SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DUPCIN 500 mg Powder for Solution for IV Injection/Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Daptomycin (from bovine milk and porcine origin) _____500 mg
Excipients with known effect:
Sodium hydroxide q.s. (for pH adjustment)
Refer to section 6.1 for excipients.

3. PHARMACEUTICAL FORM
Powder for solution for injection.
Before dilution: Pale yellow to light brown, lyophilized powder or cake.
After dilution: Clear, greenish yellow to brown solution free of visible particles.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
DUPCIN is indicated for the treatment of adult patients with *Staphylococcus aureus* bacteremia, including adult patients with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates, as well as for the treatment of patients with complicated skin and soft-tissue infections.

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

DUPCIN is active against Gram-positive bacteria only. In mixed infections where Gram-negative and/or certain types of anaerobic bacteria are suspected, DUPCIN should be co-administered with appropriate antibacterial agent(s).

Care should be given to official guidance on the appropriate use of antibacterial agents.

DUPCIN is not indicated for the treatment of pneumonia (see section 4.4).

4.2 Posology and method of administration
Dosage/frequency and duration
Complicated skin and soft tissue infections
The recommended dose for adults is 4 mg/kg once every 24 hours for 7-14 days or until the infection is resolved. DUPCIN should not be used more frequently than once a day. Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly) during treatment (see section 4.4 Special warnings and precautions for use).

Staphylococcus aureus bacteremia (including right-sided endocarditis)
The recommended dose for adults, based on the diagnosis determined by the treating physician, is 6 mg/kg once every 24 hours for a period longer than 2 weeks. DUPCIN should not be used more frequently than once a day. Creatine phosphokinase (CPK) levels should be monitored at baseline and at regular intervals (at least weekly) during treatment (see section 4.4 Special warnings and precautions for use).

Method of administration
DUPCIN is administered by injection over a 2-minute period and in 0.9% sodium chloride.

Preparation of DUPCIN for administration:
500 mg presentation:
DUPCIN is presented as a sterile, lyophilized powder in single-use vials containing 500 mg daptomycin. It does not contain preservatives or bacteriostatic agents. Aseptic techniques should be used to prepare the final intravenous solution.

To dilute DUPCIN to a concentration of 50 mg/ml, aseptic technique should be followed as outlined below:
1. Remove the polypropylene cap by leaving the center portion of the rubber stopper intact.
2. Inject an appropriate volume (10 ml) of 0.9% sodium chloride injection slowly into the vial through the center of the rubber stopper, directing the solution toward the vial wall.
3. Rotate the vial gently to ensure the powder is thoroughly wetted.
4. Allow the wetted powder to stand for 10 minutes.
5. Rotate or mix the vial gently for a few minutes to obtain a clear diluted solution.

Note: To avoid foaming, do not shake/mix the solution vigorously during or after dilution.

Parenteral products should be inspected visually for the absence of particles before use.

Additional information on special populations
Kidney Failure
Since daptomycin is primarily eliminated by the kidneys, dose adjustments are recommended in patients with creatinine clearance (CrCl) < 30 ml/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

For patients with creatinine clearance ≥ 30 mL/min, the recommended dose is 4 mg/kg once every 24 hours for skin and soft tissue infections or 6 mg/kg once every 24 hours for S. aureus bacteremia.

In patients with creatinine clearance < 30 mL/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD), the dose is 4 mg/kg every 48 hours for skin and soft tissue infections or 6 mg/kg every 24 hours for bacteremia caused by S. Aureus. Alternatively, hemodialysis patients may be dosed 3 times a week. If possible, on dialysis days, DUPCIN should be administered after dialysis is completed.

In patients with renal failure, both kidney function and CPK levels are monitored more frequently than once a week.

Liver Failure
In patients with mild to moderate liver failure (Child-Pugh Class B), no dosage adjustment is required during DUPCIN administration. In patients with severe liver failure (Child-Pugh Class C), the pharmacokinetics of daptomycin have not been evaluated.

