NEW ZEALAND DATA SHEET

1. PRODUCT NAME

CUBICIN 500 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of CUBICIN 500 mg contains 500 mg daptomycin.

CUBICIN contains daptomycin, a cyclic lipopeptide antibacterial agent.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

Single-dose 10 mL vial, containing a pale yellow to light brown lyophilised cake or powder.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Complicated skin and skin structure infections
Adult (≥18 years of age) and paediatric (1 to 17 years of age) patients with complicated skin and skin structure infections (cSSSI) caused by Gram-positive susceptible isolates.

Daptomycin is active against Gram-positive bacteria only. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

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

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

Daptomycin is active against Gram-positive bacteria only. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms.

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

4.2 Dose and method of administration

Dosage and administration pertain to adults, adolescents and children (at least 1 year old) with complicated skin and skin structure infections, and *Staphylococcus aureus* bloodstream infections (bacteraemia).

Dosage in Adults (18 years of age and above)
Complicated skin and skin structure infections
CUBICIN 4 mg/kg is administered to adult patients intravenously in 0.9 % sodium chloride for injection once every 24 hours for 7 to 14 days or until the infection is resolved, either by injection over a 2-minute period or by infusion over a 30-minute period. Do not dose CUBICIN more frequently than once a day, and measure creatine phosphokinase (CPK) levels at baseline and at regular intervals (at least weekly) (see section 6.6).

For dosage in paediatric patients see Special populations.

Staphylococcus aureus bloodstream infections (bacteraemia)
CUBICIN 6 mg/kg is administered to adult patients intravenously in 0.9 % sodium chloride for injection once every 24 hours for 2 to 6 weeks, either by injection over a 2-minute period or by infusion over a 30-minute period. Duration of treatment is based on the treating physician's working diagnosis. Do not dose CUBICIN more frequently than once a day, and measure CPK levels at baseline and at regular intervals (at least weekly) (see section 6.6).

For dosage in paediatric patients see Special populations.

Special populations
Renal impairment
Daptomycin is eliminated primarily by the kidneys; therefore, an adjustment of CUBICIN dosage interval is recommended for adult patients with creatinine clearance (CL_{CR}) < 30 mL/min, including patients receiving haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

The recommended dosing regimen for these adult patients is 4 mg/kg (cSSSI) or 6 mg/kg (*S. aureus* bloodstream infections) once every 48 hours. Alternatively, adult patients on haemodialysis can be dosed three times per week. When possible, administer CUBICIN following the completion of haemodialysis on haemodialysis days.

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

In adult patients with renal impairment, monitor both renal function and CPK more frequently than once weekly.

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

Hepatic impairment
No dosage adjustment is warranted when administering CUBICIN to patients with mild to moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

Elderly patients
No adjustment of CUBICIN dosage is warranted for elderly patients with $CL_{CR} \geq 30$ mL/min.

Paediatric patients (1 to 17 years of age)
Complicated skin and skin structure infections
CUBICIN is administered intravenously in 0.9% sodium chloride for injection once every 24 hours up to 14 days, by infusion over a 30-minute period or a 60-minute period. Do not dose CUBICIN more frequently than once a day, and measure creatine phosphokinase (CPK) levels at baseline and at regular intervals (at least weekly) (see section 6.6).

Unlike in adults, CUBICIN should not be administered by injection over a two (2) minute period in paediatric patients.

The recommended dosage regimens based on age for paediatric patients with cSSSI are shown in Table1 below.

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

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

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

Paediatric patients below the age of one year should not be given CUBICIN 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).

Staphylococcus aureus Bloodstream Infections (Bacteraemia)

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

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

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

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

Gender
No dosage adjustment is warranted based on gender when administering CUBICIN.

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

Method of administration
In adults, CUBICIN is given by intravenous (IV) administration, either by injection over a 2-minute period or by infusion over a 30-minute period.

