AUSTRALIAN PI – CUBICIN® (DAPTOMYCIN)

1 NAME OF THE MEDICINE

daptomycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CUBICIN 350 mg powder for injection
CUBICIN 500 mg powder for injection

Daptomycin is the active ingredient in CUBICIN. It is a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*.

Active ingredient:	daptomycin
Chemical names:	N-decanoly-L- tryptophyl-D-asparaginyl-L-aspartyl-L-threonylglycyl- L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3- methyl-L-glutamyl-3-anthraniloyl-L-alanine e_1-lactone
Molecular weight:	1620.67
Molecular formula	$C_{72}H_{101}N_{17}O_{26}$

CUBICIN is supplied in a single-dose 10 mL vial, as a sterile, preservative-free, pale yellow to light brown, lyophilised cake or powder containing 350 mg or 500 mg of daptomycin for intravenous (IV) use following reconstitution with 0.9 % sodium chloride injection.

Daptomycin has a high aqueous solubility (> 1 g/mL).

The only inactive ingredient is sodium hydroxide, which is used in minimal quantities for pH adjustment.

3 PHARMACEUTICAL FORM

Powder for injection.
Sterile, preservative-free, pale yellow to light brown, lyophilised cake or powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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

Daptomycin is not indicated for the treatment of pneumonia.

be in accordance with nationally or locally-endorsed guidelines for the treatment of *Staphylococcus aureus* bacteraemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

CUBICIN in 0.9 % sodium chloride is administered either by injection over a 2-minute period or infusion over a 30 minute period. Do not dose CUBICIN more frequently than once a day. Measure creatinine phosphokinase levels at baseline and at regular intervals (at least weekly (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)).

- *For complicated skin and skin structure infections (CSSSI)*:

  CUBICIN 4 mg/kg once daily for 7- 14 days or until the infection is resolved.

- *For bacteraemia or right-sided endocarditis caused by S. aureus (SAB/RIE):*
  CUBICIN 6 mg/kg is administered once daily for 2 - 6 weeks depending on the diagnosis.

For dosage in paediatric patients see Special populations.

Special populations

Patients with renal impairment

Because daptomycin is eliminated primarily by the kidneys, a dosage adjustment is recommended for adult patients with creatinine clearance (CL_{CR}) < 30 mL/min, including adult patients receiving haemodialysis or continuous ambulatory peritoneal dialysis.

Adult p *30 mL/min:* No dose adjustment is required in patients whose creatinine clearance is ³ 30 mL/min. Response to treatment and renal function should be closely monitored in all patients with renal insufficiency.

Adult patients with creatinine clearance < 30 mL/min: The dosing interval should be lengthened to a single dose once every 48 hours for these patients. Alternatively, patients on haemodialysis can be dosed three times per week after haemodialysis. Clinical response to treatment and renal function should be closely monitored in these patients.

The same dose adjustment and advice is recommended for adult patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, daptomycin should be administered following the completion of haemodialysis on haemodialysis days.

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

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

established. There is currently no dosing guidance/recommendation for paediatric patients with renal impairment.

Patients with hepatic impairment:

No dosage adjustment is warranted when administering CUBICIN to patients with mild or 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:

Elderly patients have been treated with the same dose as patients aged 18-65. No adjustment of CUBICIN dosage is warranted for elderly patients with CL_{CR} 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 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 adjustment for paediatric patients with cSSSI are shown in the Table 1 below:

Table 1 Paediatric Patients (1 to 17 years of age) with cSSSI

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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 injection once every 24 hours. For duration of therapy, please refer to Table 2.

Table 2 Paediatric Patients (1 to 17 years of age) with *S. aureus* bacteraemia

Age group	**Dosage***	**Duration of therapy**
12 to 17 years	7 mg/kg once every 24 hours infused over 30 minutes	· Local treatment guidelines should be consulted in determining duration of treatment. In the paediatric bacteraemia (SAB) study the mean duration of IV daptomycin was 12 days (median 11 days: range 1-44 days). · No patient with SAB aged 1 to <2 years was included in paediatric SAB study. Dosage for this age group is confirmed using population pharmacokinetic modelling.
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.

Instructions for Use and Handling

CUBICIN is supplied in single dose vials, each containing 500 mg or 350 mg daptomycin as a sterilised 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 7 mL of 0.9 % sodium chloride injection (for 350 mg vials) or 10 mL of 0.9 % sodium chloride injection (for 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 the transfer needle toward the wall of the vial.
4. Ensure that the entire CUBICIN product is wetted by gently rotating the vial.
5. Allow the 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 in 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 Injection over a period of 30 minutes

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

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 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 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 minute period in paediatric patients** (see Section 4.2 DOSE AND METHOD OF

ADMINISTRATION, Paediatric patients).

Prior to injection, the reconstituted product should contain no visible particulate matter.

CUBICIN contains no preservative or bacteriostatic agent. Aseptic technique must be used in preparation of final IV solution.

Compatible Intravenous Solutions

CUBICIN is compatible with 0.9% sodium chloride injection and lactated Ringer's injection.

4.3 CONTRAINDICATIONS

CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin or to the excipient.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Although daptomycin is indicated in adults for the treatment of right-sided endocarditis caused by Staphylococcus aureus, its efficacy in patients with left-sided infective endocarditis has not been demonstrated in controlled clinical trials. Therefore, use of daptomycin in left-sided endocarditis caused by *S.aureus* is not recommended and consideration should be given to instituting alternative antibacterial therapy.

Anaphylaxis/hypersensitivity reactions

Anaphylaxis/hypersensitivity reactions have been reported with nearly all antibacterial agents including CUBICIN. If an allergic reaction to CUBICIN occurs, discontinue the medicine and institute appropriate therapy.

Pneumonia

Daptomycin 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), due to binding to pulmonary surfactant and consequent inactivation (see section 4.1 THERAPEUTIC INDICATIONS).

Eosinophilic pneumonia

Eosinophilic pneumonia has been reported in patients receiving CUBICIN (see section 4.8 ADVERSE EFFECTS). In reported cases associated with CUBICIN, 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.

Skeletal muscle effects

Increases in plasma creatine phosphokinase (CPK) levels associated with muscular pains, weakness and/or rhabdomyolysis have been reported during therapy with CUBICIN (see section 4.8 ADVERSE EFFECTS).

In a Phase 1 study in adults examining doses up to 12 mg/kg q24h of daptomycin for 14 days, no skeletal muscle effects or CPK elevations were observed.

In the two Phase 3 cSSSI trials of daptomycin in adults at a dose of 4 mg/kg, elevations in CPK were reported as adverse events in 15/534 (2.8 %) daptomycin -treated patients, compared with 10/558 (1.8 %) comparator-treated patients. In only one of these two trials an elevation in CPK > 500 was detected in association with a musculoskeletal event - these findings were reported in two patients, one in each treatment group.

