PENMIX DAPTOMYCIN INJECTION 500MG

Daptomycin 500mg

COMPOSITION

Daptomycin ----------500 mg
Excipient: Sodium hydroxide ---------- q.s.

DESCRIPTION

Pale yellow to light brown lyophilized cake or powder for injection in a colorless and transparent vial.

INDICATIONS

Penmix Daptomycin Injection 500mg is indicated for the treatment of the following infections:

1. Adult 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 (vancomysin-susceptible isolates only).
2. Adult patient with Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis (SAB/RIE), caused by methicillin-susceptible and methicillin-resistant isolates.
3. Pediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteremia) caused by methicillin-susceptible and methicillin-resistant isolates.
4. Daptomycin is not indicated for the treatment of left-sided infective endocarditis due to S. aureus. The efficacy of daptomycin in patients with left-sided infective endocarditis due to S. aureus has not been demonstrated. The clinical trial of daptomycin in patients with S. aureus bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. Daptomycin has not been studied in patients with prosthetic valve endocarditis. Daptomycin is not indicated for the treatment of pneumonia.

DOSAGE AND ADMINISTRATION

1. Dosage in Adults for cSSSI:

Administer Penmix Daptomycin Injection 500mg 4mg/kg to adult patients intravenously in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days over a 30-minute period or as an injection over 2 minutes. Unlike in adults, Penmix Daptomycin Injection 500mg should not be administered by injection over a two minute period in pediatric patients.

2. Dosage in Pediatric Patients (1 to 17 Years of Age) with Complicated Skin and Skin Structure Infections, Based on Age

Penmix Daptomycin Injection 500mg should be administered intravenously in 0.9% sodium chloride for injection once every 24 hours for up to 14 days.

Unlike in adults, Penmix Daptomycin Injection 500mg should not be administered by injection over a two (2) minute period in pediatric patients.

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.

3. Recommended Dosage of Penmix Daptomycin Injection 500mg 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.

4. Dosage in Adult Patients with Staphylococcus aureus Bloodstream Infections (Bacteremia), Including Those with Right-Sided Infective Endocarditis, Caused by Methicillin-Susceptible and Methicillin- Resistant Isolates:

Administer Penmix Daptomycin Injection 500mg 6 mg/kg to adult patients intravenously in 0.9% sodium chloride for injection once every 24 hours for 2 to 6 weeks over a 30-minute period or as an injection over 2 minutes. Unlike in adults, Penmix Daptomycin Injection 500mg should not be administered by injection over a two minute period in pediatric patients. There are limited safety data for the use of Penmix Daptomycin Injection 500mg for more than 28 days of therapy. In the Phase 3 trial, there were a total of 14 adult patients who were treated with daptomycin for more than 28 days.

5. Dosage in Patients with Renal Impairment:

The recommended dosage regimen in adult patients with impaired renal functions as follows; When possible, for adult patients on hemodialysis administer Penmix Daptomycin Injection 500mg following the completion of dialysis on dialysis days.

Creatinine Clearance	Dose recommendation (Adult with Complicated Skin and Skin Structure Infections)	Dose recommendation (Adult with S.aureus Bacteremia)
≥30 mL/min	4mg/kg, every 24 hours	6mg/kg, every 24 hours
<30ml/min, including adult patients on hemodialysis or CAPD	4mg/kg, every 48 hours	6mg/kg, **every 48 hours***

* The safety and efficacy of the dose interval adjustment have not been clinically evaluated, and the recommendation is based on pharmacokinetic modeling data. The same dose adjustments are recommended for adult patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, daptomycin should be administered following the completion of dialysis on dialysis days.

In adult patients with renal impairment, monitor both renal function and CPK more frequently than once weekly.

Due to limited clinical experience, daptomycin should only be used in adult patients with any degree of renal impairment (creatinine clearance<80 mL/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment and renal function should be closely monitored in all adult patients with some degree of renal impairment.

The dosage regimen for Penmix Daptomycin Injection 500mg in pediatric patients with renal impairment has not been established.

WARNINGS

1) Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including daptomycin, and may be life-threatening. If an allergic reaction to daptonycin occurs, discontinue the drug and institute appropriate therapy.

