# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Cubicin® 350 mg powder for solution for injection or infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cubicin 350 mg powder for solution for injection or infusion
Each vial contains 350 mg daptomycin.
One ml provides 50 mg of daptomycin after reconstitution with 7 ml of sodium chloride 9 mg/ml (0.9 %) solution.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections (see sections 4.4 and 5.1).

- Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus.* It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of

the organism and should be based on expert advice. See sections 4.4 and 5.1.
- Adult and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).

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

## 4.2 Posology and method of administration

Clinical studies in patients employed infusion of daptomycin over at least 30 minutes. There is no clinical experience in patients with the administration of daptomycin as an injection over 2 minutes. This mode of administration was only studied in healthy subjects. However, when compared with the same doses given as intravenous infusions over 30 minutes there were no clinically important differences in the pharmacokinetics and safety profile of daptomycin (see sections 4.8 and 5.2).

Posology

*Adults*
- cSSTI without concurrent SAB: Cubicin 4 mg/kg is administered once every 24 hours for 7-14 days or until the infection is resolved (see section 5.1).
- cSSTI with concurrent SAB: Cubicin 6 mg/kg is administered once every 24 hours. See below for dose adjustments in patients with renal impairment. The duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.
- Known or suspected RIE due to *Staphylococcus aureus*: Cubicin 6 mg/kg is administered once every 24 hours. See below for dose adjustments in patients with renal impairment. The duration of therapy should be in accordance with available official recommendations.

Cubicin is administered intravenously in 0.9 % sodium chloride (see section 6.6). Cubicin should not be used more frequently than once a day.

Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly) during treatment (see section 4.4).

*Renal impairment*
Daptomycin is eliminated primarily by the kidney.

Due to limited clinical experience (see table and footnotes below) Cubicin should only be

used in adult patients with any degree of renal impairment (CrCl < 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment, renal function and creatine phosphokinase (CPK) levels should be closely monitored in all patients with any degree of renal impairment (see sections 4.4 and 5.2). The dosage regimen for Cubicin in paediatric patients with renal impairment has not been established.

Dose adjustments in adult patients with renal impairment by indication and creatinine clearance

| **Indication for use** | **Creatinine clearance** | **Dose recommendation** | **Comments** |
|---|---|---|---|
| cSSTI without SAB | ≥ 30 ml/min | 4 mg/kg once daily | See section 5.1 |
| | < 30 ml/min | 4 mg/kg every 48 hours | (1, 2) |
| RIE or cSSTI associated with SAB | ≥ 30 ml/min | 6 mg/kg once daily | See section 5.1 |
| | < 30 ml/min | 6 mg/kg every 48 hours | (1, 2) |
| cSSTI = complicated skin and soft-tissue infections; SAB = *S. aureus* bacteraemia<br>(1) The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical trials and the recommendation is based on pharmacokinetic studies and modelling results (see sections 4.4 and 5.2).<br>(2) The same dose adjustments, which are based on pharmacokinetic data in volunteers including PK modelling results, are recommended for adult patients on haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, Cubicin should be administered following the completion of dialysis on dialysis days (see section 5.2). | | | |

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

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

*Paediatric population (1 to 17 years of age)*
The recommended dosage regimens for paediatric patients based on age and indication are shown below.

| **Age Group** | **Indication** | | | |
|---|---|---|---|---|
| | **cSSTI without SAB** | | **cSSTI associated with SAB** | |
| | **Dosage Regimen** | **Duration of Therapy** | **Dosage Regimen** | **Duration of Therapy** |