In the *S. aureus* bacteraemia/endocarditis trial in adults, at a daptomycin dose of 6 mg/kg, elevations in CPK were reported as clinical adverse events in 8/120 (6.7 %) daptomycin - treated patients compared with 1/116 (< 1 %) comparator-treated patients. In patients with normal CPK at baseline, 25.0 % in the daptomycin group and 12.5 % in the comparator group had CPK ULN during therapy or up to 3 days post-treatment. Eighteen (75.0 %) of the 24 daptomycin patients with CPK
treatment. A total of 11 daptomycin patients had treatment-emergent elevations in CPK to > 500U/L, including 3 patients with CPK ³ ULN at baseline. Of these 11 patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor which may have contributed to these laboratory findings. Three of these 11 daptomycin patients had an elevation in CPK > 500 U/L with an associated musculoskeletal or asthenia event, 2 of whom had an alternative aetiology for these events.

Patients should be reviewed regularly while on therapy for any signs or symptoms that might represent myopathy such as muscle pain or weakness, particularly of the distal extremities. Plasma CPK levels should be monitored at baseline and at regular intervals (at least once weekly) during therapy in all patients. In addition, transaminase levels should be monitored in patients who are at increased risk for drug induced myopathies or hepatotoxicity. Patients with unexplained elevations of CPK or unexplained muscle pain, tenderness or weakness should be monitored more frequently than once weekly. CPK should be measured more frequently than once weekly in patients who are at higher risk of developing myopathy. These patients include those with severe renal impairment (creatinine clearance < 30 ml/min) and patients taking other medications known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and cyclosporin).

It cannot be ruled out that those patients with CPK greater than 5 times upper limit of normal (ULN) 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.

During post-marketing surveillance very rare isolated cases of rhabdomyolysis in patients receiving daptomycin have been reported; when clinical information on the patients was available, approximately 50 % of the cases occurred in patients with pre-existing renal impairment, or in those receiving concomitant medications known to cause rhabdomyolysis. It is recommended that other medications associated with myopathy should if possible be temporarily discontinued during treatment with daptomycin unless the benefits of concomitant administration outweigh the risk.

Daptomycin should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation > 1,000 U/L (~ 5X ULN), or in patients without reported symptoms who h 10 X ULN). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving daptomycin.

In studies of clinically-relevant duration (14-28 days), skeletal muscle effects associated with daptomycin were observed in adult rats and dogs with no changes in cardiac or smooth muscle. The lowest observed effect level (LOEL) for myopathy in adult rats and dogs occurred at exposure levels of 0.8 to 2.3-fold the mean AUC in patients with normal renal function following 30-minute continuous infusion dosing of 6 mg/kg. Skeletal muscle effects were characterized by degenerative/regenerative changes and variable elevations in creatine phosphokinase (CPK). No fibrosis or rhabdomyolysis was observed up to the highest doses tested in rats and dogs (approximately 9 and 5 times the human AUC at 6 mg/kg/day, respectively). All muscle effects, including microscopic changes, were fully reversible in rats within 30 days and in dogs within 2 months following cessation of dosing.

Peripheral nerve effects

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

In a Phase 1 study in adults examining doses up to 12 mg/kg q24h of daptomycin for 14 days, no evidence of nerve conduction deficits or symptoms of peripheral neuropathy was observed. In a small number of patients in Phase 1 and Phase 2 studies at doses up to 6 mg/kg, administration of daptomycin was associated with decreases in nerve conduction velocity and with adverse events (e.g., paraesthesias, Bell's palsy) possibly reflective of peripheral or cranial

neuropathy. However, nerve conduction deficits were also detected in a similar number of comparator subjects in these studies.

In Phase 3 cSSSI and community-acquired pneumonia (CAP) studies in adults, 7/989 (0.7 %) daptomycin-treated patients and 7/1,018 (0.7 %) comparator-treated patients experienced paraesthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In the *S. aureus* bacteraemia/endocarditis trial in adults, a total of 11/120 (9.2 %) patients in the daptomycin group and 2/120 (1.7 %) patients in the comparator group were identified who had experienced adverse events associated with the peripheral nervous system. All of the events were classified as mild to moderate in severity; most were of short duration and resolved during continued treatment with daptomycin or were likely due to an alternative aetiology.

In adult rats and dogs, effects of daptomycin on peripheral and/or spinal nerve (characterised by axonal degeneration and frequently accompanied in dogs by functional changes in nerve conduction and/or loss of reflexes, decreased pain perception, tremor and motor incoordination) were observed at doses higher than those associated with skeletal myopathy. Reversal of both the microscopic and functional effects was almost complete within 6 months post dose. Exposure margins for peripheral nerve effects in rats and dogs are 8- and 6- fold, respectively based on comparison of C_{max} values at the No Observed Effect Level (NOEL) with the C_{max} achieved with 30-minute continuous infusion dosing of 6mg/kg once daily in patients with normal renal function. Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving daptomycin.

Neonatal dogs were more sensitive to the nerve and muscle effects of daptomycin than adult or juvenile dogs. 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}

limbs, and impaired use of limbs were observed. Resulting decreases in body weights and

the dose level of 25 mg/kg/day 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-days 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.

Non-susceptible organisms

The use of antibiotics may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing daptomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Patients with deep seated infections should receive any required surgical interventions (e.g. debridement, removal of prosthetic devices, valve replacement surgery) without delay so as not to compromise successful therapy.

There is insufficient evidence to be able to draw any conclusions regarding the possible clinical efficacy of CUBICIN 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.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed in a limited number of enterococcal isolates following daptomycin therapy. Failures with daptomycin in the treatment of enterococcal bloodstream infections have been reported.

Resistance or lack of susceptibility needs to be monitored during therapy.

Antibiotic-associated Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including daptomycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicated that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic-associated colitis”.

If a diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*.

Drug/Laboratory test interactions

False prolongation of prothrombin time (PT) and elevation of International Normalised Ratio (INR) have been observed when certain recombinant thromboplastin reagents are utilised for the assay (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on Laboratory Tests).

Persisting or Relapsing *S. aureus* Infection

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

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8 %) daptomycin-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6 %) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 daptomycin -treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Use in renal impairment

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

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

Use in the elderly

Of the 534 patients treated with daptomycin in Phase 3 controlled clinical trials of cSSSI, 27.0 % were 65 years of age or older and 12.4 % were 75 years of age or older. Of the 120 patients treated with daptomycin in the Phase 3 controlled clinical trial of *S. aureus* bacteraemia/endocarditis, 25.0 % were 65 years of age or older and 15.8 % were 75 years of age or older. In Phase 3 clinical studies of cSSSI and *S. aureus* bacteraemia/endocarditis, lower

rs of age compared with those < 65 years

of age. In addition, treatment-emergent adverse events were more common in patients 65 years old than in patients < 65 years of age.

Paediatric use

CUBICIN should not be administered to paediatric patients below the age of one year 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.

Use in paediatric patients with renal impairment had not been studied and no dosage recommendations have been formulated.

Use in treatment of pneumonia is contraindicated.

Use in the following conditions has not been studied: infective endocarditis (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Effects on 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 the International Normalised Ratio (INR) when certain recombinant thromboplastin reagents are used in the assay. The possibility of an erroneously elevated PT/INR result may be minimized by drawing samples 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.

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 drawn at trough remains substantially elevated over what would otherwise be expected, consider evaluating PT/INR utilizing an alternative method.