Pediatric Population
The safety and efficacy of DUPCIN in patients under the age of 18 have not been established. Therefore, its use in this age group is not recommended.

Geriatric Population
In elderly patients with CrCl ≥ 30 ml/min, no dosage adjustment is necessary.

Gender
No dosage adjustment based on gender is required during DUPCIN administration.

Obesity
No dosage adjustment is necessary for obese patients.

4.3 Contraindications
DUPCIN should not be used in patients hypersensitive to daptomycin or any of its excipients.

4.4 Special warnings and precautions for use
Anaphylaxis/Hypersensitivity reactions
Anaphylaxis and hypersensitivity reactions have been reported with almost all antibacterial agents, including DUPCIN (see section 4.8 Undesirable effects). If an allergic reaction occurs to DUPCIN, the medication should be discontinued, and appropriate treatment should be administered.

Pneumonia
DUPCIN is not indicated for the treatment of pneumonia. Clinical studies have shown that DUPCIN is not effective in treating community-acquired pneumonia due to its binding to surfactant and subsequent inactivation.

Skeletal muscle effects
Treatment with DUPCIN has been associated with increased plasma creatine phosphokinase (CPK) levels, resulting in muscle pain, weakness, and/or rhabdomyolysis (see section 4.8 Undesirable effects).

The following actions are recommended:
- Patients using DUPCIN should be monitored for muscle pain or weakness, particularly in the extremities.
- Plasma CPK levels should be measured at the start of treatment and at regular intervals (at least once a week) throughout treatment. Patients who are concurrently using or have recently used HMG-CoA reductase inhibitors should be monitored more frequently, at least once a week.
- Patients experiencing unexplained increases in CPK levels while on DUPCIN should be monitored more frequently than once a week.
- DUPCIN treatment should be stopped in patients with unexplained myopathy along with a CPK increase above 1000 U/L (approximately five times the normal range) or in those with a significant CPK increase above 2000 U/L (≥10x ULN) without any symptoms.
- Consider temporarily discontinuing agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients using DUPCIN.

Peripheral neuropathy
Healthcare providers should be vigilant for signs and symptoms of peripheral neuropathy during treatment with DUPCIN (see section 4.8 Undesirable effects). If symptoms occur, DUPCIN treatment should be discontinued as needed.

Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving daptomycin (see section 4.8 Undesirable effects). In reported cases, fever, hypoxic respiratory failure with dyspnea, and diffuse lung infiltrates developed. Eosinophilic pneumonia generally occurred 2 to 4 weeks after daptomycin was started, and improvement was noted when daptomycin was discontinued and steroid therapy was initiated. The condition recurred upon re-exposure. Patients exhibiting these symptoms during daptomycin treatment should undergo immediate medical evaluation, including bronchoalveolar lavage if appropriate, to rule out other causes (e.g., bacterial infection, fungal infection, parasites, and other drugs), and daptomycin therapy should be stopped immediately.

Systemic steroid treatment is recommended.

Clostridioides difficile-associated diarrhea
Clostridioides difficile-associated diarrhea (CDAD) has been reported with the use of daptomycin and other antibacterial agents (see section 4.8 Undesirable effects). If CDAD is suspected or confirmed, DUPCIN should be discontinued, and appropriate treatment should be initiated as clinically indicated.

Continuing or recurrent S. aureus bacteremia/endocarditis
In patients with ongoing or recurrent S. aureus bacteremia/endocarditis or those with poor clinical response, repeat blood cultures should be performed. If a blood culture is positive for S. aureus, the isolate should undergo minimum inhibitory concentration (MIC) testing using a standardized procedure, and diagnostic evaluation should be conducted to rule out the possibility of a sequestrated infection focus. Appropriate surgical interventions (e.g., debridement, removal of prosthetic devices, valve replacement surgery) and/or changes in the antibiotic regimen may be necessary.

Renal impairment
Renal impairment has been reported during daptomycin treatment. Severe renal impairment may also lead to increased daptomycin levels, which can increase the risk of myopathy.

