1. NAME OF THE MEDICINAL PRODUCT

Pfizer Daptomycin Powder for Solution for Injection or Infusion 500 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg daptomycin.

One mL provides 50 mg of daptomycin after reconstitution with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for solution for injection/infusion.

A light yellow to light brown lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

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 study 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 (see section 4.4).

4.2 Posology and method of administration

Daptomycin is given by intravenous (IV) administration.

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

Adults

Complicated skin and skin structure infections
Daptomycin 4 mg/kg is administered to adult patients intravenously in 0.9% sodium chloride solution 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 more frequently than once a day, and measure creatine phosphokinase (CPK) levels at baseline and at regular intervals (at least weekly). Refer to section 6.6.

Staphylococcus aureus bloodstream infections (bacteraemia)
Daptomycin 6 mg/kg is administered to adult patients intravenously in 0.9% sodium chloride solution 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 more frequently than once a day, and measure CPK levels at baseline and at regular intervals (at least weekly) Refer to section 6.6.

Paediatric patients (1 to 17 years of age)

Complicated skin and skin structure infections
The recommended dose regimens based on age for paediatric patients with cSSSI are shown in Table 1. Daptomycin should be administered intravenously in 0.9% sodium chloride solution for injection once every 24 hours for up to 14 days.

Unlike in adults, Daptomycin should not be administered by injection over a 2-minute period in paediatric patients.

Table 1 Recommended Dosage of Daptomycin in Paediatric 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 paediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for paediatric patients with renal impairment has not been established.

Staphylococcus aureus bloodstream infections (bacteraemia)
The recommended dose regimens based on age for paediatric patients with *S. aureus* bloodstream infections (bacteraemia) are shown in Table 2. Daptomycin should be administered intravenously in 0.9% sodium chloride solution for injection once every 24 hours for up to 42 days.

Table 2 Recommended Dosage of Daptomycin in Paediatric 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 paediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for paediatric patients with renal impairment has not been established.
(1) Minimum duration for paediatric bacteraemia should be in accordance with the perceived risk of complications in the individual patient.

Special population

Renal impairment
Daptomycin is eliminated primarily by the kidney; therefore, an adjustment of daptomycin dosage interval is recommended for adult patients with creatinine clearance (CL_{CR}) < 30 mL/min, including patients receiving haemodialysis 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 following the completion of haemodialysis on haemodialysis days. In adult patients with renal impairment, monitor both renal function and CPK more frequently than once weekly.

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

Due to limited clinical experience, daptomycin should only be used in adult patients with any degree of renal impairment ($CL_{CR} < 80$ 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 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	4 mg/kg every 24 hours
	< 30 mL/min	4 mg/kg every 48 hours*
Staphylococcus aureus Bacteraemia Including Right-sided Endocarditis (Dosing duration: 2 to 6 weeks)	≥ 30 mL/min	6 mg/kg every 24 hours
	< 30 mL/min	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 modelling data. The same dose adjustments are recommended for adult patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, daptomycin should be administered following the completion of dialysis on dialysis days.

The dose regimen for daptomycin in paediatric patients with renal impairment has not been established.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
If a focus of infection other than cSSSI or RIE is identified after initiation of daptomycin therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis/hypersensitivity reactions
Anaphylaxis/hypersensitivity reactions have been reported with daptomycin. If an allergic reaction to daptomycin occurs, discontinue use and institute appropriate therapy.

Pneumonia
It has been demonstrated in clinical studies that daptomycin is not effective in the treatment of pneumonia. Pfizer Daptomycin is therefore not indicated for the treatment of pneumonia.

RIE due to *Staphylococcus aureus*
Clinical data on the use of daptomycin to treat RIE due to *Staphylococcus aureus* are limited to 19 adult patients. The safety and efficacy of daptomycin in children and adolescents aged below 18 years with RIE due to *Staphylococcus aureus* have not been established.

The efficacy of daptomycin in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated.

Deep-seated infections
Patients with deep-seated infections should receive any required surgical interventions (e.g. debridement, removal of prosthetic devices, valve replacement surgery) without delay.