In paediatric patients, CUBICIN is given by intravenous (IV) infusion over a 30 or 60-minute period depending on the age of the patient (see section 6.6).

4.3 Contraindications

CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

4.4 Special warnings and precautions for use

Anaphylaxis/hypersensitivity reactions
Anaphylaxis/hypersensitivity reactions have been reported with the use of nearly all antibacterial agents, including CUBICIN (see section 4.8). If an allergic reaction to CUBICIN occurs, discontinue the drug and institute appropriate therapy.

Pneumonia
CUBICIN is not indicated for the treatment of pneumonia. It has been demonstrated in clinical studies that CUBICIN is not effective in the treatment of community-acquired pneumonia (inhalational or airborne pneumonia), due to binding to pulmonary surfactant and consequent inactivation.

Clostridioides difficile-associated diarrhoea
Clostridioides difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including CUBICIN (see section 4.8). If CDAD is suspected or

confirmed, CUBICIN may need to be discontinued and appropriate treatment instituted as clinically indicated.

Persisting or relapsing *S. aureus* bacteraemia/endocarditis
Patients with persisting or relapsing *S. aureus* bacteraemia/endocarditis or poor clinical response should have repeat blood cultures. If a blood culture is positive for *S. aureus,* minimum inhibitory concentration (MIC) susceptibility testing of the isolate should be performed using a standardised procedure, and diagnostic evaluation of the patient should be performed to rule out sequestered foci of infection. Appropriate surgical interventions (e.g. debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibacterial regimen may be required.

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

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).

Skeletal muscle effects
Increases in plasma CPK levels, muscular pains, weakness, and/or rhabdomyolysis have been reported during therapy with CUBICIN (see section 4.8).

It is recommended that:
- Patients receiving CUBICIN be monitored for the development of muscle pain or weakness, particularly of the distal extremities.
- In patients who receive CUBICIN, CPK levels be measured at baseline and at regular intervals (at least weekly), and more frequently in patients who received concomitant or recent prior therapy with an HMG-CoA reductase inhibitor.
- Patients who develop elevations in CPK while receiving CUBICIN be monitored more frequently than once weekly.
- CUBICIN be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevations to levels greater than 1000 U/L (approximately 5 times upper limit of normal [ULN]) and in patients without reported symptoms who have marked elevations in CPK, with levels greater than 2000 U/L (≥ 10 x ULN).
- Consideration be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN.

Peripheral neuropathy
Physicians should be alert to signs and symptoms of peripheral neuropathy in patients receiving CUBICIN (see section 4.8).

Renal impairment
In adult patients with renal insufficiency, both renal function and CPK should be monitored more frequently than once a week.

Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving CUBICIN (see section 4.8). In the reported cases, patients developed fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organising pneumonia. In general, patients developed eosinophilic pneumonia 2 to 4 weeks after starting CUBICIN and improved when CUBICIN 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 CUBICIN should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage, to exclude other causes (e.g. bacterial infection, fungal infection, parasites, other drugs), and CUBICIN should be discontinued immediately. Treatment with systemic steroids is recommended.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
DRESS has been reported in post-marketing experience with daptomycin. Patients who develop fever, skin rash, peripheral eosinophilia, and systemic organ (for example, hepatic, pulmonary or renal) impairment while receiving CUBICIN should undergo medical evaluation. If DRESS is suspected, CUBICIN should be discontinued promptly and appropriate treatment instituted.

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

Paediatric Patients

The safety and effectiveness of CUBICIN in patients 1 to 17 years are supported by evidence from adequate and well-controlled studies in adults, pharmacokinetic data in paediatric patients, and additional data from two prospective studies in paediatric patients 1 to 17 years of age with cSSSI and paediatric patients 2 to 17 years of age with *Staphylococcus aureus* Bloodstream Infections (bacteraemia).