For patients with a creatinine clearance <30 ml/min, dose adjustments within the dosing range of daptomycin are necessary (see sections 4.2 and 5.2). The safety and efficacy of adjusting the dosing frequency have not been evaluated in controlled clinical studies, and the recommendation is mainly based on pharmacokinetic modeling data. Daptomycin should only be used in these patients if the expected clinical benefit outweighs the potential risk.

Daptomycin should be used with caution in patients with any degree of renal impairment (creatinine clearance <80 ml/min) before starting treatment. Regular renal function monitoring is recommended.

Additionally, when potentially nephrotoxic agents are co-administered, regular renal function monitoring is recommended, regardless of the patient's previous renal function.

Obesity
In obese volunteers with a BMI >40 kg/m² and creatinine clearance >70 ml/min, the AUC_{0_∞} of daptomycin was significantly higher (on average, 42% higher) compared to matched non-obese controls. Since information regarding the safety and efficacy of daptomycin in very obese individuals is limited, caution should be exercised. However, there is no evidence to suggest that dose reduction is necessary.

Enterococcal infections
There is insufficient evidence to draw conclusions regarding the potential clinical effectiveness of daptomycin for treating infections caused by enterococci, including Enterococcus faecalis and Enterococcus faecium. Additionally, no suitable dosing regimens have been defined for treating enterococcal infections with or without bacteremia. Treatment failures with daptomycin have been reported in cases of enterococcal infections, particularly with bacteremia. In some instances, treatment failure has been associated with reduced sensitivity to daptomycin or the selection of resistant organisms.

Deep-seated infections

In patients with deep infections, all necessary surgical interventions (e.g., debridement, removal of prosthetic devices, valve replacement surgery) should be promptly performed.

Medicine/Laboratory test interactions
When certain recombinant thromboplastin reagents are used for testing, prolonged prothrombin time (PT) and increased International Normalized Ratio (INR) may be observed (see section 4.5, Interaction with other medicinal products and other forms of interaction).

Resistant organisms
The use of antibiotics may lead to the overgrowth of resistant microorganisms. If superinfection occurs during treatment, appropriate measures should be taken.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose. No side effects are expected at this level.

4.5 Interaction with other medicinal products and other forms of interaction
Daptomycin is not metabolized via the Cytochrome P450 (CYP450) system, or it is metabolized to a very small extent. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolized via the P450 system.

Daptomycin has been studied in drug/drug interaction studies with aztreonam, tobramycin, warfarin, simvastatin, and probenecid. Daptomycin had no effect on the pharmacokinetics of aztreonam, warfarin, and probenecid, and these drugs did not alter the pharmacokinetics of daptomycin. Daptomycin pharmacokinetics were not significantly changed by aztreonam.

During concurrent administration of 2 mg/kg daptomycin with tobramycin, small changes in the pharmacokinetics of both drugs were observed, but these changes did not reach statistical significance. The interaction between daptomycin and tobramycin with clinical doses is unknown. Caution is recommended when using daptomycin with tobramycin.

Experience with the concurrent use of daptomycin and warfarin is limited. No studies have been conducted with daptomycin and other anticoagulants. For patients using daptomycin and warfarin, anticoagulant activity should be monitored during the initial days after starting daptomycin therapy.

Due to limited experience with HMG-CoA reductase inhibitors and daptomycin, it may be considered to temporarily discontinue the use of HMG-CoA reductase inhibitors in patients undergoing daptomycin therapy.

Daptomycin is primarily cleared by renal filtration, and thus, plasma levels may increase during concurrent administration with medicinal products that reduce renal filtration (e.g., NSAIDs and COX-2 inhibitors). Additionally, there is a potential for pharmacodynamic interactions that may occur due to additional renal effects during concurrent administration. Therefore, caution is advised when daptomycin is administered concurrently with other medicinal products known to reduce renal filtration.

