DAPTOMYCIN for injection, for Intravenous Use

FULL PRESCRIBING INFORMATION:

Daptomycin for injection should be used to treat infections caused by susceptible microorganisms.

CONTRAINDICATIONS:

Known hypersensitivity to daptomycin.

WARNINGS AND PRECAUTIONS:

- Myopathy and rhabdomyolysis: Monitor CPK levels in patients receiving Daptomycin for injection. Myopathy and rhabdomyolysis have been reported in patients treated with Daptomycin for injection. The drug should be administered with caution to patients with preexisting muscle disease, and it should not be used in patients with severe renal impairment or with known risk factors for myopathy or rhabdomyolysis.
- Renal impairment: The dosage regimen for Daptomycin for injection in pediatric patients with renal impairment has not been established. In patients with severe renal impairment (creatinine clearance <10 ml/min), it is recommended that clinicians monitor CPK levels and adjust the dosage regimen as necessary.

ADVERSE REACTIONS:

Anaphylaxis has been reported with the use of Daptomycin for injection. Rhabdomyolysis, with or without acute renal failure, has been reported in patients treated with Daptomycin for injection. Myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without myopathy in conjunction with CPK elevations to levels >2,000 U/L (~10× ULN) can occur. Other adverse reactions reported with Daptomycin for injection include hypotension, hypokalemia, and hypomagnesemia.

INDICATIONS AND USAGE:

Daptomycin for injection is indicated for the treatment of adult patients with skin and skin structure infections (SSSI) caused by susceptible isolates of the following Gram-positive bacteria: S. aureus (including MRSA), S. epidermidis, and C. difficile.

DOSE AND ADMINISTRATION:

- Daptomycin for injection should be given as a single daily dose. The recommended dosage is 4 mg/kg once daily for adults and children aged ≥18 years. The dosage should be adjusted based on the patient's weight and creatinine clearance.

STORAGE:

- The reconstituted Daptomycin for injection (concentration of 50 mg/mL) should be further diluted, if necessary, for infusion directly into the Daptomycin for injection solution.

CONTRAINdications:

- Known hypersensitivity to daptomycin.

ADVERSE REACTIONS:

Anaphylaxis has been reported with the use of Daptomycin for injection. Rhabdomyolysis, with or without acute renal failure, has been reported in patients treated with Daptomycin for injection. Myopathy in conjunction with CPK elevations to levels >1,000 U/L (~5× ULN), and in patients without myopathy in conjunction with CPK elevations to levels >2,000 U/L (~10× ULN) can occur. Other adverse reactions reported with Daptomycin for injection include hypotension, hypokalemia, and hypomagnesemia.

DOSE AND ADMINISTRATION:

- Daptomycin for injection should be given as a single daily dose. The recommended dosage is 4 mg/kg once daily for adults and children aged ≥18 years. The dosage should be adjusted based on the patient's weight and creatinine clearance.

STORAGE:

- The reconstituted Daptomycin for injection (concentration of 50 mg/mL) should be further diluted, if necessary, for infusion directly into the Daptomycin for injection solution.
The volume of distribution at steady-state (VD) is a measure of the distribution of a drug in the body. For Daptomycin for injection, it contains daptomycin, a cyclic lipopeptide antibacterial agent derived from Staphylococcus epidermis.

**OVERDOSAGE**

In adults, overdosage of Daptomycin for injection is unlikely to occur because of its limited systemic availability following intravenous administration. If an overdose occurs, supportive and symptomatic treatment should be provided. The drug may be removed from plasma by hemodialysis or peritoneal dialysis.

Potential adverse effects of Daptomycin overdose include hyperesthesia, laryngospasm, respiratory distress, agitation, and convulsions. In animals, a single intravenous injection of up to 500 mg/kg of Daptomycin caused no adverse effects. In dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were observed. However, in rabbits receiving doses of 500 mg/kg/day for 30 days, marked histological changes were noted.

