For the Use of a Registered Medical Practitioner or a Hospital or Laboratory only

DAPTOCCORD-500
(Daptomycin Powder for Solution for Injection or Infusion 500 mg/vial)

1. Name of the medicinal product
DAPTOCCORD-500 (Daptomycin Powder for Solution for Injection or Infusion 500 mg/vial)

2. Qualitative and quantitative composition
Each vial contains 500 mg daptomycin
For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Powder for solution for injection or infusion.
A pale yellow to light brown lyophilised cake or powder.

4. Clinical particulars
4.1 Therapeutic indications
Daptomycin is indicated for the treatment of the following infections (see sections 4.4 and 5.1).
- Complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria: Staphylococcus aureus (including methicillinresistant isolates), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. equisimilis, and Enterococcus faecalis (vancomycin-susceptible isolates only).
- Staphylococcus aureus bloodstream infections (bacteremia), including those with rightsided infective endocarditis (SAB/RIE), 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 trial of Daptomycin in patients with S. aureus bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. Daptomycin has not been studied in patients with prosthetic valve endocarditis.
Daptomycin is not indicated for the treatment of pneumonia.
Daptomycin is active against Gram-positive bacteria only (see section 5.1). In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, Daptomycin should be co-administered with appropriate antibacterial agent(s).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology
Adults
Complicated Skin and Skin Structure Infections
Daptomycin 4mg/kg is administered intravenously in 0.9% sodium chloride 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).

Staphylococcus aureus Bloodstream Infections (Bacteremia)
Daptomycin 6mg/kg is administered intravenously in 0.9% sodium chloride 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).

Renal impairment
Daptomycin is eliminated primarily by the kidney.
Due to limited clinical experience (see table and footnotes below) daptomycin should only be used in adult patients with any degree of renal impairment (CrCl< 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment, renal function and creatine phosphokinase (CPK) levels should be closely monitored in all patients with any degree of renal impairment (see also sections 4.4 and 5.2). The dosage regimen for Daptomycin in paediatric patients with renal impairment has not been established

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 once daily
	< 30 ml/min	4 mg/kg every 48 hours
Staphylococcus aureus Bacteremia Including Right-sided Endocarditis (Dosing duration: 2 to 6 weeks)	≥ 30 ml/min	6 mg/kg once daily
	< 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 modeling data. The same dose adjustments are recommended for patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, Daptomycin should be administered following the completion of dialysis on dialysis days.		

Hepatic impairment
No dose adjustment is necessary when administering Daptomycin to patients with mild or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore caution should be exercised if Daptomycin is given to such patients.

Elderly patients
The recommended doses should be used in elderly patients except those with severe renal impairment (see above and section 4.4).

Paediatric patients
Safety and effectiveness of daptomycin in patients under the age of 18 have not been established
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).

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. Daptomycin is therefore not indicated for the treatment of pneumonia.

RIE due to *Staphylococcus aureus*
The safety and efficacy of Daptomycin in children and adolescents aged below 18 years with right-sided infective endocarditis (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.

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.

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 (see section 5.1).

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.

Clostridium difficile-associated diarrhoea
Clostridium difficile-associated diarrhoea (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.

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 also 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 also 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).
• 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.
• 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. Daptomycin should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 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 Daptomycin should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.

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 trials 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 Daptomycin. Regular monitoring of renal function is advised (see also 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 also section 4.5).

The dosage regimen for Daptomycin in paediatric patients with renal impairment has not been established.

Obesity
No adjustment of daptomycin dosage is warranted in obese patients.

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 coadministration 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 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 coadministration 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 coadministration due to additive renal effects. Therefore, caution is advised when daptomycin is coadministered 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).

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 an IV dose of 6.7mg/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 mcg/ml, which is a low concentration. Therefore, until more experience is gained, breastfeeding 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.