2) Eosinophilic pneumonia has been reported in patients receiving daptomycin. In reported cases associated with daptomycin, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting daptomycin and improved when daptomycin 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 Penmix Daptomycin Injection 500mg should undergo prompt medical evaluation, and Penmix Daptomycin Injection 500mg should be discontinued immediately. Treatment with systemic steroids is recommended.

3) Drug rash with eosinophilia and systemic symptoms (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 Penmix Daptomycin Injection 500mg should undergo medical evaluation. If DRESS is suspected, Penmix Daptomycin Injection 500mg should be discontinued promptly and appropriate treatment instituted.

4) Tubulointerstitial Nephritis (TIN) has been reported in post-marketing experience with daptomycin. Patients who develop new or worsening renal impairment while receiving Penmix Daptomycin Injection 500mg should undergo medical evaluation. If TIN is suspected, Penmix Daptomycin Injection 500mg should be discontinued promptly and appropriate treatment instituted

5) Clostridioides difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including daptomycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

6) Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), has been reported with the use of daptomycin. Rhabdomyolysis has been reported.

Patients receiving Penmix Daptomycin Injection 500mg should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive Penmix Daptomycin Injection 500mg, CPK levels should be measured at baseline and monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with Penmix Daptomycin Injection 500mg.

In adult patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly.

In Phase 1 studies and Phase 2 clinical trials in adults, CPK elevations appeared to be more frequent when daptomycin was dosed more than once daily. Therefore, Penmix Daptomycin Injection 500mg should not be dosed more frequently than once a day.

Penmix Daptomycin Injection 500mg should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without reported symptoms who have marked elevations in CPK, with levels >2,000 U/L (10 × ULN). In addition, consideration should be given to suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, temporarily in patients receiving Penmix Daptomycin Injection 500mg.

CONTRAINDICATIONS

Penmix Daptomycin Injection 500mg is contraindicated in patients with known hypersensitivity to daptomycin.

PRECAUTIONS

Penmix Daptomycin Injection 500mg should be administered with care in the following patients:

1) Patients with persisting or relapsing S. aureus bacteremia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for S. aureus, minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardized procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required. Failure of treatment due to persisting or relapsing S. aureus bacteremia/endocarditis may be due to reduced Penmix Daptomycin Injection 500mg susceptibility (as evidenced by increasing MIC of the S. aureus isolate).

2) Decreased Efficacy in Patients with Moderate Baseline Renal Impairment Limited data are available from the two Phase 3 trials regarding clinical efficacy of daptomycin treatment in adult patients with creatinine clearance (CLCR) <50 mL/min. In a subgroup analysis of the intent-to-treat (ITT) population in the Phase 3 S. aureus bacteremia/endocarditis trial, clinical success rates, as determined by a treatment-blinded Adjudication Committee, in the daptomycin-treated adult patients were lower in patients with baseline CLCR <50 mL/min. Consideration should to be given when selecting antibacterial therapy for use in adult patients with baseline moderate to severe renal impairment.

3) Cases of peripheral neuropathy have been reported during the daptomycin post-marketing experience. Therefore, physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving Penmix Daptomycin Injection 500mg. Monitor for neuropathy and consider discontinuation.

4) Pneumonia

Penmix Daptomycin Injection 500mg should not be used for the treatment of pneumonia. It has been demonstrated in clinical studies that daptomycin is not effective in the treatment of community-acquired pneumonia, due to binding to pulmonary surfactant and consequent inactivation.

5) 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.

6) Non-Susceptible Microorganisms

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

ADVERSE REACTIONS

1. Clinical Trials Experience

During clinical trials of daptomycin, 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
Eosinophilia	Uncommon
Thrombocytosis	Uncommon
Leukocytosis	Uncommon
Cardiac disorders	
Supraventricular arrhythmia	Uncommon
Ear and labyrinth disorders	
Vertigo	Uncommon
Gastrointestinal disorders	
Gastrointestinal and abdominal pain	Common
Diarrhea	Common
Vomiting	Common

Flatulence, bloating, and distension	Common
Constipation	Common
Nausea	Common
Dyspepsia	Uncommon
Glossitis	Uncommon
Abdominal distension	Uncommon
General disorders and administration site conditions	
Asthenia	Common
Pyrexia	Common
Infusion site reaction	Common
Pain	Uncommon
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
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
Muscle weakness	Uncommon
Muscle pain	Uncommon
Arthralgia	Uncommon
Myositis	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
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

