg per vial

Pharmacological Therapeutic Class

CUBICIN contains daptomycin, a cyclic lipopeptide antibacterial agent.

Composition

Active Ingredient: Daptomycin

Inactive Ingredient: Sodium hydroxide

Description

A pale yellow to light brown lyophilized cake.

Freshly reconstituted solutions of CUBICIN range in color from pale yellow to light brown

Dosage Form

Type

Lyophilized powder for reconstitution.

Method/Route of Administration

CUBICIN is given by intravenous (IV) infusion.

Sterility Statement

CUBICIN is a sterile product contained in a single-dose vial.

INDICATIONS AND USAGE

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

Complicated Skin and Skin Structure Infections

Adult (≥ 18 years of age) and pediatric (1 to 17 years of age) patients with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae* subsp. *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Staphylococcus aureus Bloodstream Infections (Bacteremia)

Adult patients (≥ 18 years of age) with *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

Pediatric patients (1 to 17 years of age) with *S. aureus* bloodstream infections (bacteremia) caused by methicillin-susceptible and methicillin-resistant isolates.

Limitations of Use

CUBICIN is not indicated for the treatment of pneumonia.

CUBICIN is not indicated for the treatment of left-sided infective endocarditis due to *S. aureus*. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. CUBICIN has not been studied in patients with prosthetic valve endocarditis.

Usage

Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

When culture and susceptibility information is available, it should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility

patterns may contribute to the empiric selection of therapy. Empiric therapy may be initiated while awaiting test results.

DOSAGE AND ADMINISTRATION

Administration

CUBICIN should be administered intravenously.

Adults

Complicated Skin and Skin Structure Infections

CUBICIN 4 mg/kg should be administered to adult patients intravenously in 0.9% sodium chloride for injection once every 24 hours for 7 to 14 days by infusion over a 30-minute period.

Staphylococcus aureus Bloodstream Infections (Bacteremia)

CUBICIN 6 mg/kg should be administered to adult patients intravenously in 0.9% sodium chloride for injection once every 24 hours for 2 to 6 weeks by infusion over a 30-minute period. There are limited safety data for the use of CUBICIN for more than 28 days of therapy. In the Phase 3 trial, there were a total of 14 patients who were treated with CUBICIN for more than 28 days.

Pediatric Patients (1 to 17 Years of Age)

Complicated Skin and Skin Structure Infections

The recommended dosage regimens based on age for pediatric patients with cSSSI are shown in Table 1. CUBICIN should be administered intravenously in 0.9% sodium chloride for injection once every 24 hours for up to 14 days.

Table 1: Recommended Dosage of CUBICIN in Pediatric Patients (1 to 17 Years of Age) with Complicated Skin and Skin Structure Infections, 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 < 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)

The recommended dosage regimens based on age for pediatric patients with *S. aureus* bloodstream infections (bacteremia) are shown in Table 2. CUBICIN should be administered intravenously in 0.9% sodium chloride for injection once every 24 hours for up to 42 days.

Table 2: Recommended Dosage of CUBICIN in Pediatric Patients (1 to 17 Years of Age) with *S. aureus* Bloodstream Infections, Based on Age

Age group	Dosage*	Duration of therapy(1)
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.
(1) Minimum duration for pediatric bacteremia should be in accordance with the perceived risk of complications in the individual patient

Patients with Renal Impairment

The recommended dosage regimen for adult patients with creatinine clearance (CL_{CR}) <30 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours

(Table 3). When possible, CUBICIN should be administered following the completion of hemodialysis on hemodialysis days (see *Warnings and Precautions, Use in Specific Populations,* and *Clinical Pharmacology*).

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

Table 3. Recommended Dosage of CUBICIN in Adult Patients

Creatinine Clearance (CL_{CR})	Dosage Regimen	
	cSSSI	*S. aureus* Bloodstream Infections
≥30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
<30 mL/min, including hemodialysis and CAPD	4 mg/kg once every 48 hours*	6 mg/kg once every 48 hours*

*When possible, administer CUBICIN following the completion of hemodialysis on hemodialysis days.

Preparation of CUBICIN for Administration

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

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

1. Remove the polypropylene flip-off cap from the CUBICIN vial to expose the central portion of the rubber stopper.
2. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
3. Slowly transfer 10 mL of 0.9% sodium chloride for injection through the center of the rubber stopper into the CUBICIN vial, pointing the transfer needle toward the wall of the vial. It is recommended that a beveled sterile transfer needle that is 21 gauge or smaller

in diameter, or a needleless device is used, pointing the transfer needle toward the wall of the vial.