2. Evaluate for other causes of abnormally elevated PT/INR results.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

CUBICIN was studied in adult human drug-drug interaction studies with aztreonam, tobramycin, warfarin, simvastatin, and probenecid.

Warfarin

Concomitant administration of daptomycin (6 mg/kg q24h for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the INR was not significantly altered. As experience with the concomitant administration of daptomycin and warfarin is limited, anticoagulant activity in patients receiving daptomycin and warfarin should be monitored for the first several days after initiating therapy with daptomycin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on laboratory tests).

Other Anticoagulants

Studies of CUBICIN with anticoagulants, other than warfarin, have not been conducted.

HMG-CoA reductase inhibitors

Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in a placebo-controlled Phase 1 trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with daptomycin (4 mg/kg q24h) for 14 days. In the Phase 3 *S. aureus* bacteraemia/endocarditis trial, 5/22 daptomycin -treated patients who received prior or concomitant therapy with an HMG-CoA reductase inhibitor developed CPK elevations > 500 U/L. Experience with co-administration of HMG-CoA reductase inhibitors and daptomycin in patients is limited; therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving daptomycin (see section 4.8 ADVERSE EFFECTS).

Aztreonam, tobramycin and probenecid

CUBICIN was studied in human drug/drug interaction studies with aztreonam, tobramycin and probenecid. *Aztreonam:* The pharmacokinetics of daptomycin were not significantly altered by aztreonam. Daptomycin had no effect on the bioavailability of aztreonam. *Probenecid*: Daptomycin had no effect on the pharmacokinetics of probenecid, and nor did probenecid alter the pharmacokinetics of daptomycin. *Tobramycin*: Although small changes in the pharmacokinetics of daptomycin and tobramycin were observed during coadministration 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 daptomycin is co-administered with tobramycin.

Interactions with other antibiotics

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

studies is unclear.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the estimated human exposure level based upon AUCs.

Use in pregnancy (Category B1)

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, have revealed no evidence of harm to the foetus due to daptomycin. There are, however, no adequate and well-controlled studies in pregnant women.

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

Use in lactation.

In a single case study, CUBICIN was 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 studies on the effects on the ability to drive and use machines have been performed.

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

4.8 ADVERSE EFFECTS (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 organized by system organ class, and the frequency categories for these adverse drug reactions are reported below as follows:

Very common: 10 %); uncommon:

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

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 test 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) including, but not limited to: anaphylaxis, angioedema, drug rash with eosinophilia and systemic symptoms (DRESS) and pulmonary eosinophilia

Musculoskeletal, connective tissue and bone disorders

Rhabdomyolysis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Nervous system disorders

Peripheral neuropathy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Infections and infestations

Clostridium difficile-associated diarrhoea (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Investigations

Myoglobin increased, platelet count decreased

Skin and subcutaneous tissue disorders

Vesiculobullous rash, with or without mucous membrane involvement

Acute generalised exanthematous pustulosis

Respiratory, thoracic and mediastinal disorders

Eosinophilic pneumonia (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), organising pneumonia, cough.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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).

For information on the management of overdose, contact the *Poisons Information Centre* on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. Daptomycin is a natural product that has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. Daptomycin retains potency against antibiotic-resistant Gram-positive bacteria, including isolates resistant to methicillin, vancomycin, and linezolid.

Mechanism of action

The mechanism of action of daptomycin is distinct from that of any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarisation of membrane potential in both growing and stationary phase cells. This loss of membrane potential causes inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

Resistance

The mechanism of daptomycin 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 antibiotics.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed in both *S. aureus* and enterococcal isolates following CUBICIN therapy.

PK/PD relationship

Daptomycin exhibits rapid, concentration dependent bactericidal activity against sensitive Gram-positive organisms *in vitro*.

Based on animal models of infection, the antimicrobial activity of daptomycin appears to correlate with the AUC/MIC (area under the concentration-time curve/minimum inhibitory concentration) ratio for certain pathogens, including *S. aureus*. The principal pharmacokinetic/pharmacodynamics parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with CUBICIN.

Clinical trials

Complicated Skin and Skin Structure Infections (cSSSI)

Skin and skin structure infections are defined as infections of the epidermis, dermis or subcutaneous tissue, and have highly diverse aetiologies and clinical manifestations. The complicated category includes deep soft tissue infections which require significant medical intervention, and abnormal skin or wound infections, which typically occur in compromised patients and may require surgical intervention.

Adults with cSSSI

Adult patients with clinically documented cSSSI (Table 3) were enrolled in two randomised, multinational, multicentre, investigator-blinded studies comparing daptomycin (4 mg/kg IV q24h) with either vancomycin (1 g IV q12h) or an anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, or flucloxacillin; 4 to 12 g IV per day). In these trials cSSSIs included wound infections, major abscesses, severe carbunculosis, infected ulcers and infections in the presence of a complicating factor, such as infections involving deep soft tissue, fascia, or muscle and infections in immunosuppressed patients (e.g. HIV infection, chronic systemic steroids, diabetes mellitus).

Patients known to have bacteraemia at baseline were excluded. Patients with creatinine

clearance (CL_{CR}) between 30 and 70 mL/min were to receive a lower dose of daptomycin as specified in the protocol; however, the majority of patients in this subpopulation did not have the dose of daptomycin adjusted. In Study DAP-SST-9801 (9801), 16 % of the ITT patients treated with daptomycin had their regimen adjusted for renal function. In Study DAP-SST-9901 (9901), only 2 % had their regimen adjusted. Patients could switch to oral therapy after a minimum of 4 days of IV treatment if clinical improvement was demonstrated.

Study 9801 was conducted primarily in the United States and South Africa, whilst Study 9901 was conducted outside of the US, including 5 sites in Australia. Both studies were similar in design but differed in patient characteristics, including history of diabetes and peripheral vascular disease. There were a total of 534 patients treated with daptomycin and 558 treated with comparator in the two studies. The majority (89.7 %) of patients received IV medication exclusively.

The efficacy endpoints in both studies were the clinical success rates in the intent-to-treat (ITT) population and in the clinically evaluable (CE) population. The ITT population included all enrolled subjects who had a complicated skin and soft tissue infection and received at least one dose of study medication. The CE population consisted of all subjects in the ITT population who met specific pre-defined criteria such that the clinical outcome of their infection could be inferred to reflect the effect of the study drug.

In study 9801, clinical success rates in the ITT population were 62.5 % (165/264) in patients treated with daptomycin and 60.9 % (162/266) in patients treated with comparator drugs. Clinical success rates in the CE population were 76.0 % (158/208) in patients treated with daptomycin and 76.7 % (158/206) in patients treated with comparator drugs. In study 9901, clinical success rates in the ITT population were 80.4 % (217/270) in patients treated with daptomycin and 80.5 % (235/292) in patients treated with comparator drugs. Clinical success rates in the CE population were 89.9 % (214/238) in patients treated with daptomycin and 90.4 % (226/250) in patients treated with comparator drugs.

The success rates by pathogen for microbiologically evaluable patients are presented in Table 4.

Overall clinical efficacy results are provided in Tables 5 and 6 in terms of the sponsor-defined primary clinical efficacy parameters at the Test of Cure visit (7-12 days after cessation of antibiotic treatment) for MITT and CE populations.