Medicine-Laboratory Test Interactions
When specific recombinant thromboplastin reagents are used for testing, clinically significant plasma daptomycin concentrations have been observed to cause prolonged prothrombin time (PT) and increased International Normalized Ratio (INR). The likelihood of obtaining falsely elevated PT/INR results due to interaction with a recombinant thromboplastin reagent can be minimized by taking plasma samples when daptomycin concentrations are at their trough levels. However,

sufficient daptomycin concentrations may still exist at trough levels to cause interaction (see section 4.4 Special warnings and precautions).

If an abnormally high PT/INR result is obtained in a patient receiving daptomycin, the following actions are recommended for healthcare providers:

1. Request that the PT/INR assessment be repeated, preferably just before the next dose of daptomycin (i.e., at trough levels). If the PT/INR value taken at trough levels remains significantly above what is otherwise expected, alternative methods for evaluating PT/INR should be considered.
2. Investigate other possible causes of the abnormal increase in PT/INR.

Additional information on special populations
Clinical interaction studies have not been conducted in special populations.

Pediatric population
Clinical interaction studies have not been conducted in pediatric population.

4.6 Pregnancy and lactation

General principles
Pregnancy category "B".

Women of Childbearing Potential/Contraception
Female patients should use their preferred method of contraception during daptomycin treatment, and this is considered safe.

Pregnancy
No clinical data are available regarding exposure to daptomycin during pregnancy. Animal studies have not shown direct or indirect harmful effects on pregnancy, embryonal/fetal development, parturition, or postnatal development (see section 5.3). However, caution should be exercised when prescribing daptomycin to pregnant women. Therefore, daptomycin should be used during pregnancy only if the maternal benefit outweighs the potential fetal risk.

Breastfeeding
In a single human case study, daptomycin was administered intravenously at a dose of 500 mg/day for 28 days to a breastfeeding mother, and samples were collected from the mother's milk on the 27th day over a 24-hour period. The highest measured daptomycin concentration in breast milk was 0.045 mcg/mL, which is a low concentration.

When deciding whether to discontinue breastfeeding or daptomycin treatment, the benefit of breastfeeding to the child and the benefit of daptomycin treatment to the breastfeeding mother should be considered. Breastfeeding women should be advised to avoid breastfeeding while using daptomycin.

Fertility
Reproductive toxicity tests did not show any evidence of effects on fertility, embryonal/fetal, or postnatal development. However, daptomycin can cross the placenta in pregnant rats.

4.7 Effects on ability to drive and use machines

No studies available on the effects of daptomycin regarding ability to drive or use machines.

4.8 Undesirable effects

In clinical studies involving daptomycin, the following adverse reactions have been reported during treatment and follow-up.

Adverse drug reactions are classified by frequency: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

Infections and Infestations
Common : Fungal infections, urinary tract infections, candida infection
Uncommon : Fungal infections

Blood and Lymphatic System Disorders
Common : Anemia
Uncommon : Eosinophilia, thrombocytosis
Rare : Prolonged prothrombin time

Metabolism and Nutrition Diseases
Uncommon : Appetite reduction, hyperglycemia, electrolyte imbalance

Psychiatric Disorders
Uncommon : Anxiety, insomnia

Nervous System Disorders
Common : Headache, dizziness
Uncommon : Paresthesia, taste disturbance, tremor

Ear and Inner Ear Disorders
Uncommon : Dizziness

Cardiac Disorders
Uncommon : Supraventricular tachycardia, extrasystole

Vascular Disorders
Common : Hypertension, hypotension
Uncommon : Flushing

Gastrointestinal Disorders
Common : Gastrointestinal pain and abdominal pain, constipation, diarrhea, nausea, vomiting, gas, bloating and fullness
Uncommon : Indigestion, inflammation of the uvula

Hepatobiliary Disorders
Rare : Jaundice

Skin and Subcutaneous Tissue Disorders
Common : Rash, itching
Uncommon : Urticaria

Musculoskeletal Disorders, Connective Tissue and Bone Diseases
Common : Limb pain