4. Ensure that all of the CUBICIN powder is wetted by gently rotating the vial.
5. Allow the wetted product to stand undisturbed for 10 minutes.
6. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.
7. Slowly remove reconstituted liquid (50 mg daptomycin/mL) from the vial using a beveled sterile needle that is 21 gauge or smaller in diameter.

Adults

Intravenous Infusion over a period of 30 minutes

- For IV infusion over a period of 30 minutes in adult patients, the appropriate volume of the reconstituted CUBICIN (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride for injection.

Pediatric Patients (1 to 17 Years of Age)

Intravenous Infusion over a period of 30 or 60 minutes

- For IV infusion over a period of 30 minutes in pediatric patients, reconstituted CUBICIN (concentration of 50 mg/mL) is further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride for injection. The infusion rate should be maintained at 1.67 mL/min over the 30 minute period.
- For IV infusion over a period of 60 minutes in pediatric patients, reconstituted CUBICIN (concentration of 50 mg/mL) is further diluted, using aseptic technique, into an IV infusion bag containing 25 mL of 0.9% sodium chloride for injection. The infusion rate should be maintained at 0.42 mL/min over the 60 minute period.

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

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Stability studies have shown that the reconstituted solution

is stable in the vial for 12 hours at room temperature and up to 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F).

The diluted solution is stable in the infusion bag for 12 hours at room temperature and 48 hours if stored under refrigeration at 2 to 8°C (36 to 46°F). The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) should not exceed 12 hours at room temperature or 48 hours under refrigeration at 2 to 8°C (36 to 46°F).

CUBICIN vials are for single use only.

Compatible Intravenous Solutions

The compatible diluent for reconstitution is 0.9% sodium chloride for injection and lactated Ringer's injection.

For IV infusion, reconstituted CUBICIN (concentration of 50 mg/mL) is further diluted, using aseptic technique, with 0.9% sodium chloride for injection.

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

Incompatibilities

CUBICIN is not compatible with dextrose-containing diluents.

CUBICIN should not be used in conjunction with ReadyMED® elastomeric infusion pumps (Cardinal Health, Inc.). Stability studies of CUBICIN solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the CUBICIN solution.

Because only limited data are available on the compatibility of CUBICIN with other IV substances, additives and other medications should not be added to CUBICIN single-dose vials or infusion bags, or infused simultaneously 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.

CONTRAINDICATIONS

CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin or to any of the excipients.

WARNINGS AND PRECAUTIONS

Anaphylaxis/Hypersensitivity Reactions

Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including CUBICIN. If an allergic reaction to CUBICIN occurs, discontinue the drug and institute appropriate therapy.

Pneumonia

CUBICIN should not be used for the treatment of pneumonia. It has been demonstrated in clinical studies that CUBICIN is not effective in the treatment of community-acquired pneumonia, due to binding to pulmonary surfactant and consequent inactivation.

Skeletal Muscle Effects

Increases in plasma CPK levels, muscular pains, weakness, and/or rhabdomyolysis have been reported during therapy with CUBICIN.

It is recommended that:

• Patients receiving CUBICIN be monitored for the development of muscle pain or weakness, particularly of the distal extremities.
• In patients who receive CUBICIN, CPK levels be measured at baseline and at regular intervals (at least weekly), and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with CUBICIN.
• In adult patients with renal impairment, both renal function and CPK be monitored more frequently than once weekly.
• CUBICIN be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels greater than 1000 U/L (approximately 5 times upper limit of normal [ULN]) and in patients without reported symptoms who have marked elevations in CPK, with levels greater than 2000 U/L (≥10× ULN).
• Consideration be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving CUBICIN.

Peripheral Neuropathy

Physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving CUBICIN.

Pediatric patients younger than one year old should not be given CUBICIN 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.

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 should undergo prompt medical evaluation, and CUBICIN should be discontinued immediately. Treatment with systemic steroids is recommended.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in post-marketing experience with daptomycin. Patients who develop fever, skin rash, peripheral eosinophilia and systemic organ (for example, hepatic, pulmonary or renal) impairment while receiving CUBICIN should undergo medical evaluation. If DRESS is suspected, CUBICIN should be discontinued promptly and appropriate treatment instituted.

