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

DAPTOCORD-500
(Daptomycin powder for solution for infusion 500mg/vial)

1. Name of the medicinal product
DAPTOCORD-500 (Daptomycin powder for solution for infusion 500mg/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
Lyophilized Powder for Infusion
A pale yellow to light brown lyophilised cake or powder.

4. Clinical particulars
4.1 Therapeutic indications
Daptocord is indicated for the treatment of the infections listed below.

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

Staphylococcus aureus Bloodstream Infections (Bacteremia)
Adult patients (≥ 18 years of age) with Staphylococcus aureus bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.
Pediatric patients (1 to 17 years of age) with S. aureus bloodstream infections (bacteremia) caused by methicillin-susceptible and methicillin-resistant isolates.

Limitations of Use
Daptocord is not indicated for the treatment of pneumonia.
Daptocord is not indicated for the treatment of left-sided infective endocarditis due to S. aureus. The clinical trial of Daptocord in patients with S. aureus bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor. Daptocord has not been studied in patients with prosthetic valve endocarditis.

Usage
Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Daptocord and other antibacterial drugs, Daptocord should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.
When culture and susceptibility information is available, it should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy. Empiric therapy may be initiated while awaiting test results.

4.2 Posology and method of administration
Administration
Daptocord should be administered intravenously.

Posology

Adults
Complicated Skin and Skin Structure Infections
Daptocord 4 mg/kg should be administered to adult patients intravenously in 0.9% sodium chloride injection once every 24 hours for 7 to 14 days by infusion over a 30-minute period.

***Staphylococcus aureus* Bloodstream Infections (Bacteremia)**
Daptocord 6 mg/kg should be administered to adult patients intravenously in 0.9% sodium chloride injection once every 24 hours for 2 to 6 weeks by infusion over a 30-minute period. There are limited safety data for the use of Daptocord for more than 28 days of therapy. In the Phase 3 trial, there were a total of 14 patients who were treated with Daptocord for more than 28 days.

Pediatric Patients (1 to 17 Years of Age)
Complicated Skin and Skin Structure Infections
The recommended dosage regimens based on age for pediatric patients with cSSSI are shown in Table 1. Daptocord should be administered intravenously in 0.9% sodium chloride injection once every 24 hours for up to 14 days.

Table 1: Recommended Dosage of Daptocord in Pediatric Patients (1 to 17 Years of Age) with Complicated Skin and Skin Structure Infections, Based on Age

Age group	Dosage*	Duration of therapy
12 to 17 years	5 mg/kg once every 24 hours infused over 30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once every 24 hours infused over 30 minutes	
2 to 6 years	9 mg/kg once every 24 hours infused over 60 minutes	
1 to < 2 years	10 mg/kg once every 24 hours infused over 60 minutes	

*Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.

***Staphylococcus aureus* Bloodstream Infections (Bacteremia)**
The recommended dosage regimens based on age for pediatric patients with S. aureus bloodstream infections (bacteremia) are shown in Table 2. Daptocord should be administered intravenously in 0.9% sodium chloride injection once every 24 hours for up to 42 days.

Table 2: Recommended Dosage of Daptocord in Pediatric Patients (1 to 17 Years of Age) with *S. aureus* Bloodstream Infections, Based on Age

Age group	Dosage*	Duration of (1)
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once every 24 hours infused over 30 minutes	
1 to 6 years	12 mg/kg once every 24 hours infused over 60 minutes	

*Recommended dosage is for pediatric patients (1 to 17 years of age) with normal renal function. Dosage adjustment for pediatric patients with renal impairment has not been established.
(1) Minimum duration for pediatric bacteremia should be in accordance with the perceived risk of complications in the individual patient

Patients with Renal Impairment
The recommended dosage regimen for adult patients with creatinine clearance (CLCR) <30 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), is 4 mg/kg (cSSSI) or 6 mg/kg (S. aureus bloodstream infections) once every 48 hours (Table 3). When possible, Daptocord should be administered following the completion of hemodialysis on hemodialysis days.

The dosage regimen for Daptocord pediatric patients with renal impairment has not been established.

