PRODUCT INFORMATION

DAPTOMYCIN-AFT POWDER FOR SOLUTION FOR INJECTION OR INFUSION 500 MG/VIAL

1 INDICATION AND USAGE

Daptomycin-AFT is indicated for the treatment of the infections listed below.

1.1 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).

1.2 *Staphylococcus aureus* BLOODSTREAM INFECTIONS (BACTEREMIA)

Adult patients (≥18 years of age) with *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis (SAB/RIE), 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.

Daptomycin-AFT 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-AFT has not been studied in patients with prosthetic valve endocarditis.

Daptomycin-AFT is not indicated for the treatment of pneumonia [See 5 WARNINGS AND PRECAUTIONS, 5.2 Pneumonia].

2 DOSAGE AND ADMINISTRATION

2.1 GENERAL

Daptomycin-AFT is given by intravenous (IV) administration.

Daptomycin-AFT is a sterile product contained in a single-dose vial.

2.2 ADULTS

2.2.1 Complicated Skin and Skin Structure Infections

Daptomycin-AFT 4 mg/kg is administered to adult patients intravenously in 0.9% sodium chloride for injection once every 24 hours for 7 to 14 days, either by injection over a 2-minute period or by infusion over a 30-minute period. Do not dose Daptomycin-AFT more frequently than once a day, and measure creatine phosphokinase (CPK) levels at baseline

and at regular intervals (at least weekly). [See 3 INSTRUCTIONS FOR USE, 3.1 Preparation of Daptomycin-AFT for Administration.]

2.2.2 *Staphylococcus aureus* Bloodstream Infections (Bacteremia)

Daptomycin-AFT 6 mg/kg is administered to adult patients intravenously in 0.9% sodium chloride for injection once every 24 hours for 2 to 6 weeks, either by injection over a 2-minute period or by infusion over a 30-minute period. Duration of treatment is based on the treating physician's working diagnosis. Do not dose Daptomycin-AFT more frequently than once a day, and measure CPK levels at baseline and at regular intervals (at least weekly). [See 3 INSTRUCTIONS FOR USE, 3.1 Preparation of Daptomycin-AFT for Administration.]

2.3 PEDIATRIC PATIENTS (1 TO 17 YEARS OF AGE)

2.3.1 Complicated Skin and Skin Structure Infections

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

Unlike in adults, Daptomycin-AFT should not be administered by injection over a two (2) minute period in pediatric patients.

Table 1: Recommended Dosage of Daptomycin-AFT 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.

2.3.2 *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. Daptomycin-AFT 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 Daptomycin-AFT 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.

2.4 RENAL IMPAIRMENT

Daptomycin is eliminated primarily by the kidneys; therefore, an adjustment of Daptomycin-AFT dosage interval is recommended for adult patients with creatinine clearance (CLCR) <30 mL/min, including patients receiving hemodialysis or continuous ambulatory peritoneal dialysis (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. When possible, administer Daptomycin-AFT 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 CLCR ≥30 mL/min.

Due to limited clinical experience, Daptomycin-AFT 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.

Dose adjustments in adult 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*

*: 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-AFT should be administered following the completion of dialysis on dialysis days.

The dosage regimen for Daptomycin-AFT in pediatric patients with renal impairment has not been established.

3 INSTRUCTIONS FOR USE

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

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

1. Remove the aluminium-plastic cap from the vial to expose the central portion of the rubber stopper.
2. Wipe top of rubber stopper with 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 centre of the rubber stopper into the vial using a bevelled sterile transfer needle that is 21 gauge or smaller diameter, or a needleless device, pointing the transfer needle toward the wall of the vial.
4. Ensure that the entire Daptomycin-AFT product is wetted by gently rotating the vial.
5. Allow the 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 bevelled sterile needle 21 gauge or smaller in diameter.

3.1 ADULTS

3.1.1 Intravenous Injection over a period of 2 minutes

For IV injection over a period of 2 minutes in adult patients, reconstituted Daptomycin-AFT is administered at a concentration of 50 mg/mL.

3.1.2 Intravenous Infusion over a period of 30 minutes

For IV infusion over a period of 30 minutes in adult patients, reconstituted Daptomycin-AFT (concentration of 50 mg/mL) is further diluted, using aseptic technique, with 0.9% sodium chloride for injection.