Uncommon : Arthralgia, muscle pain, muscle weakness

Kidney and Urinary Tract Disorders
Uncommon : Kidney failure and kidney dysfunction including renal insufficiency

Reproductive System and Breast Disorders
Uncommon : Vaginitis

General Disorders and Administration Site Conditions
Common : Infusion site reactions, fever, asthenia
Uncommon : Fatigue, chills

Research Findings
Common : Increased serum creatine phosphokinase (CPK), abnormal liver function tests (increased AST, ALT, and alkaline phosphatase)
Uncommon : Increased lactate dehydrogenase (LDH), increased serum creatinine, increased International Normalized Ratio (INR)
Rare : Prolongation of prothrombin time (PT)

Post-Marketing Experience (frequency unknown)
Adverse reactions reported in the post-marketing phase that are not listed above and with unknown frequency include:

Infections and Infestations
Clostridium difficile-associated diarrhea*

Immune System Disorders
Anaphylaxis, angioedema, eosinophilia, and drug rash with systemic symptoms (DRESS), and pulmonary eosinophilia, among others, including but not limited to hypersensitivity reactions*

Nervous System Disorders
Peripheral neuropathy*

Respiratory, Thoracic, and Mediastinal Disorders
Eosinophilic pneumonia*, cough

Skin and Subcutaneous Tissue Disorders
Vesiculobullous rash with or without mucous membrane involvement

Musculoskeletal, Connective Tissue and Bone Disorders
Rhabdomyolysis*

Research Findings
Increased myoglobin

Disorders related to the application site
Infusion site reactions
*See section 4.4 Special warnings and precautions for use

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via the national reporting system.

4.9 Overdose

In an overdose event, supportive care is advised. Daptomycin is slowly cleared from body by hemodialysis (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 naturally occurring cyclic lipopeptide that is active only against Gram-positive bacteria. Its mechanism of action involves binding to the bacterial membranes of both proliferating and stationary phase cells (in the presence of calcium ions), leading to depolarization and resulting in inhibition of rapid protein, DNA, and RNA synthesis. This leads to bacterial cell death with negligible cell lysis.

Pharmacokinetic/Pharmacodynamic relationship

Daptomycin exhibits concentration-dependent bactericidal activity against Gram-positive organisms in both in vitro and in vivo animal models. In animal models, the EAA/MIC and C_{max}/MIC ratios correlate with in vivo predicted bacterial death and efficacy at single doses of 4 mg/kg and 6 mg/kg, equivalent to human doses.

Resistance mechanisms

Strains with reduced susceptibility to daptomycin have been reported, particularly during the treatment of difficult-to-treat infections or after prolonged treatment. Treatment failures associated with reduced susceptibility or the selection of resistant organisms during therapy have been reported, especially in bacteremic patients infected with Staphylococcus aureus, Enterococcus faecalis, or Enterococcus faecium. The mechanism(s) of resistance to daptomycin are not fully understood.

Breakpoints

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has set the minimum inhibitory concentration (MIC) breakpoint for Staphylococci and Streptococci (excluding S. pneumoniae) as Sensitive ≤1 mg/l and Resistant >1 mg/l.

Susceptibility

Resistance prevalence can vary geographically and over time for selected species, and regional information on resistance is particularly desirable for the treatment of severe infections. In regions with suspected high resistance prevalence for certain infection types, expert advice should be sought.

Commonly Susceptible Species
Staphyloccous aureus *
Staphylococcus haemolvticus

Coagulase-negative staphylococci
Streptococcus agalactiae *
Streptococcus dysgalactiae subspecies *equisimilis**
*Streptococcus pyogenes**
Group G streptococci
*Clostridium perfringens**
Peptostreptococcus spp
Naturally resistant organisms
Gram-negative organisms

* Species for which activity has been predictively demonstrated in clinical studies.