Table 3. Recommended Dosage of Daptocord in Adult Patients

Creatinine Clearance (CLCR)	Dosage Regimen	
	cSSSI	*S. aureus* Bloodstream Infections
≥30 mL/min	4 mg/kg once every 24 hours	6 mg/kg once every 24 hours
<30 mL/min, including hemodialysis and CAPD	4 mg/kg once every 48 hours*	6 mg/kg once every 48 hours*

*When possible, administer Daptocord following the completion of hemodialysis on hemodialysis days.

For preparation of Daptocord for Administration, refer section 6.6.

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 cSSTI 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.

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.

Clostridium difficile-associated diarrhoea
Clostridium difficile-associated diarrhoea (CDAD) has been reported with daptomycin. 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.

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. 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;), 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.

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.

Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving daptomycin. 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.

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. 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.

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.

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

Obesity

In obese subjects with Body Mass Index (BMI) > 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.

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.

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 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.

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.

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 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.

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
As per clinical trials report of Daptomycin, the following adverse drug reactions were reported during therapy and during follow-up. The adverse drug reactions are organized by system organ class, and the frequency categories for these adverse drug reactions are reported in the table below as follows:

Very common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%

Table 1 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:*	*Clostridium difficile*-associated diarrhoea**
Blood and lymphatic system disorders	*Common:*	Anaemia
	Uncommon:	Thrombocythaemia, eosinophilia, international normalised ratio (INR) increased, leukocytosis
	Rare:	Prothrombin time (PT) prolonged
	Not known:*	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, eye irritation 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[1] **, cough
Gastrointestinal disorders	*Common:* *Uncommon:*	Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension Dyspepsia, glossitis
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[3] **
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.

** See section *Special warnings and precautions for use*.

[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.
Based on these study results, both methods of daptomycin administration, 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.

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. In animal models AUC/MIC and C_{max}/MIC correlate with efficacy and predicted bacterial kill *in vivo* at single doses equivalent to human adult doses of 4 mg/kg and 6 mg/kg once daily.

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.

Breakpoints
Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and streptococci (except *S. pneumoniae*) are Susceptible ≤ 1 mg/l and Resistant > 1 mg/l.

Susceptibility
The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly Susceptible Species
*Staphylococcus aureus**
Staphylococcus haemolyticus
Coagulase negative staphylococci
*Streptococcus agalactiae**
Streptococcus dysgalactiae subsp *equisimilis**
*Streptococcus pyogenes**
Group G streptococci
Clostridium perfringens
Peptostreptococcus spp.
Inherently resistant organisms
Gram-negative organisms

* denotes species against which it is considered that activity has been satisfactorily demonstrated in clinical studies.

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.

Comparable exposure (AUC and C_{max}) was demonstrated in healthy adult subjects following administration of daptomycin as a 30-minute intravenous infusion

Animal studies showed that daptomycin is not absorbed to any significant extent after oral administration.

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 in a concentration independent manner. In healthy adult volunteers and adult patients treated with daptomycin, protein binding averaged about 90% including subjects with renal impairment.

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 50% of the dose. About 5% 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.

Obesity
Relative to non-obese subjects daptomycin systemic exposure measured by AUC was about 28% higher in moderately obese subjects (Body Mass Index of 25-40 kg/m^2) and 42% higher in extremely obese subjects (Body Mass Index of > 40 kg/m^2). However, no dose adjustment is considered to be necessary based on obesity alone.

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.

Based on pharmacokinetic data and modelling, the daptomycin AUC during the first day after administration of a 6 mg/kg dose to adult patients on HD or CAPD was 2-fold higher than that observed in adult patients with normal renal function who received the same dose. On the second day after administration of a 6 mg/kg dose to HD and CAPD adult patients the daptomcyin AUC was approximately 1.3-fold higher than that observed after a second 6 mg/kg dose in patients with normal renal function. On this basis, it is recommended that patients on HD or CAPD receive daptomycin once every 48 hours at the dose recommended for the type of infection being treated. The dosage regimen for daptomycin in paediatric patients with renal impairment has not been established.

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.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

DAPTOCORD-500 is not compatible with dextrose-containing diluents.
DAPTOCORD-500 should not be used in conjunction with ReadyMED® elastomeric infusion pumps (Cardinal Health, Inc.). Stability studies of Daptomycin solutions stored in ReadyMED® elastomeric infusion pumps identified an impurity (2-mercaptobenzothiazole) leaching from this pump system into the Daptomycin solution.
Because only limited data are available on the compatibility of DAPTOCORD-500 with other IV substances, additives and other medications should not be added to DAPTOCORD-500 single-dose vials or infusion bags, or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of different drugs, the line should be flushed with a compatible intravenous solution before and after infusion with DAPTOCORD-500.