Tubulointerstitial Nephritis (TIN)

TIN has been reported in post-marketing experience with daptomycin. Patients who develop new or worsening renal impairment while receiving CUBICIN should undergo medical evaluation. If TIN is suspected, CUBICIN should be discontinued promptly and appropriate treatment instituted.

Clostridioides difficile–Associated Diarrhea

Clostridioides difficile–associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including CUBICIN. If CDAD is suspected or confirmed, CUBICIN may need to be discontinued and appropriate treatment instituted as clinically indicated.

Persisting or Relapsing *S. aureus* Bacteremia/Endocarditis

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

Drug-Laboratory Test Interactions

False prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) have been observed when certain recombinant thromboplastin reagents are utilized for the assay (see *Undesirable Effects, Drug-Laboratory Test Interactions*).

Non-Susceptible Microorganisms

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

UNDESIRABLE EFFECTS

Undesirable Effects Identified during Clinical Trials

During clinical trials of CUBICIN, the following adverse drug reactions were reported during therapy and during follow-up. The adverse drug reactions are organized by system organ class, and the frequency categories for these adverse drug reactions are reported in the table below as follows:

Very common:	≥1/10 (≥10%)
Common:	≥1/100 and <1/10 (≥1% and <10%)
Uncommon:	≥1/1000 and <1/100 (≥0.1% and <1%)
Rare:	≥1/10,000 and <1/1000 (≥0.01% and <0.1%)
Very rare:	<1/10,000 (<0.01%)

Adverse Drug Reaction	Frequency Category
Blood and lymphatic system disorders	
Anemia	Common
Thrombocytosis	Uncommon
Eosinophilia	Uncommon
Leukocytosis	Uncommon
Cardiac disorders	
Supraventricular arrhythmia	Uncommon
Ear and labyrinth disorders	
Vertigo	Uncommon
Gastrointestinal disorders	
Gastrointestinal and abdominal pain	Common
Diarrhea	Common

Adverse Drug Reaction	Frequency Category
Vomiting	Common
Flatulence, bloating, and distension	Common
Constipation	Common
Nausea	Common
Dyspepsia	Uncommon
Abdominal distension	Uncommon
General disorders and administration site conditions	
Asthenia	Common
Pyrexia	Common
Infusion site reaction	Common
Chills	Uncommon
Fatigue	Uncommon
Hepatobiliary disorders	
Jaundice	Rare
Infections and infestations	
Urinary tract infection	Common
Fungal infection	Common
Candida infection	Common
Fungemia	Uncommon
Investigations	
Blood creatine phosphokinase increased	Common
Liver function test abnormal (increased ALT, AST, or ALP)	Common
Blood creatinine increased	Uncommon
International Normalized Ratio increased	Uncommon
Blood lactate dehydrogenase increased	Uncommon

Adverse Drug Reaction	Frequency Category
Prothrombin time prolonged	Rare
Metabolism and nutrition disorders	
Hyperglycemia	Uncommon
Electrolyte imbalance	Uncommon
Decreased appetite	Uncommon
Musculoskeletal, connective tissue, and bone disorders	
Limb pain	Common
Muscular weakness	Uncommon
Muscle pain	Uncommon
Arthralgia	Uncommon
Muscle cramps	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Paresthesia	Uncommon
Tremor	Uncommon
Taste disorder	Uncommon
Eye irritation	Uncommon
Psychiatric disorders	
Anxiety	Common
Insomnia	Common
Renal and urinary disorders	
Renal impairment, including renal failure and renal insufficiency	Uncommon

Adverse Drug Reaction	Frequency Category
Reproductive system and breast disorders	
Vaginitis	Uncommon
Skin and subcutaneous tissue disorders	
Pruritus	Common
Rash	Common
Urticaria	Uncommon
Vascular disorders	
Hypertension	Common
Hypotension	Common
Flushing	Uncommon

Undesirable Effects Reported Post-Marketing

The following adverse drug reactions, not listed above, have been reported during worldwide post-marketing experience:

Blood and lymphatic system disorders

Thrombocytopenia

Immune system disorders

Hypersensitivity reactions, including, but not limited to, anaphylaxis, angioedema and pulmonary eosinophilia