Clinical study information
In two clinical studies conducted on complicated skin and soft tissue infections, 36% of the patients treated with daptomycin met the criteria for systemic inflammatory response syndrome (SIRS). The most common infection type treated was wound infection (38% of patients), and 21% had major abscesses.

These limitations of the treated patient population should be considered when deciding on daptomycin use.

In a randomized controlled open-label study of 235 patients with Staphylococcus aureus bacteremia (i.e., at least one positive blood culture for Staphylococcus aureus before the first dose), 19 out of 120 patients treated with daptomycin met the criteria for refractory infectious events (RIE). Of these 19 patients, 11 were infected with methicillin-sensitive and 8 with methicillin-resistant Staphylococcus aureus. Success rates for RIE patients are shown in the table below.

Population	**Daptomycin**	**Comparator**	**Difference in Success**
	n/N (%)	**n/N** (%)	Rates (%95 CI)
RIE ITT (intention to treat) Population	8/19 (%42. 1)	7/16 (%43.8)	-%1.6 (-34.6, 31.3)
RIE PP (per protocol) Population	6/12 (%50.0)	4/8 (%50.0)	%0.0 (-44.7, 44.7)

Treatment failure due to resistant or recurrent Staphylococcus aureus infections was observed in 19/120 (15.8%) patients treated with daptomycin, 9/53 (16.7%) patients treated with vancomycin, and 2/62 (3.2%) patients treated with anti-staphylococcal beta-lactam. In these failures, 6 patients treated with daptomycin and 1 patient treated with vancomycin had Staphylococcus aureus infection, and increased daptomycin MICs developed during or after treatment (see "Resistance mechanisms" above). Most of the patients with failure due to resistant or recurrent Staphylococcus aureus infections had deep infections, and necessary surgical intervention was not performed.

5.2. Pharmacokinetic properties
General characteristics
Absorption
Administered intravenously.

Distribution
In healthy adult volunteers, the steady-state volume of distribution of daptomycin was found to be

approximately 0.1 L/kg. Animal studies following both single and multiple doses suggest that daptomycin appears to cross the blood-brain barrier and placenta barrier only minimally.

Daptomycin binds reversibly to human plasma proteins, independent of concentration. The protein-binding rate for daptomycin in healthy volunteers and patients with renal insufficiency receiving daptomycin treatment is approximately 90%.

Biotransformation
In vitro studies have shown that daptomycin is not metabolized by human liver microsomes. In vitro studies using human hepatocytes revealed that daptomycin does not inhibit or induce human cytochrome P450 isoforms (1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). Daptomycin is unlikely to induce or inhibit the metabolism of drugs metabolized by cytochrome P450.

After the infusion of 14C-labeled daptomycin in healthy adults, plasma radioactivity correlated with the concentration determined by microbiological assay. The difference between total radioactive concentrations and microbiologically active concentrations revealed the presence of inactive metabolites in the urine. Another study showed no metabolites in plasma and identified low amounts of three oxidative metabolites and one unidentified compound. The site of metabolism has not been defined.

Elimination
Daptomycin is primarily eliminated through the kidneys. There is no or minimal active tubular secretion of daptomycin.

The plasma clearance of daptomycin is approximately 7-9 mL/hour/kg, and renal clearance is 4-7 mL/hour/kg.

In a mass balance study using radio-labeled daptomycin, 78% of the administered dose (based on total radioactivity) was recovered in the urine. Approximately 52% of the dose was excreted unchanged in the urine. Approximately 5% of the administered radioactive dose was excreted in feces.

Linearity/non-linearity
The pharmacokinetics of daptomycin are generally linear and time-independent for doses of 4-12 mg/kg administered once daily for up to 14 days. Steady-state concentrations are reached by the third dose.

Characteristics in patients
Pediatric patients
Following a single 4 mg/kg dose of daptomycin, the pharmacokinetics of daptomycin were evaluated in three groups of pediatric patients with Gram-positive infections. Despite lower exposure, the pharmacokinetic profile in adolescents aged 12 to 17 years was similar to that in healthy adults. In the two younger groups (7 to 11 years and 2 to 6 years), total clearance was higher compared with adolescents; this led to a lower exposure (AUC and C_{max}) and elimination half-life. Efficacy was not evaluated in this study.