<table>
<tr><th rowspan="2">Age Group</th><th colspan="4">Indication</th></tr>
<tr><th colspan="2">cSSTI without SAB</th><th colspan="2">cSSTI associated with SAB</th></tr>
<tr><th>Dosage Regimen</th><th>Duration of Therapy</th><th>Dosage Regimen</th><th>Duration of Therapy</th></tr>
<tr><td>12 to 17 years</td><td>5 mg/kg once every 24 hours infused over 30 minutes</td><td rowspan="4">Up to 14 days</td><td>7 mg/kg once every 24 hours infused over 30 minutes</td><td rowspan="4">(1)</td></tr>
<tr><td>7 to 11 years</td><td>7 mg/kg once every 24 hours infused over 30 minutes</td><td>9 mg/kg once every 24 hours infused over 30 minutes</td></tr>
<tr><td>2 to 6 years</td><td>9 mg/kg once every 24 hours infused over 60 minutes</td><td>12 mg/kg once every 24 hours infused over 60 minutes</td></tr>
<tr><td>1 to < 2 years</td><td>10 mg/kg once every 24 hours infused over 60 minutes</td><td>12 mg/kg once every 24 hours infused over 60 minutes</td></tr>
<tr><td colspan="5">cSSTI = complicated skin and soft-tissue infections; SAB = S. aureus bacteraemia;<br>(1) Minimum duration of Cubicin for paediatric SAB should be in accordance with the perceived risk of complications in the individual patient. The duration of Cubicin may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient. In the paediatric SAB study, the mean duration of IV Cubicin was 12 days, with a range of 1 to 44 days. The duration of therapy should be in accordance with available official recommendations.</td></tr>
</table>

Cubicin is administered intravenously in 0.9 % sodium chloride (see section 6.6). Cubicin should not be used more frequently than once a day.

Creatine phosphokinase (CPK) levels must be measured at baseline and at regular intervals (at least weekly) during treatment (see section 4.4).

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).

Method of administration

In adults, Cubicin is given by intravenous infusion (see section 6.6) and administered over a 30-minute period or by intravenous injection (see section 6.6) and administered over a 2-minute period.

In paediatric patients aged 7 to 17 years, Cubicin is given by intravenous infusion over a 30-minute period (see section 6.6). In paediatric patients aged 1 to 6 years, Cubicin is given by intravenous infusion over a 60-minute period (see section 6.6).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

## 4.4 Special warnings and precautions for use

General
If a focus of infection other than cSSTI or RIE is identified after initiation of Cubicin therapy consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Anaphylaxis/hypersensitivity reactions
Anaphylaxis/hypersensitivity reactions have been reported with Cubicin. If an allergic reaction to Cubicin occurs, discontinue use and institute appropriate therapy.

Pneumonia
It has been demonstrated in clinical studies that Cubicin is not effective in the treatment of pneumonia. Cubicin is therefore not indicated for the treatment of pneumonia.

RIE due to *Staphylococcus aureus*
Clinical data on the use of Cubicin to treat RIE due to *Staphylococcus aureus* are limited to 19 adult patients (see "Clinical efficacy in adults" in section 5.1). The safety and efficacy of Cubicin in children and adolescents aged below 18 years with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus* have not been established.
The efficacy of Cubicin in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated.

Deep-seated infections
Patients with deep-seated infections should receive any required surgical interventions (e.g. debridement, removal of prosthetic devices, valve replacement surgery) without delay.

Enterococcal infections
There is insufficient evidence to be able to draw any conclusions regarding the possible clinical efficacy of 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. Failures with daptomycin in the treatment of enterococcal infections that were mostly accompanied by bacteraemia have been reported. In some instances treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin (see section 5.1).

Non-susceptible micro-organisms
The use of antibacterials may promote the overgrowth of non-susceptible micro-organisms. If superinfection occurs during therapy, appropriate measures should be taken.

*Clostridioides difficile*-associated diarrhoea
*Clostridioides difficile*-associated diarrhoea (CDAD) has been reported with Cubicin (see section 4.8). If CDAD is suspected or confirmed, Cubicin may need to be discontinued and appropriate treatment instituted as clinically indicated.

Drug/laboratory test interactions
False prolongation of prothrombin time (PT) and elevation of international normalised ratio (INR) have been observed when certain recombinant thromboplastin reagents are utilised for the assay (see section 4.5).

Creatine phosphokinase and myopathy
Increases in plasma creatine phosphokinase (CPK; MM isoenzyme) levels associated with muscular pains and/or weakness and cases of myositis, myoglobinaemia and rhabdomyolysis have been reported during therapy with Cubicin (see sections 4.5, 4.8 and 5.3). In clinical studies, marked increases in plasma CPK to > 5x Upper Limit of Normal (ULN) without muscle symptoms occurred more commonly in Cubicin-treated patients (1.9 %) than in those that received comparators (0.5 %). Therefore, it is recommended that:

- Plasma CPK should be measured at baseline and at regular intervals (at least once weekly) during therapy in all patients.
- CPK should be measured more frequently (e.g. every 2-3 days at least during the first two weeks of treatment) in patients who are at higher risk of developing myopathy. For example, patients with any degree of renal impairment (creatinine clearance < 80 ml/min; see also section 4.2), including those on haemodialysis or CAPD, and patients taking other medicinal products known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
- It cannot be ruled out that those patients with CPK greater than 5 times upper limit of normal at baseline may be at increased risk of further increases during daptomycin therapy. This should be taken into account when initiating daptomycin therapy and, if daptomycin is given, these patients should be monitored more frequently than once weekly.
- Cubicin should not be administered to patients who are taking other medicinal products associated with myopathy unless it is considered that the benefit to the patient outweighs the risk.
- Patients should be reviewed regularly while on therapy for any signs or symptoms that might represent myopathy.
- Any patient that develops unexplained muscle pain, tenderness, weakness or cramps should have CPK levels monitored every 2 days. Cubicin should be discontinued in the presence of unexplained muscle symptoms if the CPK level reaches greater than 5 times upper limit of normal.

Peripheral neuropathy
Patients who develop signs or symptoms that might represent a peripheral neuropathy during therapy with Cubicin should be investigated and consideration should be given to discontinuation of daptomycin (see sections 4.8 and 5.3).

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

Eosinophilic pneumonia
Eosinophilic pneumonia has been reported in patients receiving Cubicin (see section 4.8). In most reported cases associated with Cubicin, patients developed fever, dyspnoea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates or organising pneumonia. The majority of cases occurred after more than 2 weeks of treatment with 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 medicinal products). Cubicin should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and vesiculobullous rash with or without mucous membrane involvement (Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)), which could be life-threatening or fatal, have been reported with daptomycin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, Cubicin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a severe cutaneous adverse reaction with the use of daptomycin, treatment with daptomycin must not be restarted in this patient at any time.

Tubulointerstitial nephritis
Tubulointerstitial nephritis (TIN) has been reported in post-marketing experience with daptomycin. Patients who develop fever, rash, eosinophilia and/or new or worsening renal impairment while receiving Cubicin should undergo medical evaluation. If TIN is suspected, Cubicin should be discontinued promptly and appropriate therapy and/or measures should be taken.

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 development of myopathy (see above).

An adjustment of Cubicin dose interval is needed for adult patients whose creatinine clearance is < 30 ml/min (see sections 4.2 and 5.2). The safety and efficacy of the dose interval adjustment have not been evaluated in controlled clinical trials and the recommendation is mainly based on pharmacokinetic modelling data. Cubicin should only be used in such patients when it is considered that the expected clinical benefit outweighs the potential risk.

Caution is advised when administering Cubicin to patients who already have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with Cubicin. Regular monitoring of renal function is advised (see section 5.2).

In addition, regular monitoring of renal function is advised during concomitant administration of potentially nephrotoxic agents, regardless of the patient's pre-existing renal function (see section 4.5).

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

Obesity
In obese subjects with Body Mass Index (BMI) > 40 $kg/m^2$ but with creatinine clearance > 70 ml/min, the $AUC_{0-\infty}$ daptomycin was significantly increased (mean 42 % higher) compared with non-obese matched controls. There is limited information on the safety and efficacy of daptomycin in the very obese and so caution is recommended. However, there is currently no evidence that a dose reduction is required (see section 5.2).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

Interaction studies for Cubicin were performed with aztreonam, tobramycin, warfarin and probenecid. Daptomycin had no effect on the pharmacokinetics of warfarin or probenecid, nor did these medicinal products alter the pharmacokinetics of daptomycin. The pharmacokinetics of daptomycin were not significantly altered by aztreonam.

Although small changes in the pharmacokinetics of daptomycin and tobramycin were observed during co-administration 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 an approved 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. Anticoagulant activity in patients receiving Cubicin and warfarin should be monitored for the first several days after therapy with Cubicin is initiated.

There is limited experience regarding concomitant administration of daptomycin with other medicinal products that may trigger myopathy (e.g. HMG-CoA reductase inhibitors). However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in adult patients taking one of these medicinal products at the same time as Cubicin. It is recommended that other medicinal products associated with myopathy should if possible be temporarily discontinued during treatment with Cubicin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CPK levels should be measured more frequently than once weekly and patients should be closely monitored for any signs or symptoms that might represent myopathy. See sections 4.4, 4.8 and 5.3.