In clinical trials, 372 paediatric patients (3 months to 17 years of age) were given intravenous CUBICIN. Pharmacokinetic studies enrolled a total of 61 paediatric patients, and an additional 256 and 55 paediatric patients received CUBICIN in the prospective studies of cSSSI (DAP-PEDS-07-03) and bacteraemia (DAP-PEDBAC-11-02), respectively.

4.5 Interaction with other medicines 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 drugs metabolised by the P450 system.

CUBICIN was studied in adult human drug-drug interaction studies with aztreonam, tobramycin, warfarin, simvastatin, and probenecid. Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these drugs alter the pharmacokinetics of daptomycin. The pharmacokinetics of daptomycin were not significantly altered by aztreonam.

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

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

Experience with co-administration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consider temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving CUBICIN.

Drug/Laboratory Tests
Clinically relevant plasma concentrations of daptomycin have been observed to cause a significant concentration-dependant false prolongation of prothrombin time (PT) and elevation of International Normalised Ratio (INR) when certain recombinant thromboplastin reagents are utilised for the assay. The possibility of an erroneously elevated PT/INR result due to interaction with a recombinant thromboplastin reagent may be minimised by drawing specimens for PT or INR testing near the time of trough plasma concentrations of daptomycin. However, sufficient daptomycin concentrations may be present at trough to cause interaction (see section 4.4).

If confronted with an abnormally high PT/INR result in a patient being treated with CUBICIN, it is recommended that clinicians:

1. Repeat the assessment of PT/INR, requesting that the specimen be drawn just prior to the next CUBICIN dose (i.e., at trough concentration). If the PT/INR value obtained at trough remains substantially elevated above what would otherwise be expected, consider evaluating PT/INR utilising an alternative method.
2. Evaluate for other causes of abnormally elevated PT/INR results.

4.6 Fertility, pregnancy and lactation

Pregnancy
Embryo/foetal development studies performed in rats and rabbits at doses of up to 75 mg/kg (approximately 2 and 4 times the recommended 6 mg/kg human dose, respectively, on a body surface area basis) revealed no evidence of harm to the foetus due to daptomycin. There are, however, no adequate and well-controlled studies in pregnant women. CUBICIN should be used during pregnancy only if the potential benefit outweighs the possible risk.

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

Breast-feeding
In a single human case study, CUBICIN was intravenously administered daily for 28 days to a nursing mother at a dose of 500 mg/day, and samples of the patient's breast milk were collected over a 24-hour period on day 27. The highest measured concentration of

daptomycin in the breast milk was 0.045 µg/mL, which is a low concentration. Women should be instructed to avoid breast-feeding while receiving CUBICIN.

4.7 Effects on ability to drive and use machines

No specific recommendations.

4.8 Undesirable effects

During clinical trials of CUBICIN, the following adverse drug reactions were reported during therapy and during follow-up. The adverse drug reactions are organised by system organ class, and the frequency categories for these adverse drug reactions are reported below as follows:

very common: ≥1/10 (≥10%); common: ≥1/100 and <1/10 (≥1% and <10%); uncommon: ≥1/1000 and <1/100 (≥0.1% and <1%); rare:≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare: <1/10,000 (<0.01%).

Infections and Infestations	
Common	Fungal infection, urinary tract infection, candida infection
Uncommon	Fungemia
Blood and Lymphatic System Disorders	
Common:	Anaemia
Uncommon	Eosinophilia, thrombocytosis, leukocytosis
Metabolism and Nutrition Disorders	
Uncommon:	Decreased appetite, hyperglycaemia, electrolyte imbalance
Psychiatric Disorders	
Common	Anxiety, insomnia
Nervous System Disorders	
Common	Dizziness, headache
Uncommon	Paraesthesia, taste disorder, tremor, eye irritation
Ear and Labyrinth Disorders	
Uncommon	Vertigo
Cardiac Disorders	
Uncommon	Supraventricular arrhythmia
Vascular Disorders	
Common	Hypertension, hypotension