Enterococcal infections
There is insufficient evidence to be able to draw any conclusions regarding the possible clinical efficacy of daptomycin against infections due to enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*. In addition, dose regimens of daptomycin that might be appropriate for the treatment of enterococcal infections, with or without bacteraemia, have not been identified. Failures with daptomycin in the treatment of enterococcal infections that were mostly accompanied by bacteraemia have been reported. In some instances treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin.

Non-susceptible micro-organisms
The use of antibacterials may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Clostridioides difficile-associated diarrhoea (CDAD)
CDAD has been reported with daptomycin (see section 4.8). If CDAD is suspected or confirmed, daptomycin may need to be discontinued and appropriate treatment instituted as clinically indicated.

Persisting or relapsing *S. aureus* bacteraemia/endocarditis
Patients with persisting or relapsing *S. aureus* bacteraemia/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 standardised procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical intervention (e.g. debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required.

Drug/laboratory test interactions
False prolongation of prothrombin time (PT) and elevation of international normalised ratio (INR) have been observed when certain recombinant thromboplastin reagents are utilised for the assay (see section 4.5).

Creatine phosphokinase and myopathy
Increases in plasma creatine phosphokinase (CPK; MM isoenzyme) levels associated with muscular pains and/or weakness and cases of myositis, myoglobinaemia and rhabdomyolysis have been reported during therapy with daptomycin (see sections 4.5, 4.8 and 5.3). In clinical studies, marked increases in plasma CPK to > 5x Upper Limit of Normal (ULN) without muscle symptoms occurred more commonly in daptomycin-treated patients (1.9%) than in those that received comparators (0.5%). Therefore, it is recommended that:

- Plasma CPK should be measured at baseline and at regular intervals (at least once weekly) during therapy in all patients.
- CPK should be measured more frequently (e.g. every 2-3 days at least during the first two weeks of treatment) in patients who are at higher risk of developing myopathy. For example, patients with any degree of renal impairment (creatinine clearance < 80 mL/min; see also section 4.2), including those on haemodialysis or CAPD, and patients taking other medicinal products known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin). Temporary suspension of HMG-CoA reductase inhibitors and fibrates should be considered during therapy with daptomycin.
- It cannot be ruled out that those patients with CPK greater than 5 times upper limit of normal at baseline may be at increased risk of further increases during daptomycin therapy. This should be taken into account when initiating daptomycin therapy and, if daptomycin is given, these patients should be monitored more frequently than once weekly.
- Pfizer Daptomycin should not be administered to patients who are taking other medicinal products associated with myopathy unless it is considered that the benefit to the patient outweighs the risk.
- Patients should be reviewed regularly while on therapy for any signs or symptoms that might represent myopathy.

- Any patient that develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days. Pfizer Daptomycin should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 times upper limit of normal and in patients without reported symptoms who have marked elevations in CPK, with levels greater than 10 times upper limit of normal.

Peripheral neuropathy
Patients who develop signs or symptoms that might represent a peripheral neuropathy during therapy with daptomycin should be investigated and consideration should be given to discontinuation of daptomycin (see sections 4.8 and 5.3).

Paediatric population
Paediatric patients below the age of one year should not be given daptomycin 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 (see section 5.3).

Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving daptomycin (see section 4.8). In most reported cases associated with daptomycin, patients developed fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organising pneumonia. The majority of cases occurred after more than 2 weeks of treatment with 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 should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, other medicinal products). Daptomycin should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and vesiculobullous rash with or without mucous membrane involvement (Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)), which could be life-threatening or fatal, have been reported with daptomycin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, daptomycin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a severe cutaneous adverse reaction with the use of daptomycin, treatment with daptomycin must not be restarted in this patient at any time.

Tubulointerstitial nephritis
Tubulointerstitial nephritis (TIN) has been reported in post-marketing experience with daptomycin. Patients who develop fever, rash, eosinophilia and/or new or worsening renal impairment while receiving daptomycin should undergo medical evaluation. If TIN is suspected, daptomycin should be discontinued promptly and appropriate therapy and/or measures should be taken.

Renal impairment
Renal impairment has been reported during treatment with daptomycin. Severe renal impairment may in itself also pre-dispose to elevations in daptomycin levels which may increase the risk of development of myopathy (see above).