Table 3 Investigator's Primary Diagnosis in the cSSSI Studies (Population: ITT)

	Adult Patients CUBICIN/Comparator*		
Primary Diagnosis	**Study 9801 N=264/N=266**	**Study 9901 N=270/N=292**	**Pooled N=534/N=558**
Wound Infection	99 (37.5 %)/ 116 (43.6 %)	102 (37.8 %)/ 108 (37.0 %)	201 (37.6 %)/ 224 (40.1 %)
Major Abscess	55 (20.8 %)/ 43 (16.2 %)	59 (21.9 %)/ 65 (22.3 %)	114 (21.3 %)/ 108 (19.4 %)
Ulcer Infection	71 (26.9 %)/ 75 (28.2 %)	53 (19.6 %)/ 68 (23.3 %)	124 (23.2 %)/ 143 (25.6 %)
Other Infection†	39 (14.8%)/ 32 (12.0 %)	56 (20.7 %)/ 51 (17.5 %)	95 (17.8 %)/ 83 (14.9 %)

*. Vancomycin or anti-staphylococcal semi-synthetic penicillins.

† The majority of cases were subsequently categorised as complicated cellulitis, major abscesses, or traumatic wound infections.

Table 4 Clinical Success Rates by Infecting Pathogen, Primary Comparative cSSSI Studies (Population: Microbiologically Evaluable)

Pathogen	**Success Rate**	
	Daptomycin n/N (%)	**Comparator[a] n/N (%)**
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[b]	170/198 (85.9)	180/207 (87.0)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[b]	21/28 (75.0)	25/36 (69.4)
Streptococcus pyogenes	79/84 (94.0)	80/88 (90.9)
Streptococcus agalactiae	23/27 (85.2)	22/29 (75.9)
Streptococcus dysgalactiae subsp. *equisimilis*	8/8 (100)	9/11 (81.8)
Enterococcus faecalis (vancomycin-susceptible only)	27/37 (73.0)	40/53 (75.5)

a. Vancomycin or anti-staphylococcal semi-synthetic penicillins

b. As determined by the central laboratory

Table 5 Clinical efficacy outcome (MITT population)

	Study 9801		Study 9901		Pooled Results	
Clinical Response	CUBICIN (N=215) n (%)	Comparator[a] (N=216) n (%)	CUBICIN (N=213) n (%)	Comparator[a] (N=255) n (%)	CUBICIN (N=428) n (%)	Comparator[a] (N=471) n (%)
Clinical Success	140 (65.1)	140 (64.8)	179 (84.0)	212 (83.1)	319 (74.5)	352 (74.7)
Cure	90 (41.9)	84 (38.9)	82 (38.5)	109 (42.7)	172 (40.2)	193 (41.0)
Clinical Improvement	50 (23.3)	56 (25.9)	97 (45.5)	103 (40.4)	147 (34.3)	159 (33.8)

Clinical Failure	75 (34.9)	76 (35.2)	34 (16.0)	43 (16.9)	109 (25.5)	119 (25.3)

[a] Vancomycin or anti-staphylococcal semi-synthetic penicillins

Table 6 Clinical efficacy outcome (CE population)

	Study 9801		Study 9901		Pooled Results	
Clinical Response	CUBICIN (N=208) n (%)	Comparator[a] (N=206) n (%)	CUBICIN (N=238) n (%)	Comparator[a] (N=250) n (%)	CUBICIN (N=446) n (%)	Comparator[a] (N=456) n (%)
Clinical Success	158 (76.0)	158 (76.7)	214 (89.9)	226 (90.4)	372 (83.4)	384 (84.2)
Cure	105 (50.5)	96 (46.6)	103 (43.3)	117 (46.8)	208 (46.6)	213 (46.7)
Clinical Improvement	53 (25.5)	62 (30.1)	111 (46.6)	109 (43.6)	164 (36.8)	171 (37.5)
Clinical Failure	50 (24.0)	48 (23.3)	24 (10.1)	24 (9.6)	74 (16.6)	72 (15.8)

[a] Vancomycin or anti-staphylococcal semi-synthetic penicillins

Paediatric Patients (1 to 17 Years of Age) with cSSSI

The safety and efficacy of daptomycin was evaluated in paediatric patients 1 to 17 years of age (DAP-PEDS-07-03) with cSSSI caused by Gram-positive pathogens. Patients were enrolled in a stepwise approach into well-defined age groups and given age-dependent doses once daily up to 14 days as follows:

- Age Group 1 (n=113): 12 to 17 years treated with daptomycin dosed at 5 mg/kg or standard of care (SOC);
- Age Group 2 (n=113): 7 to 11 years treated with daptomycin dosed at 7 mg/kg or SOC;
- Age Group 3 (n=125): 2 to 6 years treated with daptomycin dosed at 9 mg/kg or SOC;
- Age Group 4 (n=45): 1 to < 2 years treated with daptomycin dosed at 10 mg/kg or SOC.

The primary objective of Study DAP-PEDS-07-03 was to assess the safety of treatment. Secondary objectives included an assessment of efficacy of age-dependent doses of IV daptomycin in comparison with standard-of-care therapy. The key efficacy endpoint was the sponsor-defined clinical outcome at Test-of-Cure (TOC), which was defined by a blinded medical director.

A total of 389 subjects were treated in the study, including 256 subjects who received daptomycin and 133 subjects who received standard-of-care. In all populations the clinical success rates were comparable between the daptomycin and SOC treatment arms supporting the primary efficacy analysis in the ITT population (see Table 7).

Table 7 Summary of sponsor-defined clinical outcome at test-of-cure for paediatric patients (1 to 17 years of age) with cSSSI

	Clinical Success		
	DAP	SOC	
	n/N (%)	n/N (%)	% Diff.
Intent-to-Treat	227/257 (88.3%)	114/132 (86.4%)	2.0
Modified Intent-to-Treat	186/210 (88.6%)	92/105 (87.6%)	0.9
Clinically Evaluable	204/207 (98.6%)	99/99 (100%)	-1.5
Microbiologically Evaluable	164/167 (98.2%)	78/78 (100%)	-1.8

The overall therapeutic response rate also was similar for the daptomycin and SOC treatment arms for infections caused by MRSA, MSSA and *Streptococcus pyogenes* (Table 8; ME population); response rates were > 94% for both treatment arms across these common pathogens.