Elderly
The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly volunteers (aged 75 years and older) and 11 healthy young controls (aged 18-30 years).

Following the infusion of a single 4 mg/kg dose of daptomycin over 30 minutes, the average total clearance of daptomycin was approximately 35% lower and the average AUC was approximately

58% higher in elderly individuals compared to young volunteers. No difference was observed in Cmax. No dose adjustment is required for elderly patients without renal impairment.

Obesity
The pharmacokinetics of daptomycin were evaluated in six volunteers with moderate to severe obesity (Body Mass Index (BMI) 25-39.9 kg/m²). The AUC was approximately 28% higher in moderately obese volunteers and 42% higher in severely obese volunteers compared to non-obese controls.

Gender
There have been no clinically significant differences observed in daptomycin pharmacokinetics based on gender.

Renal impairment
After an IV daptomycin dosing of 4 mg/kg or 6 mg/kg over a 30-minute period in volunteers with varying 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 modeling, after the administration of a 6 mg/kg dose to patients undergoing hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD), the AUC on the first day was approximately twice as high as that in patients with normal renal function receiving the same dose. On the second day, the AUC in HD and CAPD patients after a second 6 mg/kg dose was approximately 1.3 times higher than the AUC observed in patients with normal renal function after the second dose.

On this basis, patients undergoing HD or CAPD are recommended to receive daptomycin once every 48 hours at the recommended dose for the type of infection being treated.

Liver failure
The pharmacokinetics of daptomycin have been evaluated in volunteers with moderate hepatic insufficiency (Child-Pugh Class B) and compared with healthy volunteers matched for gender, age, and weight (N=9). In volunteers with moderate hepatic insufficiency, the pharmacokinetics of daptomycin remained unchanged. The pharmacokinetics of daptomycin have not been evaluated in patients with severe hepatic insufficiency (Child-Pugh Class C).

5.3 Preclinical safety data
In clinically relevant duration studies (14-28 days), daptomycin administration in rats and dogs was related to minimal to mild degenerative/regenerative changes in skeletal muscle. Microscopic changes in skeletal muscle were minimal (about 0.05% of myofibrils affected), and at higher doses, these were accompanied by increases in CPK. No fibrosis or rhabdomyolysis was observed. Depending on the study duration, all muscle effects, including microscopic changes, completely resolved within 1-3 months after the drug discontinuation. No functional or pathological changes were observed in smooth muscle or cardiac muscle.

In rats and dogs, the lowest observed effect level (LOEL) for myopathy occurred at exposure levels 0.8 to 2.3 times the human therapeutic levels (6 mg/kg intravenous infusion over 30 minutes) for patients with normal renal function. Given the similar pharmacokinetics (see section 5.2), the safety limits are quite similar for both methods of administration.

A study in dogs showed that skeletal myopathy was reduced with once-daily administration compared to split doses with the same total daily dose, suggesting that myopathic effects in animals are primarily related to the interval between doses.

Effects on peripheral nerves were observed at higher doses than those associated with skeletal muscle effects in adult rats and dogs and were primarily related to plasma Cmax values. Peripheral nerve changes were characterized by minimal to mild axonal degeneration, often accompanied by functional changes. Both microscopic and functional effects completely resolved within 6 months after dose administration. Safety limits for peripheral nerve effects in rats and dogs were based on comparison of Cmax values from once-daily administration of 6 mg/kg over 30-minute intravenous infusion for patients with normal renal function, and were found to be 8 and 6 times higher than the no-effect level (NOEL) respectively.

In vitro and some *in vivo* studies designed to investigate the mechanism of daptomycin myotoxicity suggest that plasma membrane of spontaneously contracting muscle cells is the target of toxicity. No specific cell surface component has been identified as a direct target. Mitochondrial loss/damage was also observed, though its role and significance in the overall pathology is unknown. This finding has not been related to an effect on muscle contraction.

