### DOSAGE AND ADMINISTRATION

#### 2.2 Dosage in Pediatric Patients (1 to 17 Years of Age)

When culture and susceptibility information is available, it should be considered in selecting or modifying antibacterial therapy. In adult patients with renal impairment, both renal function and CPK should be monitored more frequently than once weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor (see Nonclinical Toxicology). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK), has been reported in adult patients with renal impairment treated with daptomycin for Injection. When used in patients with renal impairment, daptomycin for Injection should be administered with caution and the dosage should be decreased to the lowest effective dose. In patients who receive daptomycin for Injection, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor.

#### 2.4 Dosage in Special Populations

- **Complications of diabetes mellitus:**
  - Administer daptomycin for Injection to patients with complications of diabetes mellitus intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period.

- **Obstructive uropathy:**
  - Patients with obstructive uropathy have been treated with daptomycin for Injection, and clinical recovery occurred with one patient being managed with peritoneal dialysis. For the remaining patients, there were insufficient data from clinical studies to determine drug infusion rates for patients with obstructive uropathy.

- **Hemodialysis:**
  - Hemodialysis patients have been treated with daptomycin for Injection intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period.

- **Renal impairment:**
  - Patients with severe to moderate renal impairment (creatinine clearance [CrCl] less than 30 to 50 mL/min) have been treated with daptomycin for Injection. See Table 6 for the relationship between CrCl and daptomycin for Injection dosage.

#### 2.3 Dosage in Pediatric Patients (1 to 17 Years of Age)

Daptomycin for Injection is indicated for the treatment of adult and pediatric patients (1 to 17 years of age) with complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: Staphylococcus aureus and Enterococcus faecalis. The safety and efficacy of daptomycin for Injection in pediatric patients with infections other than cSSSI have not been established.

- **Dosage in pediatric patients:**
  - Administer daptomycin for Injection to pediatric patients intravenously in 0.9% sodium chloride injection for injection or 5% dextrose injection for injection to achieve a concentration of 50 mg/mL. The total volume of the reconstituted Daptomycin for Injection (concentration of 50 mg/mL) should be further diluted, using at least 50 mL of infusion solution, to a concentration not exceeding 5 mg/mL. The resulting volume of the diluted Daptomycin for Injection solution must not exceed 500 mL. A 500-mL infusion bag containing 250 mg of Daptomycin for Injection as a single dose is commercially available to facilitate reconstitution and administration. The 500-mL volume bag of Daptomycin for Injection contains 0.9% sodium chloride injection for injection. The resulting concentration of the diluted Daptomycin for Injection solution must not exceed 5 mg/mL. The resulting volume of the diluted solution must not exceed 500 mL.

- **Dosage in adult patients:**
  - Administer daptomycin for Injection to adult patients intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period. The recommended dosage of daptomycin for Injection is 7 mg/kg once every 24 hours infused over 30 minutes. The total volume of the reconstituted Daptomycin for Injection (concentration of 50 mg/mL) should be further diluted, using at least 50 mL of infusion solution, to a concentration not exceeding 5 mg/mL. The resulting volume of the diluted Daptomycin for Injection solution must not exceed 500 mL. A 500-mL infusion bag containing 250 mg of Daptomycin for Injection as a single dose is commercially available to facilitate reconstitution and administration. The 500-mL volume bag of Daptomycin for Injection contains 0.9% sodium chloride injection for injection. The resulting concentration of the diluted Daptomycin for Injection solution must not exceed 5 mg/mL. The resulting volume of the diluted solution must not exceed 500 mL.

### WARNINGS AND PRECAUTIONS

#### 5.2 Anaphylaxis/hypersensitivity reactions

Anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including daptomycin for Injection. If an allergic reaction to daptomycin for Injection occurs, discontinue the drug and institute appropriate therapy. Signs/symptoms of anaphylaxis/hypersensitivity reactions may include, but are not limited to, anaphylactic shock, angioedema, urticaria, rash, or pruritus.

#### 5.3 Coadministration of Daptomycin with Potential Nervous System and/or Muscular System Effects

The following events have been reported with coadministration of daptomycin with potential nervous system and/or muscular system effects:

- Posterior Reversible Encephalopathy Syndrome
- Pseudobulbar Palsy
- Peripheral and/or Central Nervous System Immobility
- Syncope
- Sensory Peripheral Neuropathy
- Pneumonitis
- Acute Kidney Injury
- Renal Insufficiency
- Renal Failure
- Tubulointerstitial Nephritis
- Myopathy
- Myalgia
- Rhabdomyolysis
- Elevated Creatine Phosphokinase (CPK)
- Urinary Tract Infection

#### 5.4 Coadministration of Daptomycin with an HMG-CoA reductase inhibitor

An HMG-CoA reductase inhibitor decreases serum levels of the CoA ester of cholesterol by inhibiting cholesterol synthesis at the level of mevalonic acid, which is the first committed step in the synthesis of sterols and sterol intermediates. Daptomycin does not inhibit the cholesterol synthesis pathway. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in CPK, has been reported in adult patients with renal impairment treated with daptomycin for Injection. When used in patients with renal impairment, daptomycin for Injection should be administered with caution and the dosage should be decreased to the lowest effective dose. In patients who receive daptomycin for Injection, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor.