Table 8 Summary of overall therapeutic response by type of baseline pathogen (ME population) for paediatric patients (1 to 17 years of age) with cSSSI

Pathogen	Success Rate n/N (%)	
	CUBICIN	Comparator
Methicillin-susceptible *Staphylococcus aureus* (MSSA)[a]	68/69 (99%)	28/29 (97%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)[a]	63/66 (96%)	34/34 (100%)
Streptococcus pyogenes	17/18 (94%)	5/5 (100%)

[a]Subjects with both clinical success and microbiological success are classified as overall therapeutic success

S. aureus Bacteraemia/Endocarditis

Adults with S. Aureus Bacteraemia/Endocarditis

The efficacy of daptomycin in the treatment of patients with *S. aureus* bacteraemia (SAB) was demonstrated in a randomised, controlled, multinational, multicentre open-label study. In this study, adult patients with at least one positive blood culture for *S. aureus* obtained within 2 calendar days prior to the first dose of study drug and irrespective of source were enrolled and randomized to either daptomycin (6 mg/kg IV q24h) or standard of care [anti-staphylococcal semi-synthetic penicillin 2 g IV q4h (nafcillin, oxacillin, cloxacillin, or flucloxacillin) or vancomycin 1 g IV q12h, both with initial gentamicin 1 mg/kg IV every 8 hours for first 4 days]. Of the patients in the comparator group, 93 % received initial gentamicin for a median of 4 days compared with 1 patient (< 1 %) in the daptomycin group. Patients with prosthetic

heart valves, intravascular foreign material that was not planned for removal within 4 days after the first dose of study medication, severe neutropenia, known osteomyelitis, polymicrobial bloodstream infections, creatinine clearance < 30 mL/min, shock unresponsive to treatment for 4 hours and pneumonia were excluded.

Upon entry, patients were classified for likelihood of endocarditis using the modified Duke criteria (Possible, Definite, or Not Endocarditis). Echocardiography, including a transoesophageal echocardiogram (TEE), was performed within 5 days following study enrolment. The choice of comparator agent was based on the oxacillin susceptibility of the *S. aureus* isolate. The duration of study treatment was based on the investigator's clinical diagnosis. Final diagnoses and outcome assessments at Test of Cure (6 weeks after the last treatment dose) were made by a treatment-blinded Adjudication Committee, using protocol-specified clinical definitions and a composite primary efficacy endpoint (clinical and microbiological success) at the Test of Cure visit.

18 years of age (124 daptomycin, 122 comparator) with *S. aureus* bacteraemia were randomised from 48 centres in the US and Europe. In the ITT population, 120 patients received daptomycin and 115 received comparator (62 anti-staphylococcal semi-synthetic penicillin and 53 vancomycin). Thirty-five patients treated with anti-staphylococcal semi-synthetic penicillins received vancomycin initially for 1 to 3 days, pending final susceptibility results for the *S. aureus* isolates. The median age among the 235 patients in the ITT population was 53 years (range: 21 to 91 years); 30/120 (25 %) in the daptomycin group ge. Of the 235 ITT patients, there were 141 (60 %) males and 156 (66 %) Caucasians across the two treatment groups. In addition, 176 (75 %) of the ITT population had systemic inflammatory response syndrome (SIRS) and 85 (36 %) had surgical procedures within 30 days of onset of the *S. aureus* bacteraemia. Eighty-nine patients (38 %) had bacteraemia caused by MRSA. Entry diagnosis was based on the modified Duke criteria and included 37 (16 %) Definite, 144 (61 %) Possible, and 54 (23 %) Not Endocarditis. Of the 37 patients with an entry diagnosis of Definite Endocarditis, all (100 %) had a final diagnosis of infective endocarditis, and of the 144 patients with an entry diagnosis of Possible Endocarditis, 15 (10 %) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee. Of the 54 patients with an entry diagnosis of Not Endocarditis, 1 (2 %) had a final diagnosis of infective endocarditis as assessed by the Adjudication Committee.

There were 182 patients with bacteraemia and 53 patients with infective endocarditis as assessed by the Adjudication Committee in the ITT population, including 35 with right-sided and 18 with left-sided endocarditis. The 182 patients with bacteraemia included 121 with complicated and 61 with uncomplicated *S. aureus* bacteraemia.

Complicated bacteraemia was defined as *S. aureus* isolated from blood cultures obtained on at least 2 different calendar days, and/or metastatic foci of infection (deep tissue involvement),

and classification of the patient as not having endocarditis according to the modified Duke criteria. Uncomplicated bacteraemia was defined as *S. aureus* isolated from blood culture(s) obtained on a single calendar day, no metastatic foci of infection, no infection of prosthetic material, and classification of the patient as not having endocarditis according to the modified Duke criteria. The definition of right-sided endocarditis (RIE) used in the clinical trial was Definite or Possible Endocarditis according to the modified Duke criteria and no echocardiographic evidence of predisposing pathology or active involvement of either the mitral or aortic valve. Complicated RIE included patients who were not intravenous drug users, had a positive blood culture for MRSA, serum creatinine 2.5 mg/dL, or evidence of extrapulmonary sites of infection. Patients who were intravenous drug users, had a positive blood culture for MSSA, serum creatinine < 2.5 mg/dL, and were without evidence of extrapulmonary sites of infection were considered to have uncomplicated RIE.

The co-primary efficacy endpoints in the study were the Adjudication Committee success rates at the Test of Cure visit (6 weeks after the last treatment dose) in the ITT and Per Protocol (PP) populations. The overall Adjudication Committee success rates in the ITT population were 44.2 % (53/120) in patients treated with daptomycin and 41.7 % (48/115) in patients treated with comparator (difference = 2.4 % [95 % CI 10.2, 15.1]). The success rates in the PP population were 54.4 % (43/79) in patients treated with daptomycin and 53.3 % (32/60) in patients treated with comparator (difference = 1.1 % [95 % CI 15.6, 17.8]).

Adjudication Committee success rates are shown in Table 9.

Table 9 Adjudication Committee Success Rates at Test of Cure in the Bacteraemia/Endocarditis Trial in Adult Patients (Population: ITT)

Population	Daptomycin 6 mg/kg n/N (%)	Comparator[a] n/N (%)	Difference: (Confidence Interval)
Overall	53/120 (44.2 %)	48/115 (41.7 %)	[c]
Baseline Pathogen			
MSSA	33/74 (44.6 %)	34/70 (48.6 %)	[d]
MRSA	20/45 (44.4 %)	14/44 (31.8 %)	[d]
Entry Diagnosis[b]			
Definite or Possible infective endocarditis	41/90 (45.6 %)	37/91 (40.7 %)	[d]
Not Infective endocarditis	12/30 (40.0 %)	11/24 (45.8 %)	[d]
Final Diagnosis			
Uncomplicated bacteraemia	18/32 (56.3 %)	16/29 (55.2 %)	[e]
Complicated bacteraemia	26/60 (43.3 %)	23/61 (37.7 %)	[e]
Right-sided infective endocarditis	8/19 (42.1 %)	7/16 (43.8 %)	[e]
Uncomplicated right-sided infective endocarditis	3/6 (50.0 %)	1/4 (25.0 %)	[e]
Complicated right-sided infective endocarditis	5/13 (38.5 %)	6/12 (50.0 %)	[e]
Left-sided infective endocarditis	1/9 (11.1 %)	2/9 (22.2 %)	[e]

[a] Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (i.e., nafcillin, oxacillin, cloxacillin, flucloxacillin; 2 g IV q4h), each with initial low-dose gentamicin

[b] According to the modified Duke criteria

[c] 95 % Confidence Interval

[d] 97.5 % Confidence Interval (adjusted for multiplicity)

[e] 99 % Confidence Interval (adjusted for multiplicity)

Eighteen (18/120) patients in the daptomycin arm and 19/116 patients in the comparator arm died during the study. These include 3/28 daptomycin -treated and 8/26 comparator-treated patients with endocarditis, as well as 15/92 daptomycin -treated and 11/90 comparator-treated patients with bacteraemia. Among patients with persisting or relapsing *S. aureus* infections, 8/19 daptomycin -treated and 7/11 comparator-treated patients died.