Unlike adult dogs, juvenile dogs appear to be more sensitive to peripheral nerve lesions than to skeletal myopathy. Peripheral and spinal nerve lesions developed in juvenile dogs at lower doses than those associated with skeletal muscle toxicity.

Reproductive toxicity tests showedy no evidence of an effect on fertility, embryofetal, or postnatal development. However, daptomycin can cross the placenta in pregnant rats (see section 5.2). Daptomycin transfer into the milk of lactating animals has not been studied.

Long-term carcinogenicity studies in rodents have not been conducted. Daptomycin has not been found to be mutagenic or clastogenic in a series of in vivo and in vitro genotoxicity tests.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

6.2 Incompatibilities

Daptomycin is incompatible with diluents containing dextrose.

Due to limited data on the compatibility of daptomycin with other IV substances, no additives or other drugs should be introduced via the same IV line as daptomycin, except for the nine drugs listed in the section " Compatible intravenous solutions and other medical products".

Compatible intravenous solutions and other medical products

Daptomycin is compatible with 0.9% sodium chloride and lactated Ringer’s injection.

The following have been shown to be compatible when administered via the same IV line as daptomycin from different infusion bags: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin, and lidocaine.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in a refrigerator at 2–8°C. Do not freeze.

Once diluted, use within 12 hours if stored below 25°C or within 48 hours if stored at 2–8°C.

From a microbiological perspective, the product should be used immediately. If it is not used immediately, the storage times during use are the responsibility of the user, and unless dilution is

performed under controlled and approved aseptic conditions, those times will not exceed 24 hours at 2-8°C.

6.5 Nature and contents of container

The primary packaging materials for the product are a 15 ml, transparent, colorless, Type I glass vial with a gray-colored, notched, bromobutyl rubber stopper, and a blue-colored flip-off cap for sealing the vials. Each cardboard box contains one vial and a package leaflet.

6.6 Special precautions for disposal and other handling

DUPCIN vials are for single use only. Any unused portion in the vial must be discarded.

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

Daptomycin can be administered intravenously either as an infusion over 30 minutes or as an injection over 2 minutes. The preparation of the infusion solution requires an additional dilution step, as detailed below.

30-minute intravenous infusion of DUPCIN

Note: To prevent foaming of the product, vigorous shaking/mixing during or after dilution should be avoided.

1. The polypropylene flip-off cap should be removed to expose the central portions of the rubber stopper.
2. Using an appropriate volume of 0.9% sodium chloride (7 mL for 350 mg vial or 10 mL for 500 mg vial), slowly add it to the center of the rubber stopper, directing the transfer needle towards the vial wall. Water should not be used to prepare the DUPCIN injectable solution.
3. Gently rotate the vial to ensure the complete wetting of the DUPCIN powder.
4. Leave the wet product to stand for 10 minutes.
5. The vial contents should be gently rotated or rolled for a few minutes to achieve a completely diluted solution.
6. The diluted DUPCIN should be further diluted using aseptic techniques with 0.9% sodium chloride (typical volume 50 mL).

Parenteral preparations should be visually inspected for particulate matter before administration.

2-minute intravenous injection of DUPCIN

Note: To prevent foaming of the product, vigorous shaking/mixing during or after dilution should be avoided.

1. The polypropylene flip-off cap should be removed to expose the central portions of the rubber stopper.
2. Using an appropriate volume of 0.9% sodium chloride (7 mL for 350 mg vial or 10 mL for 500 mg vial), slowly add it to the center of the rubber stopper, directing the transfer needle towards the vial wall. Water should not be used to prepare the DUPCIN injectable solution.
3. Gently rotate the vial to ensure the complete wetting of the DUPCIN powder.
4. Leave the wet product to stand for 10 minutes.
5. The vial contents should be gently rotated or rolled for a few minutes to achieve a completely diluted solution.

7 MARKETING AUTHORIZATION HOLDER

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