Infections and infestations

Clostridioides difficile–associated diarrhea

Investigations

Myoglobin increased, platelet count decreased

Musculoskeletal, connective tissue, and bone disorders

Rhabdomyolysis

Nervous system disorders

Peripheral neuropathy

Renal and urinary disorders

Tubulointerstitial nephritis (TIN)

Respiratory, thoracic, and mediastinal disorders

Cough

Eosinophilic pneumonia

Organizing pneumonia

Skin and subcutaneous tissue disorders

Vesiculobullous rash with or without mucous membrane involvement (Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN))

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Acute generalized exanthematous pustulosis

INTERACTIONS

Interactions with Other Medicinal Products

CUBICIN was studied in adult human drug-drug interaction studies with aztreonam, tobramycin, warfarin, simvastatin, and probenecid. Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these drugs alter the pharmacokinetics of daptomycin. The pharmacokinetics of daptomycin were not significantly altered by aztreonam.

Experience with the concomitant administration of CUBICIN and warfarin is limited. Studies of CUBICIN with anticoagulants other than warfarin have not been conducted. Monitor anticoagulant activity in patients receiving CUBICIN and warfarin for the first several days after therapy with CUBICIN is initiated.

Experience with the coadministration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consider suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving CUBICIN.

Although small changes in the pharmacokinetics of daptomycin and tobramycin were observed during coadministration by IV infusion over a 30-minute period using a CUBICIN dose of 2 mg/kg, the changes were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of CUBICIN is unknown. Caution is warranted when CUBICIN is coadministered with tobramycin.

Drug-Laboratory Test Interactions

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

Risk Summary

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

Excretion of daptomycin into milk of lactating animals has not been studied. In a single human case study, CUBICIN was administered daily for 28 days to a nursing mother at an IV dose of 6.7 mg/kg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of daptomycin in the breast milk was 0.045 µg/mL, which is a low concentration. Until more experience is gained, women should be instructed to avoid breast-feeding while receiving CUBICIN.

Pediatric

The safety and effectiveness of CUBICIN in patients 1 to 17 years are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in pediatric patients, and additional data from two prospective studies in pediatric patients 1 to 17 years of age with cSSSI and pediatric patients 2 to 17 years of age with *Staphylococcus aureus* Bloodstream Infections (bacteremia).

In clinical trials, 372 pediatric patients (3 months to 17 years of age) were given intravenous CUBICIN. Pharmacokinetic studies enrolled a total of 61 pediatric patients, and an additional 256 and 55 pediatric patients received CUBICIN in the prospective studies of cSSSI (DAP-PEDS-07-03) and bacteremia (DAP-PEDBAC-11-02), respectively.

Elderly

No adjustment of CUBICIN dosage is warranted for elderly patients with CL_{CR} ≥30 mL/min.

Renal Impairment

Daptomycin is eliminated primarily by the kidneys; therefore, an adjustment of CUBICIN dosage interval is recommended for adult patients with CL_{CR} <30 mL/min, including patients receiving

hemodialysis or CAPD. The recommended dosing regimen for these adult patients is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours. Alternatively, adult patients on hemodialysis can be dosed three times per week. When possible, administer CUBICIN following the completion of hemodialysis on hemodialysis days. In adult patients with renal impairment, monitor both renal function and CPK more frequently than once weekly.

No dosage interval adjustment is required for adult patients with CL_{CR} ≥30 mL/min.

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

Hepatic Impairment

No dosage adjustment is warranted when CUBICIN is administered to patients with mild to moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

Gender

No dosage adjustment is warranted based on gender when CUBICIN is administered.

Obesity

No adjustment of CUBICIN dosage is warranted in obese patients.

OVERDOSE

In the event of overdose, supportive care is advised. Daptomycin is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 hours) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 hours).

CLINICAL PHARMACOLOGY

Pharmacokinetic Properties

General Characteristics

Daptomycin pharmacokinetics were generally linear (dose-proportional) and time-independent at CUBICIN doses of 4 to 12 mg/kg administered by IV infusion over a 30-minute period as a single daily dose for up to 14 days in adults. Steady-state concentrations were achieved by the third daily dose.