Overall, there was no difference in time to clearance of *S. aureus* bacteraemia between daptomycin and comparator. The median time to clearance in patients with MSSA was 4 days and in patients with MRSA was 8 days.

Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8 %) daptomycin-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6 %) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 daptomycin-treated patients and 1 vancomycin-treated patient developed increasing MICs for daptomycin (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS).

Paediatric Patients (1 to 17 years of Age) with S. aureus Bacteraemia

The paediatric *S. aureus* bacteraemia study was designed as a prospective multi-centre, randomised, comparative trial to treat paediatric patients aged 1 to 17 years with bacteraemia. Patients known to have any of the following conditions at baseline were excluded:

- Presence of shock or hypotension unresponsive to fluids or vasopressors for ≥4 hours
- Renal insufficiency in terms of estimated creatinine clearance rate (CL_{cr}) <50 ml/min/1.73m^2
- History of clinically significant muscular disease, for example, creatine phosphokinase (CPK) elevation ≥10 X ULN (upper limit of normal) without symptoms or ≥5 X ULN with symptoms such as myalgia, muscle stiffness, muscle weakness
- Suspected or confirmed empyema, meningitis, endocarditis or pneumonia

Patients were enrolled in a stepwise approach into three age groups and given age-dependent doses of CUBICIN once daily for up to 42 days. The different age groups and doses evaluated were as follows:

- Age Group 1 (n=14): 12-17 years treated with CUBICIN dosed at 7 mg/kg once daily;
- Age Group 2 (n=19): 7-11 years treated with CUBICIN dosed at 9 mg/kg once daily;

· Age Group 3 (n=22); 2-6 years treated with CUBICIN dosed at 12 mg/kg once daily.

No patients 1 to <2 years of age were enrolled.

Patients were randomised 2:1 to receive CUBICIN or a standard of care comparator, which included intravenous therapy with vancomycin, semi-synthetic penicillin, first generation cephalosporin or clindamycin. Patients could switch to oral therapy after clinical improvement was demonstrated (no minimum IV dosing was required).

The primary objective of Study DAP-PEDBAC-11-02 was to assess the safety of intravenous daptomycin versus SOC antibiotics. Efficacy outcomes included: Clinical outcome based on the blinded Evaluator's assessment of clinical response (success [cure, improved], failure, or non-evaluable) at the TOC visit (see Table 10); and Microbiological response (success, failure, or non-evaluable) based on evaluation of Baseline infecting pathogen at TOC (see Table 11).

Of the 82 subjects randomised in the study, 81 subjects were treated with CUBICIN or comparator and included in the safety population, and 73 had a proven *S. aureus* bacteraemia at Baseline. Of these, 51 subjects were randomised to the CUBICIN group and 22 subjects were randomised to the comparator group. The mean duration of IV therapy was 12 days with a range of 1 to 44 days. Forty-eight subjects switched to oral therapy, and the mean duration of oral therapy was 21 days. The clinical success rates determined at 7 to 14 days after last dose of therapy (IV and oral) (TOC visit) were 88% (45/51) for CUBICIN and 77% (17/22) for comparator.

Table 10 Summary of clinical outcome at test of cure/safety visit by treatment group

Clinical Success in Paediatric SAB				
	Daptomycin n/N (%)	Comparator n/N (%)	% difference	95% confidence interval of difference
Modified intent-to-treat (MITT)	46/52 (88.5%)	19/24 (79.2%)	9.3%	-9.1, 27.7
Microbiologically modified intent-to-treat (mMITT)	45/51 (88.2%)	17/22 (77.3%)	11.0%	-8.7, 30.6
Clinically evaluable (CE)	36/40 (90.0%)	9/12 (75.0%)	15.0%	-11.2, 41.2

The microbiological outcome at TOC for the daptomycin and SOC treatment arms for infections caused by MRSA and MSSA are presented in Table 11.

Attachment 1: Product AusPAR CUBICIN - daptomycin - MSD Australia Pty Ltd - PM-2017-04652-1-2 FINAL 20 November 2019. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Table 11 Summary of pathogen-level microbiological outcome at the test of cure/safety visit by treatment group (mMITT population)

Pathogen	Microbiological Success rate in Paediatric SAB n/N (%)	
	Daptomycin	Comparator
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	43/44 (97.7%)	19/19 (100.0%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	6/7 (85.7%)	3/3 (100.0%)

5.2 PHARMACOKINETIC PROPERTIES

The mean (SD) pharmacokinetic parameters of daptomycin at steady-state following IV administration of 4 to 12 mg/kg q24h to healthy young adults are summarised in Table 12.

Daptomycin pharmacokinetics were generally linear (dose-proportional) and time-independent at CUBICIN doses of 4 to 12 mg/kg q24h. Steady-state trough concentrations were achieved by the third daily dose. The mean (SD) steady-state trough concentrations attained following administration of 4, 6, 8, 10, and 12 mg/kg q24h in healthy adults were 5.9 (1.6), 6.7 (1.6), 10.3 (5.5), 12.9 (2.9), and 13.7 (5.2) µg/mL, respectively.

Table 12 Mean (SD) Daptomycin Pharmacokinetic Parameters in Healthy Adult Volunteers at Steady-State

Dose[b] (mg/kg)	**Pharmacokinetic Parameters[a]**				
	AUC_{0-24} (µg*h/mL)	**$t_{1/2}$ (h)**	**V_{ss} (L/kg)**	**CL_T (mL/h/kg)**	**C_{max} (µg/mL)**
4 (N=6)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	57.8 (3.0)
6 (N=6)	632 (78)	7.9 (1.0)	0.101 (0.007)	9.1 (1.5)	93.9 (6.0)
8 (N=6)	858 (213)	8.3 (2.2)	0.101 (0.013)	9.0 (3.0)	123.3 (16.0)
10 (N=9)	1039 (178)	7.9 (0.6)	0.098 (0.017)	8.8 (2.2)	141.1 (24.0)
12 (N=9)	1277 (253)	7.7 (1.1)	0.097 (0.018)	9.0 (2.8)	183.7 (25.0)

a. AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; $t_{½}$, terminal elimination half-life; V_{ss}, volume of distribution at steady-state; CL_T, plasma clearance; C_{max}, maximum plasma concentration.

b. Doses of Daptomycin in excess of 6 mg/kg have not been approved

Distribution

Daptomycin is reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The overall mean binding ranged from 90 to 93 %.

In clinical studies, mean serum protein binding in adult subjects with CL_{CR} comparable to that observed in healthy adult subjects with normal renal function. However, there was a trend toward decreasing serum protein binding among adult subjects with CL_{CR} <30 mL/min (87.6 %), including those receiving haemodialysis (85.9 %) and continuous ambulatory peritoneal dialysis (CAPD) (83.5 %). The protein binding of daptomycin in adult subjects with hepatic impairment (Child-Pugh B) was similar to that in healthy adult subjects.