An adjustment of daptomycin dose interval is needed for adult patients whose creatinine clearance is < 30 mL/min (see sections 4.2 and 5.2). The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical studies and the recommendation is mainly based on pharmacokinetic modelling data. Daptomycin should only be used in such patients when it is considered that the expected clinical benefit outweighs the potential risk.

Caution is advised when administering daptomycin to patients who already have some degree of renal impairment (creatinine clearance < 80 mL/min) before commencing therapy with Pfizer Daptomycin. Regular monitoring of renal function is advised (see section 5.2).

In addition, regular monitoring of renal function is advised during concomitant administration of potentially nephrotoxic agents, regardless of the patient's pre-existing renal function (see section 4.5).

The dose regimen for daptomycin in paediatric patients with renal impairment has not been established.

Hepatic impairment
No dosage adjustment is warranted when daptomycin 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.

Obesity
In obese subjects with Body Mass Index (BMI) $\geq$ 40 kg/m^2 but with creatinine clearance > 70 mL/min, the $AUC_{0-\infty}$ daptomycin was significantly increased (mean 42% higher) compared with non-obese matched controls. There is limited information on the safety and efficacy of daptomycin in the very obese and so caution is recommended. However, there is currently no evidence that a dose reduction is required (see section 5.2).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Daptomycin undergoes little to no Cytochrome P450 (CYP450)-mediated metabolism. It is unlikely that daptomycin will inhibit or induce the metabolism of medicinal products metabolised by the P450 system.

Interaction studies for daptomycin were performed with aztreonam, tobramycin, warfarin and probenecid. Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these medicinal products alter the pharmacokinetics of daptomycin. The pharmacokinetics of daptomycin were not significantly altered by aztreonam.

Although small changes in the pharmacokinetics of daptomycin and tobramycin were observed during co-administration by intravenous 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 an approved dose of daptomycin is unknown. Caution is warranted when daptomycin is co-administered with tobramycin.

Experience with the concomitant administration of daptomycin and warfarin is limited. Studies of daptomycin with anticoagulants other than warfarin have not been conducted. Anticoagulant activity in patients receiving daptomycin and warfarin should be monitored for the first several days after therapy with Pfizer Daptomycin is initiated.

There is limited experience regarding concomitant administration of daptomycin with other medicinal products that may trigger myopathy (e.g. HMG-CoA reductase inhibitors). However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in adult patients taking one of these medicinal products at the same time as daptomycin. It is recommended that other medicinal products associated with myopathy should if possible be temporarily discontinued during treatment with daptomycin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CPK levels should be measured more frequently than once weekly and patients should be closely monitored for any signs or symptoms that might represent myopathy (see sections 4.4, 4.8 and 5.3).

Daptomycin is primarily cleared by renal filtration and so plasma levels may be increased during co-administration with medicinal products that reduce renal filtration (e.g. NSAIDs and COX-2 inhibitors). In addition, there is a potential for a pharmacodynamic interaction to occur during co-administration due to additive renal effects. Therefore, caution is advised when daptomycin is co-administered with any other medicinal product known to reduce renal filtration.

During post-marketing surveillance, cases of interference between daptomycin and particular reagents used in some assays of prothrombin time/international normalised ratio (PT/INR) have been reported. This interference led to a false prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking daptomycin, consideration should be given to a possible *in vitro* interaction with the laboratory test. The possibility of erroneous results may be minimised by drawing samples for PT or INR testing near the time of trough plasma concentrations of daptomycin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on pregnancies are available for daptomycin. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Pfizer Daptomycin should not be used during pregnancy unless clearly necessary i.e., only if the expected benefit outweighs the possible risk.

Breast-feeding

In a single human case study, daptomycin was intravenously administered daily for 28 days to a nursing mother at a dose of 500 mg/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. Therefore, until more experience is gained, breast-feeding should be discontinued when daptomycin is administered to nursing women.