Distribution

Daptomycin is reversibly bound to human plasma proteins (mean binding range of 90 to 93%) in a concentration-independent manner, and serum protein binding trended lower (mean binding range of 84 to 88%) in adult subjects with significant renal impairment (CL_{CR} <30 mL/min or on dialysis). The protein binding of daptomycin in adult subjects with mild to moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

The volume of distribution at steady-state of daptomycin in healthy adult subjects was approximately 0.1 L/kg and was independent of dose. Tissue distribution studies in rats showed that daptomycin appears to penetrate the blood-brain barrier and the placental barrier only minimally following single and multiple doses.

Metabolism

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

After infusion of ^{14}C-daptomycin in healthy adults, the plasma radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference between total radioactive concentrations and microbiologically active concentrations. In a separate study, no metabolites were observed in plasma, and minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Elimination

Daptomycin is excreted primarily by the kidneys. There is minimal to no active tubular secretion of daptomycin. In a mass balance study of adult subjects using radiolabeled daptomycin, 78% of the administered dose was recovered from the urine based on total radioactivity, while urinary recovery of unchanged daptomycin was approximately 52% of the dose. About 6% of the administered dose was excreted in the feces based on total radioactivity. Plasma clearance of daptomycin is approximately 7 to 9 mL/h/kg, and its renal clearance is 4 to 7 mL/h/kg.

Specific Populations

Elderly

The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥75 years of age) and 11 healthy young adult controls (18 to 30 years of age). Following administration of a single 4 mg/kg dose of CUBICIN by IV infusion over a 30-minute period, the mean total clearance of daptomycin was approximately 35% lower and the mean AUC was approximately 58% higher in elderly subjects than in healthy young adult subjects. There were no differences in C_{max}.

Renal Impairment

Following administration of a single 4 mg/kg or 6 mg/kg dose of CUBICIN by IV infusion over a 30-minute period to adult subjects with various degrees of renal impairment, total daptomycin clearance was lower and systemic exposure (AUC) was higher than in subjects with normal renal function. The mean AUC for patients with CL_{CR} <30 mL/min and for patients on dialysis (CAPD and hemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function.

Hepatic Impairment

The pharmacokinetics of daptomycin were evaluated in 10 adult subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with those in healthy adult volunteers (N=9) matched for gender, age, and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

Pediatric

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 4).

Table 4: Mean (SD) Daptomycin Population Pharmacokinetic Parameters in cSSSI Pediatric Patients

Age	Pharmacokinetic Parameters					
	Dose (mg/kg)	AUC_{ss} (mcg•h/mL)	$t_{1/2}$ (h)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (mcg/mL)

12 to 17 years (N=6)	5	434 (67.9)	7.1 (0.9)	8200 (3250)	11.8 (2.15)	76.4 (6.75)
7 to 11 years (N=2)	7	543*	6.8*	4470*	13.2*	92.4*
2 to 6 years (N=7)	9	452 (93.1)	4.6 (0.8)	2750 (832)	20.8 (4.29)	90.3 (14.0)
1 to <2 years (N=27)	10	462 (138)	4.8 (0.6)	1670 (446)	23.1 (5.43)	81.6 (20.7)

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalized to body weight;

V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life

*Mean is calculated from N=2

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in pediatric patients (1 to 17 years old, inclusive) with SAB. 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 5).

Table 5: Mean (SD) of Daptomycin Population Pharmacokinetic Parameters in Bacteremia Pediatric Patients

Age	Pharmacokinetic Parameters						
	Dose (mg/kg)	Infusion Duration (min)	AUC_{ss} (mcg•h/mL)	$t_{1/2}$ (hr)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (mcg/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)

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalized to body weight;

V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life

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 12 mg/kg once daily would be comparable to that in adult patients receiving 6 mg/kg once daily.

Gender

No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed.

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. The AUC was approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in nonobese controls.

Microbiology

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

that are resistant to other antibacterials, including isolates resistant to methicillin, vancomycin, and linezolid.

Mechanism of Action

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

Mechanism of Resistance

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

There is no cross-resistance due to resistance mechanisms that are specific for another class of antibacterials.

Emergent decreases in susceptibility have been observed in both *S. aureus* and enterococcal isolates following CUBICIN therapy.

PK/PD Relationship

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive bacteria *in vitro* and in *in vivo* animal models.