The volume of distribution at steady-state (V_{ss}) of daptomycin in healthy adult subjects was approximately 0.1 L/kg and was independent of dose.

Metabolism

In *in vitro studies*, daptomycin was not metabolised by human liver microsomes. *In vitro* studies with human hepatocytes indicate that daptomycin does not inhibit or induce the activities of the following human cytochrome P450 isoforms: 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4. It is unlikely that daptomycin will inhibit or induce the metabolism of drugs metabolised by the P450 system.

In 5 healthy young adults after infusion of radiolabelled ^{14}C-daptomycin, the plasma total radioactivity was similar to the concentration determined by microbiological assay. In a separate study, no metabolites were observed in plasma on Day 1 following administration of daptomycin at 6 mg/kg to subjects. Inactive metabolites have been detected in urine, as determined by the difference in total radioactive concentrations and microbiologically active concentrations. Minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Excretion

Daptomycin is excreted primarily by the kidney. Concomitant administration of probenecid and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting 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 5 healthy adult subjects using radiolabelled daptomycin, approximately 78 % of the administered dose was recovered from urine based on total radioactivity (approximately 52 % of the dose based on microbiologically active concentrations) and 5.7 % of the administered dose was recovered from faeces (collected for up to 9 days) based on total radioactivity.

Because renal excretion is the primary route of elimination, dosage adjustment is necessary in patients with severe renal impairment (CL_{CR} <30 mL/min) (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Special patient groups

Elderly: The pharmacokinetics of daptomycin were evaluated in 12 healthy elderly subjects adult controls (18 to 30 years of age). Following administration of a single 4 mg/kg IV dose, the mean total clearance of daptomycin was approximately 35 % lower and the mean $AUC_{0-¥}$ was approximately 58 % higher in elderly subjects compared with young healthy adult subjects. There were no differences in C_{max}. No dosage adjustment is warranted for elderly patients with normal renal function.

Paediatric: The pharmacokinetics of daptomycin after a single 4 mg/kg dose of CUBICIN were evaluated in three groups of paediatric patients with Gram-positive infections. The pharmacokinetic profile in adolescents, 12-17 years of age, showed reduced exposure. In the two younger age groups (7 to 11 years and 2 to 6 years), total clearance was higher compared with that in adolescents, resulting in lower exposure (AUC and C_{max}) and elimination half-life. As the adolescent exposure is less than adults it is possible that inadequate exposure may occur with the 4mg/kg dose that is not the recommended dose in these two groups.

A separate study was conducted to evaluate the pharmacokinetics of daptomycin after a single 8 mg/kg or 10mg/kg dose of CUBICIN as either a 1 or 2 hour infusion in paediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infection who were receiving standard antibacterial therapy.

The mean exposure (AUC_{0-} was approximately 429 and 550 µg*hr/ml after the administration of 8 and 10 mg/kg single doses, respectively, similar to the exposure seen in adults at the 4 mg/kg dose at steady state (495 µg*hr/ml). The pharmacokinetics of daptomycin appears to be linear in the dose range studied. The half-life, clearance and volume of distribution were similar at both dose levels.

A Phase 4 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 (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical trials). Intravenous daptomycin doses of 5 to 10 mg/kg were administered and 256 children received daptomycin, from which pharmacokinetic sampling was performed on 45 children from across the age groups.

Daptomycin pharmacokinetic parameters following the administration of multiple doses, are provided in Table 13. Daptomycin exposure (AUC_{ss} and $C_{max,\ ss}$) was similar across the

different age groups after dose adjustment based on body weight and age.

Table 13 Mean (Standard Deviation) of Daptomycin Pharmacokinetics in Paediatric cSSSI Patients (1 to 17 Years of Age) in Study DAP-PEDS-07-03

Age Range	12-17 years (N=6)	7-11 years (N=2)[a]	2-6 years (N=7)	1 to <2 years (N=30)[b]
Dose Infusion Time	5 mg/kg 30 minutes	7 mg/kg 30 minutes	9 mg/kg 60 minutes	10 mg/kg 60 minutes
$AUC_{0\text{-}24hr}$ (mg×hr/ml)	387 (81)	438	439 (102)	466
C_{max} (mg/ml)	62.4 (10.4)	64.9, 74.4	81.9 (21.6)	79.2
Apparent $t_{1/2}$ (hr)	5.3 (1.6)	4.6	3.8 (0.3)	5.04
CL/wt (ml/hr/kg)	13.3 (2.9)	16.0	21.4 (5.0)	21.5

Pharmacokinetic parameter values estimated by noncompartmental analysis

[a]Individual values reported as only two patients in this age group provided pharmacokinetic samples to enable pharmacokinetic analysis; AUC, apparent $t_{1/2}$ and CL/wt could be determined for only one of the two patients

[b]Pharmacokinetic analysis conducted on the pooled pharmacokinetic profile with mean concentrations across subjects at each time point

A study was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years of age, inclusive) with *S. aureus* bacteraemia. Patients were enrolled into 3 age groups (see CLINICAL TRIALS), 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 14).

Table 14 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)	$t_{1/2}$ (h)	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)

2 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; $t_{1/2}$ terminal half-life

No patients 1 to <2 years of age were enrolled in the study. Simulation using a population pharmacokinetic model demonstrated that the AUC_{ss} of daptomycin in paediatric patients 1 to < 2 years of age receiving 12 mg/kg once daily would be comparable to that in adult patients receiving 6 mg/kg once daily.

Obesity: The pharmacokinetics of daptomycin were evaluated in 6 moderately obese (Body Mass Index [BMI] 25 to 39.9 kg/m^2 kg/m^2) subjects and controls matched for age, sex, and renal function. Following administration of a single 4 mg/kg IV dose based on total body weight, the plasma clearance of daptomycin normalised to total body weight was approximately 15 % lower in moderately obese subjects and 23 % lower in extremely obese subjects compared with non-obese controls. The $AUC_{0-¥}$ of daptomycin was approximately 30 % higher in moderately obese and 31 % higher in extremely obese subjects compared with non-obese controls. The differences were most likely due to differences in the renal clearance of daptomycin. No dosage adjustment of daptomycin is warranted in obese subjects.

Gender: No clinically significant gender-related differences in daptomycin pharmacokinetics have been observed. No dosage adjustment is warranted based on gender when administering daptomycin.