Fertility
No clinical data on fertility are available for daptomycin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

On the basis of reported adverse drug reactions, daptomycin is presumed to be unlikely to produce an effect on the ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile
In clinical studies, 2,011 adult subjects received daptomycin. Within these studies, 1,221 subjects received a daily dose of 4 mg/kg, of whom 1,108 were patients and 113 were healthy volunteers; 460 subjects received a daily dose of 6 mg/kg, of whom 304 were patients and 156 were healthy volunteers. In paediatric studies, 372 patients received daptomycin, of whom 61 received a single dose and 311 received a therapeutic regimen for cSSSI or SAB (daily doses ranged from 4 mg/kg to 12 mg/kg). Adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported at similar frequencies for daptomycin and comparator regimens.

The most frequently reported adverse reactions (frequency common (≥ 1/100 to < 1/10)) are: Fungal infections, urinary tract infection, candida infection, anaemia, anxiety, insomnia, dizziness, headache, hypertension, hypotension, gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension, liver function tests abnormal (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP)), rash, pruritus, limb pain, serum creatine phosphokinase (CPK) increased, infusion site reactions, pyrexia, asthenia.

Less frequently reported, but more serious, adverse reactions include hypersensitivity reactions, eosinophilic pneumonia (occasionally presenting as organising pneumonia), drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

Tabulated list of adverse reactions
The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data):

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3 Adverse Reactions from Clinical Studies and Post-marketing Reports

System organ class	Frequency	Adverse reactions
Infections and infestations	*Common:*	Fungal infections, urinary tract infection, candida infection
	Uncommon:	Fungaemia
	Not known:*	*Clostridioides difficile*-associated diarrhoea**
Blood and lymphatic system disorders	*Common:*	Anaemia
	Uncommon:	Thrombocytosis, eosinophilia, leukocytosis
	Not known:*	Thrombocytopaenia
Immune system disorders	*Not known*:*	Hypersensitivity**, manifested by isolated spontaneous reports including, but not limited to angioedema, pulmonary eosinophilia, sensation of oropharyngeal swelling, anaphylaxis**, infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste
Metabolism and nutrition disorders	*Uncommon:*	Decreased appetite, hyperglycaemia, electrolyte imbalance
Psychiatric disorders	*Common:*	Anxiety, insomnia
Nervous system disorders	*Common:*	Dizziness, headache
	Uncommon:	Paraesthesia, taste disorder, tremor, eye irritation
	Not known:*	Peripheral neuropathy**
Ear and labyrinth disorders	*Uncommon:*	Vertigo
Cardiac disorders	*Uncommon:*	Supraventricular tachycardia, extrasystole, supraventricular arrhythmia
Vascular disorders	*Common:*	Hypertension, hypotension
	Uncommon:	Flushes
Respiratory, thoracic and mediastinal disorders	*Not known*:*	Eosinophilic pneumonia[1]**, cough, organising pneumonia
Gastrointestinal disorders	*Common:*	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension
	Uncommon:	Dyspepsia, glossitis
Hepatobiliary disorders	*Rare:*	Jaundice
Skin and subcutaneous tissue disorders	*Common:*	Rash, pruritus
	Uncommon:	Urticaria
	Not known:*	Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)**, vesiculobullous rash with or without mucous membrane involvement (SJS or TEN)**
Musculoskeletal and connective tissue disorders	*Common:*	Limb pain
	Uncommon:	Myositis, muscular weakness, muscle pain, arthralgia, muscle cramps
	Not known:*	Rhabdomyolysis[3] **
Renal and urinary disorders	*Uncommon:*	Renal impairment, including renal failure and renal insufficiency
	Not known:*	Tubulointerstitial nephritis (TIN)**
Reproductive system and breast disorders	*Uncommon:*	Vaginitis
Investigation	*Common:*	Serum creatine phosphokinase (CPK)[2] increased,

System organ class	Frequency	Adverse reactions
		liver function tests abnormal[2] (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP))
	Uncommon:	Serum creatinine increased, international normalised ratio (INR) increased, serum lactate dehydrogenase (LDH) increased
	Rare:	Prothrombin time (PT) prolonged
	Not known:*	Myoglobin increased, platelet count decreased
General disorders and administration site conditions	*Common:*	Infusion site reactions, pyrexia, asthenia
	Uncommon:	Fatigue, pain, chills

* Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

** See section 4.4.

[1] While the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, to date the reporting rate of spontaneous reports is very low (< 1/10,000).