Interactions with Other Antibacterials

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

NONCLINICAL TOXICOLOGY AND ANIMAL PHARMACOLOGY

In rats and dogs, daptomycin administration has been associated with effects on skeletal muscle. However, there were no changes in cardiac or smooth muscle. Skeletal muscle effects were characterized by microscopic degenerative/regenerative changes and variable elevations in CPK. No fibrosis or rhabdomyolysis was observed. All muscle effects, including microscopic changes, were fully reversible within 30 days following the cessation of dosing.

In adult rats and dogs, effects on peripheral nerve (characterized by axonal degeneration and frequently accompanied by functional changes) were observed at daptomycin doses higher than those associated with skeletal myopathy. Reversal of both the microscopic and functional effects was essentially complete within 6 months post-dose.

Target organs of daptomycin-related effects in 7-week-old juvenile dogs were skeletal muscle and nerve, the same target organs as in adult dogs. In juvenile dogs, nerve effects were noted at lower daptomycin blood concentrations than in adult dogs following 28 days of dosing. In contrast to adult dogs, juvenile dogs also showed evidence of effects in nerves of the spinal cord as well as peripheral nerves after 28 days of dosing. Following a 28-day recovery phase, microscopic examination revealed full recovery of the skeletal muscle and the ulnar nerve effects, and partial recovery of the sciatic nerve and spinal cord effects. No nerve effects were noted in juvenile dogs following 14 days of dosing.

Effects of daptomycin were assessed in neonatal dogs following once-daily IV administration for 28 consecutive days from postnatal days (PND) 4 through 31 at nominal dosage levels of 10 [no observed adverse effect level (NOAEL)], 25, 50, and 50/75 mg/kg/day.

At dose levels of 50 and 75 mg/kg/day with associated C_{max} and AUC_{inf} values of ≥321 µg/mL and ≥1470 µg•h/mL, respectively, marked clinical signs of twitching, muscle rigidity in the limbs, and impaired use of limbs were observed. Resulting decreases in body weights and overall body condition at doses ≥50 mg/kg/day necessitated early discontinuation by PND19. At the dose level of 25 mg/kg/day with associated C_{max} and AUC_{inf} values of 147 µg/mL and 717 µg•h/mL, respectively, mild clinical signs of twitching and one incidence of muscle rigidity were observed without any effects on body weight and were reversible over a 28-day recovery period. These

data indicate a limited margin between doses associated with mild versus marked adverse clinical signs. Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle or other tissues assessed, at any dose level. No adverse clinical signs for these target organs of toxicity were observed in the dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated C_{max} and AUC_{inf} values of 62 µg/mL and 247 µg•h/mL, respectively.

Carcinogenesis/Mutagenesis

Long-term carcinogenicity studies in animals have not been conducted. Daptomycin was not mutagenic or clastogenic in a battery of *in vivo* and *in vitro* genotoxicity tests.

Reproduction

Reproductive studies performed in rats revealed no effect of daptomycin on fertility or reproductive performance.

HOW SUPPLIED

Available Commercial Size

CUBICIN is supplied in single-dose vials containing 500 mg daptomycin as a sterile, lyophilized powder.

Nature and Contents of Container

Single-dose 10 mL vial, containing a pale yellow to light brown lyophilized cake.

Storage Precautions

Store original packages at refrigerated temperatures, 2 to 8°C (36 to 46°F); avoid excessive heat.

Shelf Life

Three years from the date of manufacture. After reconstitution: Chemical and physical stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours if stored under refrigeration (2 to 8°C). Chemical and physical stability of the diluted solution in infusion bags has been established as 12 hours at 25°C and 48 hours if stored under

refrigeration at 2 to 8°C. The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) must not exceed 12 hours at 25°C or 48 hours at 2 to 8°C.

MANUFACTURERS

The finished product is manufactured & filled into vials at

Patheon Italia S.p.A.
Viale G.B. Stucchi
110 – 20900 Monza (MB)
Italy

PACKAGER

Hangzhou MSD Pharmaceutical Co., Ltd
199 Wenhai North Road Heda Hangzhou Zhejiang
Province 310018 P.R, China

PRODUCT REGISTRATION HOLDER

MERCK SHARP & DOHME (MALAYSIA) SDN. BHD.
Lot No. B-22-1 & B-22-2, Level 22
The Ascent, Paradigm No. 1
Jalan SS 7/26A, Kelana Jaya
47301 Petaling Jaya
Selangor, Malaysia

DATE OF REVISION OF TEXT

June 2022