3.2 PEDIATRIC PATIENTS (1 TO 17 YEARS OF AGE)

3.2.1 Intravenous Infusion over a period of 30 or 60 minutes

- For IV infusion over a period of 30 minutes in pediatric patients, reconstituted Daptomycin-AFT (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 Daptomycin-AFT (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.
- Unlike in adults, Daptomycin-AFT should not be administered by injection over a two (2) minute period in pediatric patients [see 2 DOSAGE AND ADMINISTRATION, 2.3 Pediatric Patients (1 to 17 Years of Age)].

3.3 STABILITY AFTER RECONSTITUTION AND DILUTION

Inspect parenteral drug products 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.

In the vial: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at room temperature (20 °C – 25 °C) or up to 48 hours if stored under refrigeration (2 °C to 8 °C).

In the infusion bag: Chemical and physical in-use stability of the diluted solution in the infusion bag has been established for 12 hours at room temperature (20 °C – 25 °C) or 48 hours if stored under refrigeration (2 °C to 8 °C).

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 under refrigeration.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/ dilution (etc.) has taken place in controlled and validated aseptic conditions.

3.4 INCOMPATIBILITIES

Daptomycin-AFT is not compatible with dextrose-containing diluents.

Do not use Daptomycin-AFT in conjunction with ReadyMED® elastomeric infusion pumps (Cardinal Health, Inc.). Stability studies of daptomycin solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the Daptomycin-AFT solution.

Other than the nine drugs listed in Section 3.5 [Compatible Intravenous Solutions], additives and other medications should not be added to Daptomycin-AFT single-dose vials or infusion bags, or infused simultaneously with Daptomycin-AFT through the same IV line, because only limited data are available on compatibility. If the same IV line is used for sequential infusion of different drugs, flush the line with a compatible intravenous solution before and after infusion with Daptomycin-AFT.

3.5 COMPATIBLE INTRAVENOUS SOLUTIONS

Daptomycin-AFT 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 daptomycin injection through the same IV line from separate infusion bags: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin, and lidocaine.

4 CONTRAINDICATIONS

Daptomycin-AFT is contraindicated in patients with known hypersensitivity to daptomycin.

5 WARNINGS AND PRECAUTIONS

5.1 ANAPHYLAXIS/HYPERSENSITIVITY REACTIONS

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

5.2 PNEUMONIA

Daptomycin-AFT 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.

5.3 SKELETAL MUSCLE EFFECTS

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

It is recommended that:

- Patients receiving Daptomycin-AFT be monitored for the development of muscle pain or weakness, particularly of the distal extremities.
- In patients who receive Daptomycin-AFT, 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 daptomycin.
- In patients with renal impairment, both renal function and CPK be monitored more frequently than once weekly.
- Daptomycin-AFT 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 Daptomycin-AFT.

5.4 PERIPHERAL NEUROPATHY

Physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving Daptomycin-AFT.

Pediatric patients younger than one year old should not be given Daptomycin-AFT 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.

5.5 EOSINOPHILIC PNEUMONIA

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 or organizing pneumonia. 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 Daptomycin-AFT should undergo prompt medical evaluation, and Daptomycin-AFT should be discontinued immediately. Treatment with systemic steroids is recommended.

5.6 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 Daptomycin-AFT should undergo medical evaluation. If DRESS is suspected, Daptomycin-AFT should be discontinued promptly and appropriate treatment instituted.

5.7 TUBULOINTERSTITIAL NEPHRITIS (TIN)

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

5.8 *Clostridioides difficile*-ASSOCIATED DIARRHEA

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.

5.9 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.

5.10 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 8 ADVERSE REACTIONS, 8.3 Interference with Laboratory Tests].

5.11 NON-SUSCEPTIBLE MICROORGANISMS

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

6 DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

6.1 EFFECTS OF DAPTOMYCIN-AFT ON OTHER DRUGS

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

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

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

7 USE IN SPECIAL POPULATION

7.1 PREGNANCY

7.1.1 Risk Summary

There are no adequate and well-controlled studies of daptomycin in pregnant women. daptomycin should be used during pregnancy only if the potential benefit outweighs the possible risk.