[2] In some cases of myopathy involving raised CPK and muscle symptoms, the patients also presented with elevated transaminases. These transaminase increases were likely to be related to the skeletal muscle effects. The majority of transaminase elevations were of Grade 1-3 toxicity and resolved upon discontinuation of treatment.

[3] When clinical information on the patients was available to make a judgement, approximately 50% of the cases occurred in patients with pre-existing renal impairment, or in those receiving concomitant medicinal products known to cause rhabdomyolysis.

The safety data for the administration of daptomycin via 2-minute intravenous injection are derived from two pharmacokinetic studies in healthy adult volunteers. Based on these study results, both methods of daptomycin administration, the 2-minute intravenous injection and the 30-minute intravenous infusion, had a similar safety and tolerability profile. There was no relevant difference in local tolerability or in the nature and frequency of adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Other antibacterials, ATC code: J01XX09

Mechanism of action
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.

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

Pharmacokinetic/pharmacodynamic relationship
Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro* and in *in vivo* animal models.

Mechanisms 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.

5.2 Pharmacokinetic properties

Absorption
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 adult 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 (CL_{CR} < 30 mL/min 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 metabolised 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 metabolised by the P450 system.

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

Elimination
Daptomycin is excreted primarily by the kidneys. There is minimal to no active tubular secretion of daptomycin. In a mass balance study of adult subjects using radiolabelled 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 faeces based on total radioactivity.

Plasma clearance of daptomycin is approximately 7 to 9 mL/h/kg and its renal clearance is 4 to 7 mL/h/kg.

Special populations

Renal insufficiency
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	4 mg/kg every 24 hours
	< 30 mL/min	4 mg/kg every 48 hours
Staphylococcus aureus Bacteraemia Including Right-sided Endocarditis (Dosing duration: 2 to 6 weeks)	≥ 30 mL/min	6 mg/kg every 24 hours
	< 30 mL/min	6 mg/kg every 48 hours

Following administration of a single 4 mg/kg or 6 mg/kg 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 haemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function.

Hepatic insufficiency
The pharmacokinetics of daptomycin was 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.

Paediatric
The pharmacokinetics of daptomycin in paediatric 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 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 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 paediatric 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 paediatric 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 4).

Table 4 Mean (Standard Deviation) Daptomycin Population Pharmacokinetic Parameters in cSSSI Paediatric Patients

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

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalised to body weight; V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life.
* Mean is calculated from N=2.

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years old, inclusive) with SAB. Patients were enrolled into 3 age

groups and intravenous doses of 7 to 12 mg/kg once daily were administered. Following administration of multiple doses, daptomycin exposure (AUC_{ss} and $C_{max,ss}$) was similar across different age groups after dose adjustment based on body weight and age (Table 5).

Table 5 Mean (Standard Deviation) of Daptomycin Population Pharmacokinetic Parameters in Bacteraemia Paediatric Patients

	Pharmacokinetic Parameters						
Age	**Dose (mg/kg)**	**Duration (min)**	**AUC_{ss} (mcg·h/mL)**	**$t_{1/2}$ (h)**	**V_{ss} (mL)**	**CL_T (mL/h/kg)**	**$C_{max,ss}$ (mcg/mL)**
12-17 years (N=13)	7	30	656 (334)	7.5 (2.3)	6420 (1980)	12.4 (3.9)	104 (35.5)
7-11 years (N=19)	9	30	579 (116)	6.0 (0.8)	4510 (1470)	15.9 (2.8)	104 (14.5)
2-6 years (N=19)	12	30	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 normalised to body weight; V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life.

No patients 1 to < 2 years of age were enrolled in the study. Simulation using a population pharmacokinetic model demonstrated that the AUC_{ss} of daptomycin in paediatric 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 intravenous 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}.

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

Race
No clinically significant differences in daptomycin pharmacokinetics have been observed in Black or Japanese subjects relative to Caucasian subjects.

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 approximately30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in nonobese controls.