Renal Impairment: Population derived pharmacokinetic parameters were determined for infected adult patients (complicated skin and skin structure infections and *S. aureus* bacteraemia) and non-infected adult subjects with varying degrees of renal function (Table 15). Plasma clearance (CL_T), elimination half-life ($t_{1/2}$), and volume of distribution at steady state (V_{ss}) were similar in patients with complicated skin and skin structure infections compared with those with *S. aureus* bacteraemia. Following the administration of daptomycin 4 mg/kg q24h, the mean CL_T was 9 %, 22 %, and 46 % lower among subjects and patients with mild (CL_{CR} 50-80 mL/min), moderate (CL_{CR} 30-50 mL/min), and severe (CL_{CR} < 30 mL/min) renal impairment, respectively, than in those with normal renal function (CL_{CR} > 80 mL/min). The mean steady-state systemic exposure (AUC), $t_{1/2}$, and V_{ss} increased with decreasing renal function, although the mean AUC was not markedly different for patients with CL_{CR} 30-80 mL/min compared with those with normal renal function. The mean AUC for patients with CL_{CR} <30 mL/min and for patients on haemodialysis (dosed post-dialysis) was approximately 2 and 3 times higher, respectively, than for patients with normal renal function. Following the administration of daptomycin 4 mg/kg q24h, the mean C_{max} ranged from 60 to 70 µg/mL in

patients with CL_{CR} 30 mL/min, while the mean C_{max} for patients with CL_{CR} < 30 mL/min ranged from 41 to 58 µg/mL. The mean C_{max} ranged from 80 to 114 µg/mL in patients with mild-to-moderate renal impairment and was similar to that of patients with normal renal function after the administration of daptomycin 6 mg/kg q24h. In patients with renal impairment, both renal function and creatine phosphokinase (CPK) should be monitored more frequently. Daptomycin should be administered following the completion of haemodialysis on haemodialysis days (see section 4.2 DOSE AND METHOD OF ADMINISTRATION for recommended dosage regimens).

Table 15 Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following Infusion of 4 mg/kg or 6 mg/kg to Infected Adult Patients and Non-infected Adult Subjects with Varying Degrees of Renal Function

Renal Function	**$t_{1/2}$[a] (h) 4 mg/kg**	**V_{ss}[a] (L/kg) 4 mg/kg**	**CL_T[a] (mL/h/kg) 4 mg/kg**	**AUC_{0-} [a] (µg*h/mL) 4 mg/kg**	**AUC_{ss}[b] (µg*h/mL) 6 mg/kg**	**$C_{min,ss}$[b] (µg*h/mL) 6 mg/kg**
Normal (CL_{CR} >80 mL/min)	9.39 (4.74) N=165	0.13 (0.05) N=165	10.9 (4.0) N=165	417 (155) N=165	545 (296) N=62	6.9 (3.5) N= 61
Mild Renal Impairment (CL_{CR} 50–80 mL/min)	10.75 (8.36) N=64	0.12 (0.05) N=64	9.9 (4.0) N=64	466 (177) N=64	637 (215) N=29	12.4 (5.6) N=29
Moderate Renal Impairment (CL_{CR} 30–<50 mL/min)	14.70 (10.50) N=24	0.15 (0.06) N=24	8.5 (3.4) N=24	560 (258) N=24	868 (349) N=15	19.0 (9.0) N=14
Severe Renal Impairment (CL_{CR} <30 mL/min)	27.83 (14.85) N=8	0.20 (0.15) N=8	5.9 (3.9) N=8	925 (467) N=8	1050 (892) N=2	24.4 (21.4) N=2
Dialysis (Haemodialysis + CAPD)	29.81 (6.13) N=21	0.15 (0.04) N=21	3.7 (1.9) N=21	1244 (374) N=21	NA	NA

Source of data: Initial Cubist cSSSI programme (for 4mg/kg) and Study DAP-IE-01-02 (for 6 mg/kg).

CUBICIN was administered over a 30-minute period.

Notes:

CL_{CR}: Creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight

AUC_{0-} : Area under the concentration-time curve extrapolated to infinity

AUC_{ss}: Area under the concentration-time curve calculated over the 24-hour dosing interval at steady-state

$C_{min,ss}$: Trough concentration at steady-state

NA: not applicable.

a. Parameters obtained following a single dose from patients with complicated skin and skin structure infections and healthy subjects

b. Parameters obtained at steady-state from patients with *S. aureus* bacteraemia

Hepatic Impairment: The pharmacokinetics of daptomycin were evaluated in 10 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared with healthy volunteers

(N= 9) matched for gender, age, and weight. The pharmacokinetics of daptomycin was not altered in subjects with moderate hepatic impairment. No dosage adjustment is warranted when administering daptomycin to patients with mild to moderate hepatic impairment. The pharmacokinetics of daptomycin in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Daptomycin was not mutagenic or clastogenic in a battery of *in vivo* and *in vitro* genotoxicity tests comprising mutation in bacteria and mammalian cells, chromosomal aberrations and DNA damage in mammalian cells, a bone marrow micronucleus assay in mice and a sister chromatid exchange assay in Chinese hamsters.

Carcinogenicity

Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

CUBICIN is not compatible with glucose-containing diluents, including dextrose. Because only limited data are available on the compatibility of CUBICIN with other IV substances, additives and other medications should not be added to CUBICIN single-dose vials or infusion bags or infused simultaneously through the same IV line (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Stability after reconstitution and dilution

In the vial: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at room temperature or up to 48 hours if stored under refrigeration (2°C to 8°C).

In the infusion bag: Chemical and physical in-use stability of the diluted solution in the infusion bag has been established for 12 hours at room temperature or 48 hours if stored under refrigeration (2°C to 8°C).

However, to reduce microbiological hazard, the reconstituted solution and the diluted solution should be used as soon as practicable after reconstitution and after dilution. If storage of the reconstituted or further diluted solution is necessary, solutions should be stored under refrigeration at 2°C to 8°C for a combined time (vial and infusion bag) of no more than 24 hours.

Because only limited data are available on the compatibility of CUBICIN with other IV substances, additives or other medications should not be added to CUBICIN single-use vials or infused simultaneously through the same IV line. If the same IV line is used for sequential infusion of several different drugs, the line should be flushed with a compatible infusion solution before and after infusion with CUBICIN.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

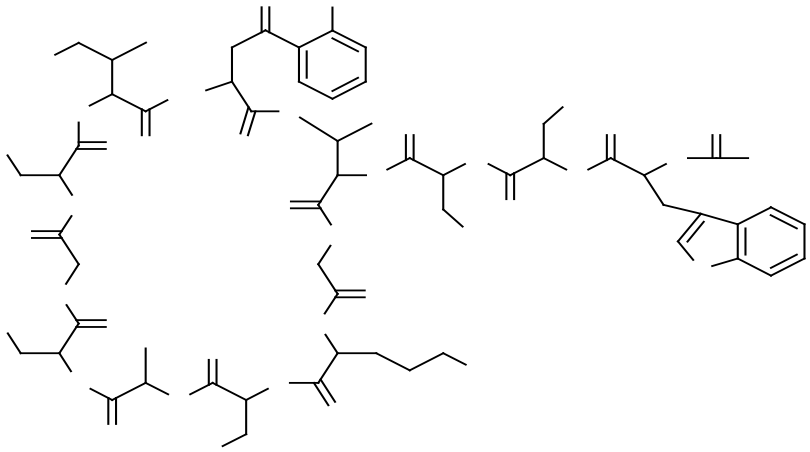
CUBICIN is supplied in single-dose vials containing 350 mg or 500 mg daptomycin as a sterile, lyophilised powder. Single-dose 10 mL capacity vial: Package of 1.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

103060-53-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, 26 Talavera Road
Macquarie Park, NSW 2013
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

8 December 2008

10 DATE OF REVISION

25 January 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4, 5.1 and 5.2	Sections updated to add information on the Paediatric Bacteraemia indication

S-CCDS-MK3009-I-022018