6.3 Shelf life
24 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 48 hours at 2°C – 8°C for concentration ranges 2.5 mg/ml, 10 mg/ml and 20 mg/ml.

The combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section *Special precautions for disposal and other handling*) at 25°C must not exceed 12 hours (or 48 hours 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 *Shelf life*.

6.5 Nature and contents of container
Daptomycin for Injection 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

Preparation of Daptocord for Administration
Daptocord is supplied in single-dose vials, each containing 500 mg daptomycin as a sterile, lyophilized powder. The contents of a Daptocord vial should be reconstituted, using aseptic technique, to 50 mg/mL as follows:

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

1. Remove the polypropylene flip-off cap from the Daptocord vial to expose the central portion of the rubber stopper.
2. 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.
3. Slowly transfer 10 mL of 0.9% sodium chloride injection through the center of the rubber stopper into the Daptocord vial, pointing the transfer needle toward the wall of the vial. It is recommended that a beveled sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device is used, pointing the transfer needle toward the wall of the vial.
4. Ensure that all of the Daptocord powder is wetted by gently rotating the vial.
5. Allow the wetted product to stand undisturbed for 10 minutes.
6. Gently rotate or swirl the vial contents for a few minutes, as needed, to obtain a completely reconstituted solution.
7. Slowly remove reconstituted liquid (50 mg daptomycin/mL) from the vial using a beveled sterile needle that is 21 gauge or smaller in diameter.

Adults

Intravenous Infusion over a period of 30 minutes

- For IV infusion over a period of 30 minutes in adult patients, the appropriate volume of the reconstituted Daptocord (concentration of 50 mg/mL) should be further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection.

Pediatric Patients (1 to 17 Years of Age)

Intravenous Infusion over a period of 30 or 60 minutes

- For IV infusion over a period of 30 minutes in pediatric patients, reconstituted Daptocord (concentration of 50 mg/mL) is further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride injection. The infusion rate should be maintained at 1.67 mL/min over the 30 minute period.
- For IV infusion over a period of 60 minutes in pediatric patients, reconstituted Daptocord (concentration of 50 mg/mL) is further diluted, using aseptic technique, into an IV infusion bag containing 25 mL of 0.9% sodium chloride injection. The infusion rate should be maintained at 0.42 mL/min over the 60 minute period.

Parenteral drug products should be inspected visually for particulate matter prior to administration.

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in the preparation of final IV solution. Stability studies have shown that the reconstituted solution is stable in the vial for 12 hours at room temperature and up to 48 hours if stored under refrigeration at 2°C to 8°C (36°F to 46°F).

The diluted solution is stable in the infusion bag for 12 hours at room temperature and 48 hours if stored under refrigeration at 2°C to 8°C (36°F to 46°F). The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) should not exceed 12 hours at room temperature or 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F).

Daptocord vials are for single use only.

Compatible Intravenous Solutions

Compatible diluents for reconstitution: 0.9% sodium chloride injection
Compatible diluents for dilution: 0.9% sodium chloride injection and lactated Ringer's injection

Reconstitute Daptocord, as directed above, to a concentration of 50 mg/mL with 0.9% sodium chloride injection. Further dilute using aseptic technique with additional 0.9% sodium chloride injection to a final concentration in the range of 2.5 to 20 mg/mL (typically 10 mg/mL).

Vial Size	Nominal Concentration of Reconstituted Solution	Approximate Available Volume of Reconstituted Solution	Volume of Additional Diluent	Total Volume of Solution for Infusion	Nominal Concentration of Solution for Infusion
500 mg	50 mg/mL	10 mL	15 mL	25 mL	20 mg/mL
500 mg	50 mg/mL	10 mL	40 mL	50 mL	10 mg/mL
500 mg	50 mg/mL	10 mL	190 mL	200 mL	2.5 mg/mL

7. Name and address of Product Registration Holder & Manufacturer
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8. Date of revision of the text
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