Uncommon	Flushing
Gastrointestinal Disorders	
Common	Gastrointestinal and abdominal pain, constipation, diarrhoea, nausea, vomiting, flatulence, bloating and distension
Uncommon	Dyspepsia, abdominal distension
Hepatobiliary Disorders	
Rare	Jaundice
Skin and Subcutaneous Tissue Disorders	
Common	Rash, pruritus
Uncommon	Urticaria
Musculoskeletal, Connective Tissue and Bone Disorders	
Common	Limb pain
Uncommon	Arthralgia, muscle pain, muscular weakness, muscle cramps
Renal and Urinary Disorders	
Uncommon	Renal impairment, including renal failure and renal insufficiency
Reproductive System and Breast Disorders	
Uncommon	Vaginitis
General Disorders and Administration Site Conditions	
Common	Infusion site reaction, pyrexia, asthenia
Uncommon	Fatigue, chills
Investigations	
Common	Blood creatine phosphokinase (CPK) increased, liver function tests abnormal (increased ALT, AST, or ALP)
Uncommon	Blood lactate dehydrogenase (LDH) increased, blood creatinine increased, International Normalised Ratio (INR) increased
Rare	Prothrombin time (PT) prolonged

Post-marketing
The following adverse drug reactions, not listed above, have been reported during worldwide post-marketing experience:

Blood and lymphatic system disorders:
Thrombocytopenia

Immune system disorders:
Hypersensitivity reactions (see section 4.4) including, but not limited to, anaphylaxis, angioedema, and pulmonary eosinophilia.

Musculoskeletal, connective tissue and bone disorders:
Rhabdomyolysis (see section 4.4).

Nervous system disorders:
Peripheral neuropathy (see section 4.4).

Renal and urinary disorders:
Tubulointerstitial nephritis (TIN) (see section 4.4).

Infections and infestations:
Clostridioides difficile-associated diarrhoea (see section 4.4).

Investigations:
Myoglobin increased, platelet count decreased.

Skin and subcutaneous tissue disorders:
Vesiculobullous rash with or without mucous membrane involvement (Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)).
Drug reaction with eosinophilia and systemic symptoms (DRESS)
Acute generalised exanthematous pustulosis.

Respiratory, thoracic and mediastinal disorders:
Eosinophilic pneumonia, organising pneumonia (see section 4.4), cough.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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) and 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.

Daptomycin belongs to the cyclic lipopeptide class of antibacterials. Daptomycin is a natural product that has clinical utility in the treatment of infections caused by aerobic, Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria. Daptomycin retains potency against Gram-positive bacteria that are resistant to other antibacterials, including isolates resistant to methicillin, vancomycin, and linezolid.

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

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

Interactions with other antibacterials
In vitro studies have investigated daptomycin interactions with other antibacterials. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions of daptomycin with aminoglycosides, β-lactam antibacterials, and rifampin have been shown against some isolates of staphylococci (including some methicillin-resistant isolates) and enterococci (including some vancomycin-resistant isolates).

Mechanism of resistance
The mechanism(s) of resistance is not fully understood. There are no known transferable elements that confer resistance to daptomycin.

There is no cross-resistance due to resistance mechanisms that are specific for another class of antibacterials.

Emergent decreases in susceptibility have been observed in both *S. aureus* and enterococcal isolates following CUBICIN therapy.

5.2 Pharmacokinetic properties

General characteristics
Daptomycin pharmacokinetics were generally linear (dose-proportional) and time-independent at CUBICIN doses of 4 to 12 mg/kg administered by intravenous infusion over a 30-minute period as a single daily dose for up to 14 days in adults. Steady-state concentrations were achieved by the third daily dose.

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 adult subjects with significant renal impairment (CL_{CR} <30 mL/min or on dialysis).

The protein binding of daptomycin in adult subjects with mild to moderate hepatic impairment (Child-Pugh Class B) was similar to that in healthy adult subjects.