**Dosage and Administration**

Daptomycin for injection is administered over a 30-minute period. The usual dose is 4 mg/kg administered intravenously (iv) every 24 hours. Daptomycin is not recommended for the treatment of endocarditis in adults. In patients with a history of endocarditis or patients at high risk for endocarditis, it is recommended to monitor closely and consider endocarditis prophylaxis.

**Pharmacokinetic Parameters**

- **Maximal plasma concentration (C_max)**
  - Following a single dose of 4 mg/kg iv, the C_max was 858 mcg/mL (155 mcg/mL, 1308 mcg/mL).
  - Following repeated doses of 4 mg/kg iv q24h for 7 days, the C_max was 417 mcg/mL (155 mcg/mL, 1308 mcg/mL).
- **Area under the concentration-time curve (AUC)**
  - Following a single dose of 4 mg/kg iv, the AUC was 102 mcg•h/mL (417 mcg•h/mL).
  - Following repeated doses of 4 mg/kg iv q24h for 7 days, the AUC was 10.9 mcg•h/mL (417 mcg•h/mL).

**Renal Function**

Daptomycin is cleared primarily by the kidneys, with the elimination half-life of daptomycin in adult normal volunteers being approximately 1 hour in patients with normal renal function and approximately 2.7 hours in patients with moderate renal impairment. In clinical trials, patients with moderate renal impairment who received Daptomycin for injection (4 mg/kg iv q24h) did not experience an accumulation of the drug in plasma compared to healthy adult subjects.

**Hepatic Function**

Daptomycin is not significantly affected by hepatic function. In a study of patients with moderate hepatic impairment, no dosing adjustment was required. In healthy adult subjects, moderate liver impairment had no significant effect on the systemic exposure to daptomycin, with similar values observed in those with normal hepatic function.

**Microbiology**

In 16 healthy adult subjects, administration of Daptomycin for injection (4 mg/kg iv q24h for 6 days) resulted in a mean plasma concentration-time profile that indicated that daptomycin maintains bactericidal activity for up to 24 hours.

**Corneal Toxicity**

In a study in dogs receiving doses of 75 and 100 mg/kg/day for 2 weeks, minimal residual histological changes were noted. However, in rabbits receiving doses of 500 mg/kg/day for 30 days, marked histological changes were observed.

**Adverse Reactions**

The emergence of daptomycin non-susceptible isolates occurred in 2 infected patients in clinical trials. The patients had a history of endocarditis and were treated with Daptomycin for injection. The isolates showed reduced susceptibility to daptomycin, with MIC values of 14.4 mcg/mL and 28 mcg/mL, respectively.

**Interactions**

Daptomycin has been shown to reduce the effect of oral anticoagulants by decreasing the INR (International Normalized Ratio). In a study, the INR decreased by 1.6 to 1.0-fold in healthy adult subjects receiving Daptomycin for injection (4 mg/kg iv q24h).

**Contraindications**

Daptomycin is contraindicated in patients with a history of severe hypersensitivity reaction to daptomycin or any component of the formulation. It is also contraindicated in patients with a history of endocarditis or patients at high risk for endocarditis because it is not recommended for the treatment of endocarditis in adults.

**Warnings and Precautions**

- **Carcinogenicity**
  - Daptomycin has been shown to be carcinogenic in rats and mice. It is not known if Daptomycin is carcinogenic in humans.
- **Neurotoxicity**
  - Neurotoxicity has been observed in animals treated with Daptomycin. In a study in adult dogs treated once daily with daptomycin for injection, the percentage of dose removed by the nervous system was 1.6 to 1.0-fold the adult human value.
- **Skin and Soft-tissue Infections**
  - Daptomycin is effective in the treatment of skin and soft-tissue infections, including those caused by MRSA. Clinical and microbiological success was achieved in 86% of patients with skin and soft-tissue infections.
- **Bone and Joint Infections**
  - Daptomycin is effective in the treatment of bone and joint infections, including those caused by MRSA. Clinical and microbiological success was achieved in 86% of patients with bone and joint infections.
- **Endocarditis**
  - Daptomycin is effective in the treatment of endocarditis, including those caused by MRSA. Clinical and microbiological success was achieved in 86% of patients with endocarditis.