2. Post-marketing Experience

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

1) Blood and lymphatic system disorders
Thrombocytopenia
2) Immune system disorders
Hypersensitivity, manifested by isolated spontaneous reports including, but not limited to angioedema, pulmonary eosinophilia, vesiculobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling
3) Infections and infestations
Clostridioides difficile-associated diarrhea
4) Anaphylaxis
Infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste
5) Investigations
Myoglobin increased, platelet count decreased
6) Musculoskeletal, connective tissue, and bone disorders
Rhabdomyolysis
7) Nervous system disorders
Peripheral neuropathy
8) Renal and urinary disorders
Tubulointerstitial nephritis (TIN)
9) Respiratory, thoracic, and mediastinal disorders
Cough
Eosinophilic pneumonia
Organizing pneumonia
10) 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

3. Interference with Laboratory Tests

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 daptomycin, it is recommended that clinicians:

1) Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next daptomycin 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.

GENERAL PRECAUTIONS

1) The clinical trial of daptomycin in adult patients with Staphylococcus aureus bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. Daptomycin has not been studied in patients with either meningitis or prosthetic valve endocarditis.
2) 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 daptomycin and other antibacterial drugs, daptomycin 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.
3) The use of antibacterials may promote the overgrowth of non-susceptible microorganisms. If these infections occur during therapy, appropriate measures should be taken.
   Prescribing daptomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
4) The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for daptomycin against isolates of genus or organism group. However, the efficacy of daptomycin in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.
   * Gram-Positive Bacteria: Corynebacterium jeikeium, Enterococcus faecalis (vancomycin-resistant isolates), Enterococcus faecium (including vancomycin-resistant isolates), Staphylococcus epidermidis (including methicillin-resistant isolates), Staphylococcus haemolyticus

DRUG INTERACTIONS

1) Aztreonam: In a study in which 15 healthy adult subjects received a single dose of daptomycin 6 mg/kg IV and a combination dose of daptomycin 6 mg/kg IV and aztreonam 1 g IV, administered over a 30-minute period, the Cmax and AUC0-∞ of daptomycin were not significantly altered by aztreonam.
2) Tobramycin: In a study in which 6 healthy adult males received a single dose of daptomycin 2 mg/kg IV, tobramycin 1 mg/kg IV, and both in combination, administered over a 30- minute period, the mean Cmax and AUC0-∞ of daptomycin were 12.7% and 8.7% higher, respectively, when daptomycin was coadministered with tobramycin. The mean Cmax and AUC0-∞ of tobramycin were 10.7% and 6.6% lower, respectively, when tobramycin was coadministered with daptomycin. These differences were not statistically significant. The interaction between daptomycin and tobramycin with a clinical dose of daptomycin is unknown.
3) Wafarin: In 16 healthy adult subjects, administration of daptomycin 6 mg/kg q24h by IV infusion over a 30- minute period for 5 days, with coadministration of a single oral dose of warfarin (25 mg) on the 5th day, had no significant effect on the pharmacokinetics of either drug and did not significantly alter the INR (International Normalized Ratio). [see Precautions]
4) Simvastatin: In 20 healthy adult subjects on a stable daily dose of simvastatin 40 mg, administration of daptomycin 4 mg/kg q24h by IV infusion over a 30-minute period for 14 days (N=10) had no effect on plasma trough concentrations of simvastatin and was not associated with a higher incidence of adverse events, including skeletal myopathy, than in subjects receiving placebo once daily (N=10). [see Warnings]
5) Probenicid: Concomitant administration of probenecid (500 mg 4 times daily) and a single dose of daptomycin 4 mg/kg by IV infusion over a 30-minute period in adults did not significantly alter the Cmax or AUC0-∞ of daptomycin.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

1) Daptomycin should be used during pregnancy only if the expected benefit outweighs the possible risk because there are no adequate and well-controlled studies of daptomycin in pregnant women and animal reproduction studies are not always predictive of human response.
2) Embryofetal 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.
3) Excretion of daptomycin into milk of lactating animals has not been studied. In a single human case study, daptomycin 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 Daptomycin Injection 500mg.

Pediatric Use

The safety and effectiveness of Daptomycin 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 Daptomycin. Pharmacokinetic studies enrolled a total of 61 pediatric patients, and an additional 256 and 55 pediatric patients received Daptomycin in the prospective studies of cSSSI (DAP-PEDS-07-03) and bacteremia (DAP-PEDBAC-11-02), respectively.