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 drugs metabolised by the P450 system.

After infusion of ^{14}C-daptomycin in healthy adults, the plasma radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference 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. There is minimal to no active tubular secretion of daptomycin.

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 of adult subjects using radiolabeled daptomycin, 78% of the administered dose was recovered from the urine based on total radioactivity, while urinary recovery of unchanged daptomycin was approximately 52% of the dose. About 6% of the administered dose was excreted in the faeces based on total radioactivity.

Linearity/non-linearity
Not applicable, see “General characteristics” above: linearity statement already made there.

Special populations:
Elderly
The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects (≥ 75 years of age) and 11 healthy young adult controls (18 to 30 years of age). Following administration of a single 4 mg/kg dose of CUBICIN by intravenous infusion over a 30-minute period, the mean total clearance of daptomycin was approximately 35% lower and the

mean AUC was approximately 58% higher in elderly subjects compared with those in healthy young adult subjects. There were no differences in C_{max}.

Children and adolescents (< 18 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 CUBICIN, total clearance and elimination half-life of daptomycin in adolescents (12-17 years of age) with Gram-positive infection were similar to adults. After a single 4 mg/kg dose of CUBICIN, 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 CUBICIN, total clearance and elimination half-life of daptomycin in younger children 2-6 years of age were similar at different doses; total clearance was higher and elimination half-life was shorter than in adolescents. After a single 6 mg/kg dose of CUBICIN, the clearance and elimination half-life of daptomycin in toddlers 13-24 months of age were similar to younger children 2-6 years of age who received a single 4-10 mg/kg dose. The results of these studies show that exposures (AUC) in paediatric patients across all doses are generally lower than those in adults at comparable doses.

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years old, inclusive) with cSSSI caused by Gram-positive pathogens. Patients were enrolled into 4 age groups, and intravenous CUBICIN doses of 5 to 10 mg/kg once daily were administered. Following administration of multiple doses, daptomycin exposure (AUC_{ss} and $C_{max,ss}$) was similar across different age groups after dose adjustment based on body weight and age (Table 3).

Table 3: Mean (SD) Daptomycin Population Pharmacokinetic Parameters in cSSSI Pediatric Patients

Age	Pharmacokinetic Parameters					
	Dose (mg/kg)	**AUC_{ss} (mcg•h/mL)**	**$t_{1/2}$ (h)**	**Vss (mL)**	**CLT (mL/h/kg)**	**Cmax,ss (mcg/mL)**
12 to17 years (N=6)	5	434 (67.9)	7.1 (0.9)	8200 (3250)	11.8 (2.15)	76.4 (6.75)
7 to 11 years (N=2)	7	543*	6.8*	4470*	13.2*	92.4*
2 to 6 years (N=7)	9	452 (93.1)	4.6 (0.8)	2750 (832)	20.8 (4.29)	90.3 (14.0)
1 to <2 years (N=27)	10	462 (138)	4.8 (0.6)	1670 (446)	23.1 (5.43)	81.6 (20.7)

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

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years old, inclusive) with SAB. Patients were enrolled into 3 age groups, and intravenous doses of 7 to 12 mg/kg once daily were administered. Following

administration of multiple doses, daptomycin exposure (AUC_{ss} and $C_{max,ss}$) was similar across different age groups after dose adjustment based on body weight and age (Table 4).