4.8 Undesirable effects

Summary of the safety profile

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 rash 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 1 Adverse reactions from clinical studies and post-marketing reports

System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	*Common:* *Uncommon:* *Not known*:*	Fungal infections, urinary tract infection, candida infection Fungaemia *Clostridium difficile*-associated diarrhoea
Blood and lymphatic system disorders	*Common:* *Uncommon:* *Rare:* *Not known*:*	Anaemia Thrombocythaemia, eosinophilia, international normalised ratio (INR) increased, leukocytosis Prothrombin time (PT) prolonged Thrombocytopaenia
Immune system disorders	*Not known*:*	Hypersensitivity, manifested by isolated spontaneous reports including, but not limited to angioedema, drug rash with eosinophilia and systemic symptoms (DRESS), pulmonary eosinophilia, vesicobullous rash with mucous membrane involvement and 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:* *Uncommon:* *Not known*:*	Dizziness, headache Paraesthesia, taste disorder, tremor, Peripheral neuropathy
Ear and labyrinth disorders	*Uncommon:*	Vertigo
Cardiac disorders	*Uncommon:*	Supraventricular tachycardia, extrasystole
Vascular disorders	*Common:* *Uncommon:*	Hypertension, hypotension Flushes
Respiratory, thoracic and mediastinal disorders	*Not known*:*	Eosinophilic pneumonia, cough
Gastrointestinal disorders	*Common:* *Uncommon:*	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension Dyspepsia, glossitis

System organ class	Frequency	Adverse reactions
Hepatobiliary disorders	*Common:* *Rare:*	Liver function tests abnormal[2] (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP)) Jaundice
Skin and subcutaneous tissue disorders	*Common:* *Uncommon:* *Not known*:*	Rash, pruritus Urticaria Acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	*Common:* *Uncommon:* *Not known*:*	Limb pain, serum creatine phosphokinase (CPK)[2] increased Myositis, increased myoglobin, muscular weakness, muscle pain, arthralgia, serum lactate dehydrogenase (LDH) increased, muscle cramps Rhabdomyolysis
Renal and urinary disorders	*Uncommon:*	Renal impairment, including renal failure and renal insufficiency, serum creatinine increased
Reproductive system and breast disorders	*Uncommon:*	Vaginitis
General disorders and administration site conditions	*Common:* *Uncommon:*	Infusion site reactions, pyrexia, asthenia Fatigue, pain

* 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.

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 is a cyclic lipopeptide natural product that is active against Gram-positive bacteria only.

The mechanism of action involves binding (in the presence of calcium ions) to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

PK/PD relationship

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

Mechanisms of resistance

Strains with decreased susceptibility to daptomycin have been reported especially during the treatment of patients with difficult-to-treat infections and/or following administration for prolonged periods. In particular, there have been reports of treatment failures in patients infected with *Staphylococcus aureus*, *Enterococcus faecalis* or *Enterococcus faecium*, including bacteraemic patients that have been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin during therapy.
The mechanism(s) of daptomycin resistance is (are) not fully understood.

5.2 Pharmacokinetic properties

Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose by 30-minute intravenous infusion for up to 14 days in healthy adult volunteers. Steady-state concentrations are 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

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 only minimally penetrate the blood-brain barrier and the placental barrier following single and multiple doses.

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 subjects with significant renal impairment (CLCR <30mL/min or on dialysis). The protein binding of daptomycin in subjects with mild to moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

Biotransformation

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 medicinal products metabolised by the P450 system.

After infusion of 14C-daptomycin in healthy adults, the plasma radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference in 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. Concomitant administration of probenecid and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting minimal to no active tubular secretion of daptomycin.

Following intravenous administration, plasma clearance of daptomycin is approximately 7 to 9 ml/h/kg and its renal clearance is 4 to 7 ml/h/kg.

In a mass balance study using radiolabelled material, 78% of the administered dose was recovered from the urine based on total radioactivity, whilst urinary recovery of unchanged daptomycin was approximately 52% of the dose. About 6% of the administered radiolabel was excreted in the faeces.

Special populations

Elderly

Following administration of a single 4 mg/kg intravenous dose of daptomycin over a 30-minute period, the mean total clearance of daptomycin was approximately 35% lower and the mean $AUC_{0-\infty}$ was approximately 58% higher in elderly subjects (≥ 75 years of age) compared with those in healthy young subjects (18 to 30 years of age). There were no differences in C_{max}. The differences noted are most likely due to the normal reduction in renal function observed in the geriatric population.