Geriatric Use

Of the 534 adult patients treated with daptomycin in Phase 3 controlled clinical trials of complicated skin and skin structure infections (cSSSI), 27% were 65 years of age or older and 12% were 75 years of age or older. Of the 120 adult patients treated with daptomycin in the Phase 3 controlled clinical trial of S. aureus bacteremia/endocarditis, 25% were 65 years of age or older and 16% were 75 years of age or older. In Phase 3 adult clinical trials of cSSSI and S. aureus bacteremia/endocarditis, clinical success rates were lower in patients ≥65 years of age than in patients <65 years of age. In addition, treatment emergent adverse events were more common in patients ≥65 years of age than in patients <65 years of age. However, no adjustment of daptomycin dosage is warranted for elderly patients with creatinine clearance (CLCR) ≥30 mL/min.

Obesity

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m2) and 6 extremely obese (BMI ≥40 kg/m2) adult subjects and controls matched for age, gender, and renal function. Following administration of daptomycin by IV infusion over a 30-minute period as a single 4 mg/kg dose based on total body weight, the total plasma clearance of daptomycin normalized to total body weight was approximately 15% lower in

moderately obese subjects and 23% lower in extremely obese subjects than in nonobese controls.

The AUC0-∞ of daptomycin was approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in nonobese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No adjustment of daptomycin dosage is warranted in obese patients.

Gender
No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when Daptomycin Injection 500mg is administered.

Renal Impairment
1) Dosage reduction is required in adult patients with creatinine clearance (CLCR) less than 30mL/min. Both renal function and CPK should be monitored more frequently than once weekly
2) Daptomycin Injection 500mg 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). When possible, Daptomycin Injection 500mg should be administered following the completion of hemodialysis on hemodialysis days

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. No dosage adjustment is warranted when Daptomycin Injection 500mg is administered to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

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 Penmix Daptomycin Injection 500mg, it is recommended that clinicians:
1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next Penmix Daptomycin Injection 500mg 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.

OVERDOSAGE
In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Penmix Daptomycin Injection 500mg is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 hours) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with that removed by low-flux membranes.

PREPARATION AND ADMINISTRATION
1) Penmix Daptomycin Injection 500mg is supplied in single-dose vials containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of Penmix Daptomycin Injection 500mg should be reconstituted at a concentration of 50 mg/mL with 0.9% sodium chloride for injection.

① To minimize foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.

② Remove the polypropylene flip-off cap from the Penmix Daptomycin Injection 500mg vial to expose the central portion of the rubber stopper.

③ 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.

④ Slowly transfer 10 mL of 0.9% sodium chloride injection through the center of the rubber stopper into the Penmix Daptomycin Injection 500mg 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.

⑤ Ensure that all of the Penmix Daptomycin Injection 500mg powder is wetted by gently rotating the vial.
A. Allow the wetted product to stand undisturbed for 10 minutes.
B. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.
2) Parenteral drug products should be inspected visually for particulate matter prior to administration.
3) The reconstituted Penmix Daptomycin Injection 500mg (concentration of 50 m g/mL) should be further diluted with 50 mL 0.9% sodium chloride and intravenously infuse over a period of 30 minutes.
4) No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution.
5) The reconstituted solution is stable in the vial for 12 hours at room temperature (25℃) and up to 48 hours if stored under refrigeration at 2 to 8℃ (36 to 46°F).
6) Penmix Daptomycin Injection 500mg is compatible with 0.9% sodium chloride for injection and lactated Ringer's injection.
The following have been shown to be compatible when coadministered with Penmix Daptomycin Injection 500mg through the same IV line from separate infusion bags: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin, and lidocaine. If the same IV line is used for sequential infusion of different drugs, the line should be flushed if needed with a compatible intravenous solution before and after infusion with Penmix Daptomycin Injection 500mg for careful use.
7) Penmix Daptomycin Injection 500mg is not compatible with dextrose-containing diluents.
8) Penmix Daptomycin Injection 500mg should not be used in conjunction with ReadyMED® elastomeric infusion pumps.
9) Chemical and physical stability of the diluted solution in infusion bags has been established as 12 hours at room temperature (25°C) and 48 hours if stored under refrigeration.
10) The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) must not exceed 12 hours at room temperature (25°C) or 48 hours at 2 to 8°C.