Table 4: Mean (SD) of Daptomycin Population Pharmacokinetic Parameters in Bacteraemia Paediatric Patients

Age	Pharmacokinetic Parameters						
	Dose (mg/kg)	Infusion Duration (min)	AUC_{ss} (mcg•h/mL)	$t_{1/2}$ (hr)	V_{ss} (mL)	CL_T (mL/h/kg)	$C_{max,ss}$ (mcg/mL)
12 to 17 years (N=13)	7	30	656 (334)	7.5 (2.3)	6420 (1980)	12.4 (3.9)	104 (35.5)
7 to 11 years (N=19)	9	30	579 (116)	6.0 (0.8)	4510 (1470)	15.9 (2.8)	104 (14.5)
1 to 6 years (N=19)	12	60	620 (109)	5.1 (0.6)	2200 (570)	19.9 (3.4)	106 (12.8)

AUC_{ss}, area under the concentration-time curve at steady state; CL_T, clearance normalised to body weight;
V_{ss}, volume of distribution at steady state; $t_{½}$, terminal half-life

Obesity
The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m^2) and 6 extremely obese (BMI ≥ 40 kg/m^2) adult subjects. The AUC was approximately 30% higher in moderately obese subjects and 31% higher in extremely obese subjects compared with that 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 dose of CUBICIN by intravenous infusion over a 30-minute period to adult subjects with various degrees of renal impairment, daptomycin clearance decreased and systemic exposure (AUC) increased. The mean AUC for patients with CL_{CR} < 30 mL/min and for patients on dialysis (CAPD and haemodialysis dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function.

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

Hepatic impairment
The pharmacokinetics of daptomycin were evaluated in 10 adult subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with those in healthy adult volunteers (N=9) matched for gender, age and weight. The pharmacokinetics of daptomycin were not altered in subjects with moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) have not been evaluated.

5.3 Preclinical safety data

In rats and dogs, daptomycin administration has been associated with effects on skeletal muscle. However, there were no changes in cardiac or smooth muscle. Skeletal muscle effects were characterised by microscopic degenerative/regenerative changes and variable elevations in CPK. No fibrosis or rhabdomyolysis was observed. All muscle effects, including microscopic changes, were fully reversible within 30 days following the cessation of dosing.

In adult rats and dogs, effects on peripheral nerve (characterised by axonal degeneration and frequently accompanied by functional changes) were observed at daptomycin doses higher than those associated with skeletal myopathy. Reversal of both the microscopic and functional effects was essentially complete within 6 months post-dose.

Target organs of daptomycin-related effects in 7-week-old juvenile dogs were skeletal muscle and nerve, the same target organs as in adult dogs. In juvenile dogs, nerve effects were noted at lower daptomycin blood concentrations than in adult dogs following 28 days of dosing. In contrast to adult dogs, juvenile dogs also showed evidence of effects in nerves of the spinal cord as well as peripheral nerves after 28 days of dosing. Following a 28-day recovery phase, microscopic examination revealed full recovery of the skeletal muscle and the ulnar nerve effects, and partial recovery of the sciatic nerve and spinal cord effects. No nerve effects were noted in juvenile dogs following 14 days of dosing.

Effects of daptomycin were assessed in neonatal dogs following once-daily IV administration for 28 consecutive days from postnatal days (PND) 4 through 31 at nominal dosage levels of 10 [no observed adverse effect level (NOAEL)], 25, 50, and 50/75 mg/kg/day.

At dose levels of 50 and 75 mg/kg/day with associated C_{max} and AUC_{inf} values of ≥321 µg/mL and ≥1,470 µg•h/mL, respectively, marked clinical signs of twitching, muscle rigidity in the limbs, and impaired use of limbs were observed. Resulting decreases in body weights and overall body condition at doses ≥50 mg/kg/day necessitated early discontinuation by PND19. At the dose level of 25 mg/kg/day with associated C_{max} and AUC_{inf} values of 147 µg/mL and 717 µg•h/mL, respectively, mild clinical signs of twitching and one incidence of muscle rigidity were observed without any effects on body weight and were reversible over a 28-day recovery period. These data indicate a limited margin between doses associated with mild versus marked adverse clinical signs. Histopathological assessment did not reveal any daptomycin-related changes in the peripheral and central nervous system tissue, as well as in the skeletal muscle and tissue assessed, at any dose level. No adverse clinical signs for these target organs of toxicity were observed in the dogs that received daptomycin at 10 mg/kg/day, the NOAEL, with associated C_{max} and AUC_{inf} values of 62 µg/mL and 247 µg•h/mL, respectively.