No dose adjustment is necessary based on age alone. However, renal function should be assessed and the dose should be reduced if there is evidence of severe renal impairment.

Children and adolescents (1 to 17 years of age)

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 normalized by weight 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 children 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. Efficacy was not assessed in these single-dose studies.

Obesity

The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9kg/m2) and 6 extremely obese (BMI ≥40kg/m2) subjects. The AUC was

approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects than in non-obese controls.

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

Renal impairment
Following administration of a single 4 mg/kg or 6 mg/kg intravenous dose of daptomycin over a 30-minute period to adult subjects with various degrees of renal impairment, total daptomycin clearance (CL) decreased and systemic exposure (AUC) increased as renal function (creatinine clearance) decreased. The mean AUC for patients with CLCR <30mL/min and for patients on dialysis (CAPD and hemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function.

Hepatic impairment
The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic impairment (Child-Pugh B classification of hepatic impairment) compared with healthy volunteers matched for gender, age and weight following a single 4 mg/kg dose. No dosage adjustment is necessary when administering daptomycin in patients with moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh C classification) have not been evaluated.

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 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 50/75mg/kg/day.
At dose levels of 50 and 75mg/kg/day with associated Cmax and AUCinf values of ≥321µg/mL and ≥1470µg•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 ≥50mg/kg/day necessitated early discontinuation by PND19. At the dose level of 25mg/kg/day with associated Cmax and AUCinf values of 147µg/mL and 717µg•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 10mg/kg/day, the NOAEL, with associated Cmax and AUCinf values of 62µg/mL and 247µg•h/mL, respectively.

Reproductive toxicity testing showed no evidence of effects on fertility, embryofetal, or postnatal development. However, daptomycin can cross the placenta in pregnant rats (see section 5.2). Excretion of daptomycin into milk of lactating animals has not been studied.

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

6. Pharmaceutical particulars

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

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

36 months

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.

After dilution:
Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 24 hours at 2°C – 8°C for concentration ranges 2.5 mg/ml, 10 mg/ml and 20 mg/ml.
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 24 at 2°C – 8°C).

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 and conditions prior to use are the responsibility of the user and would normally not 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 in a refrigerator (2°C – 8°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

Daptomycin Powder for Solution for Injection or Infusion 500 mg/vial is available in 20 ml clear glass vial closed with a grey bromobutyl rubber stopper and an aluminium royal blue colored flip off seal.
Pack sizes: 1 vial

6.6 Special precautions for disposal and other handling

Daptomycin may be administered intravenously as an infusion over 30 minutes or as an injection over 2 minutes. Preparation of the solution for infusion requires an additional dilution step as detailed below.

Daptomycin given as 30 or 60-minute intravenous infusion

A 50 mg/ml concentration of Daptomycin is obtained by reconstituting the lyophilised product with 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection.
The lyophilised product takes approximately 20 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

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

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. 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 into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
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 Daptomycin range in colour from pale yellow to light brown.

5. The reconstituted solution should then be diluted with sodium chloride 9 mg/ml (0.9%) (typical volume 50 ml).

For Dilution:

1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/ml) from the vial using a new sterile needle that is 21 gauge or smaller in diameter by inverting the vial in order to allow the solution to drain towards the stopper. Using a 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 the required solution from the inverted vial.
2. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
3. Transfer the required reconstituted dose into 50 ml sodium chloride 9 mg/ml (0.9%).
4. 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 daptomycin containing infusion solutions: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin and lidocaine.

Daptomycin given as 2-minute intravenous injection

Water should not be used for reconstitution of Daptomycin for intravenous injection. Daptomycin should only be reconstituted with sodium chloride 9 mg/ml (0.9%).

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

The lyophilised product takes approximately 20 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.
To prepare Daptomycin for intravenous injection, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute lyophilised Daptomycin.

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. 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 into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
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 Daptomycin range in colour from pale 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.
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. Name and address of Product Registrant
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8. Date of revision of the text
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