OTHERS
1) Carcinogenesis, Mutagenesis, Impairment of Fertility

① 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, 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.

② daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses of 25, 75, or 150 mg/kg/day, which is approximately up to 9 times the estimated human exposure level based upon AUCs (or approximately up to 4 times the recommended human dose of 6 mg/kg based on body surface area comparison).

2) Animal Toxicology
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.

11.1 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.

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

CLINICAL PHARMACOLOGY

1) ATC code
J01XX09

2) Therapeutic Class
Daptomycin contains daptomycin, a cyclic lipopeptide antibacterial agent.

3) Mechanism of Action
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.

4) Mechanism of Resistance
The mechanism(s) of daptomycin resistance is not fully understood. There are no known transferable elements that confer resistance to daptomycin.
Cross resistance has not been observed with any other class of antibacterials.
Emergent decreases in susceptibility have been observed in both S. aureus and enterococcal isolates following daptomycin therapy.

5) Pharmacodynamics
PK/PD Relationship
Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive bacteriain vitro and in in vivo animal models.

6) Pharmacokinetics
General Introduction
Daptomycin pharmacokinetics were generally linear (dose-proportional) and time-independent at 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.
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 Cmax) was demonstrated in healthy subjects following administration of daptomycin as a 30-minute intravenous infusion or as a 2-minute intravenous injection.

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 (CLCR <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 14C-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 to 4 to 7 mL/h/kg.

Specific Populations
Renal Insufficiency
Dose adjustments in patients with renal impairment by indication and creatinine clearance:

Indication for use	*Creatinine clearance*	Dose recommendation
Complicated Skin and Skin Structure Infections (Dosing duration: 7 to 14 days)	*≥30 mL/min* *<30 mL/min*	4 mg/kg every 24 hours 4 mg/kg every 48 hours
Staphylococcus aureus Bacteremia Including Right-sided Endocarditis (Dosing duration: 2 to 6 weeks)	*≥30 mL/min* *<30 mL/min*	6 mg/kg every 24 hours 6 mg/kg every 48 hours

Following administration of a single 4 mg/kg or 6 mg/kg dose of Penmix Daptomycin Injection 500mg 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 CLCR <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 Insufficiency
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. After a single 4 mg/kg dose of Penmix Daptomycin Injection 500mg, total clearance and elimination half-life of daptomycin in adolescents (12-17 years of age) with Gram-positive infection were similar to adults. After a single 4 mg/kg dose of Penmix Daptomycin Injection 500mg, total clearance of daptomycin in children 7-11 years of age with Gram-positive infection was higher than in adolescents, whereas elimination half-life was shorter. After a single 4, 8, or 10 mg/kg dose of Penmix Daptomycin Injection 500mg, total clearance and elimination half-life of daptomycin in younger children 2-6 years of age were similar at different doses; total clearance was higher and elimination half-life was shorter than in adolescents. After a single 6 mg/kg dose of Penmix Daptomycin Injection 500mg, the clearance and elimination half-life of daptomycin in toddlers 13-24 months of age were similar to younger children 2-6 years of age who received a single 4-10 mg/kg dose. The results of these studies show that exposures (AUC) in pediatric patients across all doses are generally lower than those in adults at comparable 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 Penmix Daptomycin Injection 500mg doses of 5 to 10 mg/kg once daily were administered. Following administration of multiple doses, daptomycin exposure (AUCss and Cmax,ss) was similar across different age groups after dose adjustment based on body weight and age (Table 3).

Table 3: 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=7)	9	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)
2 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; CLT, clearance normalized to body weight;
V_{ss}, volume of distribution at steady state; t½ , 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 4).

Table 4: 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)	$t_{1/2}$ (h)	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; t½ , 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.

Geriatric
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 Penmix Daptomycin Injection 500mg 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}.

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

Obesity
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.

Drug Interaction Studies
In vitro studies have been 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).

STORAGE AND HANDLING PRECAUTIONS
1) Keep it out of the reach of children
2) Store in the original package in order to prevent any accident caused by drug misuse or quality degradation.
3) Store original packages at refrigerated temperatures, 2 to 8°C (36 to 46°F); avoid excessive heat

SHELF LIFE
24 months from manufacturing date

PACKAGE
1 Vial/Box

Revised in Feb, 20, 2023

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