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. Because animal reproduction studies are not always predictive of human response, Daptomycin-AFT should be used during pregnancy only if the expected benefit outweighs the possible risk.

7.2 NURSING MOTHERS

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-AFT.

7.3 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.

7.4 GERIATRIC USE

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

7.5 RENAL IMPAIRMENT

Daptomycin is eliminated primarily by the kidneys; therefore, an adjustment of Daptomycin-AFT 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 patients is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours. When possible, administer Daptomycin-AFT 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 patients with CL_{CR} ≥ 30 mL/min.

The dosage regimen for daptomycin in pediatric patients with renal impairment has not been established [see 2 DOSAGE AND ADMINISTRATION, 2.4 Renal Insufficiency (or Impairment)].

7.6 HEPATIC IMPAIRMENT

No dosage adjustment is warranted when Daptomycin-AFT 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.

7.7 GENDER

No dosage adjustment is warranted based on gender when Daptomycin-AFT is administered.

7.8 OBESITY

No adjustment of Daptomycin-AFT dosage is warranted in obese patients.

8 ADVERSE REACTIONS

8.1 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

Adverse Drug Reaction	Frequency Category
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	

Adverse Drug Reaction	Frequency Category
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

8.2 POST-MARKETING EXPERIENCE

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, manifested by isolated spontaneous reports including, but not limited to angioedema, pulmonary eosinophilia, vesiculobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling

Infections and infestations

Clostridioides difficile-associated diarrhea

Anaphylaxis

Infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste

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

8.3 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-AFT, it is recommended that clinicians:

1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next Daptomycin-AFT 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.

9 OVERDOSAGE

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).

10 CLINICAL PHARMACOLOGY

10.1 THERAPEUTIC CLASS

Daptomycin-AFT contains daptomycin, a cyclic lipopeptide antibacterial agent.

10.2 MECHANISM OF ACTION

10.2.1 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.

10.2.2 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.

10.3 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.

10.4 PHARMACODYNAMICS

10.4.1 PK/PD Relationship

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

10.5 PHARMACOKINETICS

10.5.1 General Introduction

Daptomycin pharmacokinetics were generally linear (dose-proportional) and time-independent at daptomycin 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 C_{max}) was demonstrated in healthy subjects following administration of daptomycin as a 30-minute intravenous infusion or as a 2-minute intravenous injection.

10.5.2 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.

10.5.3 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.

10.5.4 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.

10.5.5 Specific Populations

10.5.5.1 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 daptomycin 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.

10.5.5.2 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.

10.5.5.3 Pediatric

The pharmacokinetics of daptomycin in pediatric subjects was evaluated in 3 single-dose pharmacokinetic studies. After a single 4 mg/kg dose of daptomycin, 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 daptomycin, 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 daptomycin, 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 daptomycin, 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 daptomycin 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 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=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; 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)**	**$t_{1/2}$ (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; CLT, 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.

10.5.5.4 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 daptomycin 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}.

10.5.5.5 Gender

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

10.5.5.6 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.

10.6 DRUG INTERACTION STUDIES

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).

11 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 AUCinf 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.

12 NAME OF THE DRUG

DAPTOMYCIN-AFT POWDER FOR SOLUTION FOR INJECTION OR INFUSION 500 MG/VIAL

13 PHARMACEUTICAL FORM AND PRODUCT DESCRIPTION

Lyophilized cake or powder for reconstitution. The solution appearance after reconstitution is yellowish green or yellow, clear liquid.

14 PHARMACEUTICAL PARTICULARS

14.1 COMPOSITION

Active ingredient

Daptomycin

Inactive ingredients (List of excipients)

Sodium hydroxide

14.2 STORAGE

Store in original packages at refrigerated temperatures of between 2 °C to 8 °C; avoid excessive heat.

14.3 SHELF-LIFE

Please refer to the expiry date on the outer carton.

Shelf-life after reconstitution: Please refer to Section 3.3 Stability After Reconstitution and Dilution

14.4 NATURE AND CONTENTS OF CONTAINER

Daptomycin-AFT is supplied in glass vials closed with a rubber stopper.

15 PRODUCT OWNER

AFT Pharmaceuticals Ltd.
129 Hurstmere Road
Takapuna, Auckland, New Zealand

16 DATE OF REVISION

November 2023