5.3 Preclinical safety data

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 characterised 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 (characterised 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 $\geq$ 321 µg/mL and $\geq$ 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 $\geq$ 50 mg/kg/day necessitated early discontinuation by PND19. At the dose level of 25 mg/kg/day with associated C_{max} and AUC_{inf} values of 147 µg/mL and 717 µg·h/mL, respectively, mild clinical signs of twitching and one incidence of muscle rigidity were observed without any effects on body weight and were reversible over a 28-day recovery period. These data indicate a limited margin between doses associated with mild versus marked adverse clinical signs. Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle or other tissues assessed, at any dose level. No adverse clinical signs for these target organs of toxicity were observed in the dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated C_{max} and AUC_{inf} values of 62 µg/mL and 247 µg·h/mL, respectively.

Carcinogenesis/Mutagenesis

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

Reproduction

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)
Citric acid (solubiliser/stabiliser)

6.2 Incompatibilities

Pfizer Daptomycin is not physically or chemically compatible with glucose-containing solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Refer to outer carton.

After reconstitution: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours at 2°C – 8°C. Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 48 hours at 2°C – 8°C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section 6.6) at 25°C must not exceed 12 hours (or 48 at 2°C – 8°C).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial (see section 6.6) at 25°C must not exceed 12 hours (or 48 hours at 2°C – 8°C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.
For storage conditions after reconstitution and after reconstitution and dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

Single use 15 mL type I clear glass vials with gray rubber closure and aluminium cap.

Available in packs containing 1 vial or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

In adults, daptomycin may be administered intravenously as an infusion over 30 minutes or as an injection over 2 minutes. Daptomycin should not be administered as a 2-minute injection to paediatric patients. Paediatric patients 7 to 17 years old should receive daptomycin infused over 30 minutes. In paediatric patients under 7 years old receiving a 9-12 mg/kg dose, daptomycin should be administered over 60 minutes (see sections 4.2 and 5.2). Preparation of the solution for infusion requires an additional dilution step as detailed below.

Pfizer Daptomycin given as 30 or 60-minute intravenous infusion
A 50 mg/mL concentration of Pfizer Daptomycin for infusion is obtained by reconstituting the lyophilised product with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

To prepare Pfizer Daptomycin for intravenous infusion, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute lyophilised Pfizer Daptomycin.

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

1. The polypropylene flip off cap should be removed to expose the central portion of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry (perform the same for the sodium chloride solution vial, if applicable). After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then SLOWLY inject through the centre of the rubber stopper directly over the product plug in the vial.
2. Release the syringe plunger and allow the syringe plunger to equalise the pressure before removing the syringe from the vial.
3. Hold the vial by the vial neck, tilt the vial and swirl vial contents until the product is completely reconstituted.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Pfizer Daptomycin range in colour from clear yellow to light brown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin/mL) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous infusion.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.

9. Transfer the reconstituted solution into a sodium chloride 9 mg/mL (0.9%) infusion bag (typical volume 50 mL).
10. The reconstituted and diluted solution should then be infused intravenously over 30 or 60 minutes as directed in section 4.2.

The following have been shown to be compatible when added to Pfizer Daptomycin containing infusion solutions: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin and lidocaine.

Pfizer Daptomycin given as 2-minute intravenous injection (adult patients only)
Water should not be used for reconstitution of Pfizer Daptomycin for intravenous injection. Pfizer Daptomycin should only be reconstituted with sodium chloride 9 mg/mL (0.9%) solution for injection.

A 50 mg/mL concentration of Pfizer Daptomycin for injection is obtained by reconstituting the lyophilised product with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

To prepare Pfizer Daptomycin for intravenous injection, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute lyophilised Pfizer Daptomycin.

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

1. The polypropylene flip off cap should be removed to expose the central portion of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry (perform the same for the sodium chloride solution vial, if applicable). After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then SLOWLY inject through the centre of the rubber stopper directly over the plug in the vial.
2. Release the syringe plunger and allow the syringe plunger to equalise the pressure before removing the syringe from the vial.
3. Hold the vial by the vial neck, tilt the vial and swirl vial contents until the product is completely reconstituted.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Pfizer Daptomycin range in colour from clear yellow to light brown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin/mL) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back

to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous injection.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
9. The reconstituted solution should then be injected intravenously slowly over 2 minutes as directed in section 4.2.

Pfizer Daptomycin vials are for single-use only.

From a microbiological point of view, the product should be used immediately after reconstitution (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

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