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

Reproductive studies performed in rats and teratology studies performed in rats and rabbits revealed no effect on fertility or reproductive performance and no evidence of harm to the foetus. However, daptomycin can cross the placenta in pregnant rats.

Excretion of daptomycin into milk of lactating animals has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

6.2 Incompatibilities

CUBICIN is not compatible with dextrose-containing diluents.

Other than the nine drugs listed in section 6.6, additives and other medications should not be added to CUBICIN single dose vials or infusion bags, or infused simultaneously with CUBICIN through the same IV line because only limited data are available on the compatibility. If the same IV line is used for sequential infusion of different drugs, flush the line with a compatible intravenous solution before and after infusion with CUBICIN.

6.3 Shelf life

3 years from the date of manufacture.

After reconstitution: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at room temperature (25°C) and up to 48 hours if stored under refrigeration (2°C to 8°C). Chemical and physical stability of the diluted solution in infusion bags has been established as 12 hours at room temperature (25°C) and 48 hours if stored under refrigeration (2°C to 8°C). The combined storage time (reconstituted solution in vial and diluted solution in infusion bag) must not exceed 12 hours at 25°C or 48 hours at 2°C to 8°C.

6.4 Special precautions for storage

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

CUBICIN must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Single dose 10 mL type 1 clear glass vial with type 1 rubber stopper and aluminium closure with yellow polypropylene flip-off cap.

6.6 Special precautions for disposal and other handling

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

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

1. Remove the polypropylene flip-off cap from the CUBICIN vial to expose the central portion of the rubber stopper.
2. Wipe top of rubber stopper with alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
3. Slowly transfer the appropriate volume of 0.9% sodium chloride for injection (10 mL for a 500 mg vial) through the centre of the rubber stopper into the CUBICIN vial using a

bevelled sterile transfer needle that is 21 gauge or smaller diameter, or a needleless device, pointing it toward the wall of the vial.
4. Ensure that all of the CUBICIN 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 bevelled sterile needle 21 gauge or smaller diameter.

Adults

Intravenous Injection over a period of 2 minutes

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

Intravenous Infusion over a period of 30 minutes

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

Paediatric 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 paediatric patients, reconstituted CUBICIN (concentration of 50 mg/mL) is further diluted, using aseptic technique, into a 50 mL IV infusion bag containing 0.9% sodium chloride for injection. The infusion rate should be maintained at 1.67 mL/min over the 30 minute period.
- For IV infusion over a period of 60 minutes in paediatric patients, reconstituted CUBICIN (concentration of 50 mg/mL) is further diluted, using aseptic technique, into an IV infusion bag containing 25 mL of 0.9% sodium chloride for injection. The infusion rate should be maintained at 0.42 mL/min over the 60 minute period.
- **Unlike in adults, CUBICIN should not be administered by injection over a two (2) minute period in paediatric patients** [See section 4.2].

Inspect parenteral drug products visually for particulate matter prior to administration.

No preservative or bacteriostatic agent is present in this product. Aseptic technique must be used in preparation of final IV solution.

Compatible Intravenous Solutions and Other Medicinal Products

CUBICIN is compatible with 0.9% sodium chloride for injection and lactated Ringer's injection. The following have been shown to be compatible when co-administered with CUBICIN through the same IV line from separate infusion bags: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin, and lidocaine.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Merck Sharp & Dohme (New Zealand) Ltd
P O Box 99 851

Newmarket
Auckland 1149
New Zealand
Tel: 0800 500 673

9. DATE OF FIRST APPROVAL

04 September 2008

10. DATE OF REVISION OF THE TEXT

17 February 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
1, 2, 6.6	Deletion of 350 mg strength from Data Sheet

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