#### 5.5 Coadministration with Concomitant Therapy with OtherAgents

As with any antibacterial, there may be a potential for drug interactions. Monitor patients for signs of toxicity. If the same IV line is used for the administration of intravenous daptomycin concurrently with an HMG-CoA reductase inhibitor, administer daptomycin for Injection through a separate IV line. If the same IV line is used for the administration of daptomycin for Injection and an HMG-CoA reductase inhibitor, daptomycin for Injection should be administered last.

#### 5.6 Hemodialysis

Hemodialysis patients have been treated with daptomycin for Injection intravenously either by injection over a two (2) minute period or by intravenous infusion over a thirty (30) minute period. The safety and efficacy of daptomycin for Injection in these patients have been confirmed by postmarketing surveillance. If possible, delay dialysis until after the completion of the intravenous infusion of daptomycin for Injection. No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of the reconstituted Daptomycin for Injection solution.
Reevaluate PT/INR near the next dose of Daptomycin for Injection.

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner, with a binding capacity of approximately 90% and a concentration-dependent capacity of approximately 10%.

Pharmacokinetic Parameters:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=165</th>
<th>N=24</th>
<th>N=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cmax (mcg/mL)</td>
<td>62</td>
<td>104</td>
<td>8</td>
</tr>
<tr>
<td>Mean AUC (mcg•h/mL)</td>
<td>247</td>
<td>466</td>
<td>4470*</td>
</tr>
<tr>
<td>Mean T1/2 (h)</td>
<td>24.4</td>
<td>10.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean Tmax (h)</td>
<td>1.2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Daptomycin is metabolized primarily by nonspecific, nonsaturable hepatic uptake mechanisms and is minimally affected by renal or hepatic impairment.

Excretion:

Daptomycin is excreted predominantly by the kidneys. No metabolites were observed in plasma on Day 1 following the administration of daptomycin for injection at 6 mg/kg/day. The mean urinary recovery of daptomycin was 77.7% (+0.1) and 116.6% (+12.2) in healthy adult subjects and patients with renal impairment, respectively. The active metabolite, 2,3-hydroxydaptomycin, was also observed in patients with renal impairment. No accumulation of active metabolite has been reported in patients treated with this drug for at least 28 days.

In 20 healthy adult subjects on a stable daily dose of simvastatin 40 mg, administration of daptomycin for injection resulted in a 40% decrease in the mean plasma concentration of simvastatin. Administration of daptomycin at 6 mg/kg/day and 10 mg/kg/day resulted in approximately 70% and 80% decreases in the mean AUC of simvastatin, respectively, compared with the dose of simvastatin alone.

Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system. No adverse effects were associated with a Cmax of 104 mcg/mL in the peripheral and central nervous system.

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in pediatric patients (1 to 18 years of age) with cSSSI, including patients with ventriculitis. In this study, patients weighing 20 kg or more were treated with a dosage of 9 mg/kg once daily, and patients weighing less than 20 kg were treated with a dosage of 6 mg/kg once daily. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 16. Clinical success rates in the CE population were 76.0% (158/208) in patients treated with daptomycin for injection and 60.9% (162/266) in patients treated with comparator drugs. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

Table 16: Clinical Success Rates in Microbiologically Evaluable Patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Comparator %</th>
<th>Daptomycin %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>60.9</td>
<td>76.0</td>
<td>0.06</td>
</tr>
<tr>
<td>MRSA</td>
<td>60.9</td>
<td>76.0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Daptomycin is generally well tolerated. The most common adverse events observed in clinical trials were nausea, vomiting, diarrhea, constipation, and headache. In patients treated with daptomycin, nausea and vomiting occurred in 12% and 6%, respectively, and diarrhea and constipation occurred in 8% and 1%, respectively. Headache occurred in 5% of patients treated with daptomycin. No cases of daptomycin-related neurotoxicity or neuroexcitation have been reported in clinical trials.

Daptomycin for Injection is administered intravenously over a 30-minute period and is contraindicated in pediatric patients younger than one year of age due to the risk of neurotoxicity. Daptomycin for Injection is also contraindicated in patients with known hypersensitivity to daptomycin or its components. Daptomycin for Injection is neither renally nor heptatically metabolized and is rapidly excreted unchanged in urine.