Daptomycin is primarily cleared by renal filtration and so plasma levels may be increased during co-administration with medicinal products that reduce renal filtration (e.g. NSAIDs and COX-2 inhibitors). In addition, there is a potential for a pharmacodynamic interaction to occur during co-administration due to additive renal effects. Therefore, caution is advised when daptomycin is co-administered with any other medicinal product known to reduce renal filtration.

During post–marketing surveillance, cases of interference between daptomycin and particular reagents used in some assays of prothrombin time/international normalised ratio (PT/INR) have been reported. This interference led to a false prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking daptomycin, consideration should be given to a possible *in vitro* interaction

with the laboratory test. The possibility of erroneous results may be minimised by drawing samples for PT or INR testing near the time of trough plasma concentrations of daptomycin (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical data on pregnancies are available for daptomycin. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Cubicin should not be used during pregnancy unless clearly necessary i.e., only if the expected benefit outweighs the possible risk.

Breast-feeding

In a single human case study, 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. Therefore, until more experience is gained, breast-feeding should be discontinued when Cubicin is administered to nursing women.

Fertility

No clinical data on fertility are available for daptomycin. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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 Undesirable effects

Summary of the safety profile

In clinical studies, 2,011 adult subjects received Cubicin. Within these trials, 1,221 subjects received a daily dose of 4 mg/kg, of whom 1,108 were patients and 113 were healthy volunteers; 460 subjects received a daily dose of 6 mg/kg, of whom 304 were patients and 156 were healthy volunteers. In paediatric studies, 372 patients received Cubicin, of whom 61 received a single dose and 311 received a therapeutic regimen for cSSTI or SAB (daily doses ranged from 4 mg/kg to 12 mg/kg). Adverse reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported at similar frequencies for Cubicin and comparator regimens.

The most frequently reported adverse reactions (frequency common (≥ 1/100 to < 1/10)) are:
Fungal infections, urinary tract infection, candida infection, anaemia, anxiety, insomnia, dizziness, headache, hypertension, hypotension, gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension, liver function tests abnormal (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP)), rash, pruritus, limb pain, serum creatine phosphokinase (CPK) increased, infusion site reactions, pyrexia, asthenia.

Less frequently reported, but more serious, adverse reactions include hypersensitivity reactions, eosinophilic pneumonia (occasionally presenting as organising pneumonia), drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema and rhabdomyolysis.

Tabulated list of adverse reactions

The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data):

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1 Adverse reactions from clinical studies and post-marketing reports**

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Infections and infestations | *Common:* | Fungal infections, urinary tract infection, candida infection |
| | *Uncommon:* | Fungaemia |
| | *Not known*:* | *Clostridioides difficile*-associated diarrhoea** |
| Blood and lymphatic system disorders | *Common:* | Anaemia |
| | *Uncommon:* | Thrombocythaemia, eosinophilia, international normalised ratio (INR) increased, leukocytosis |
| | *Rare:* | Prothrombin time (PT) prolonged |
| | *Not known*:* | Thrombocytopaenia |

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Immune system disorders | *Not known*:* | Hypersensitivity**, manifested by isolated spontaneous reports including, but not limited to angioedema, pulmonary eosinophilia, sensation of oropharyngeal swelling, anaphylaxis**, infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste |
| Metabolism and nutrition disorders | *Uncommon:* | Decreased appetite, hyperglycaemia, electrolyte imbalance |
| Psychiatric disorders | *Common:* | Anxiety, insomnia |
| Nervous system disorders | *Common:*<br>*Uncommon:*<br>*Not known*:* | Dizziness, headache<br>Paraesthesia, taste disorder, tremor, eye irritation<br>Peripheral neuropathy** |
| Ear and labyrinth disorders | *Uncommon:* | Vertigo |
| Cardiac disorders | *Uncommon:* | Supraventricular tachycardia, extrasystole |
| Vascular disorders | *Common:*<br>*Uncommon:* | Hypertension, hypotension<br>Flushes |
| Respiratory, thoracic and mediastinal disorders | *Not known*:* | Eosinophilic pneumonia[1]**, cough |
| Gastrointestinal disorders | *Common:*<br><br><br>*Uncommon:* | Gastrointestinal and abdominal pain, nausea, vomiting, constipation, diarrhoea, flatulence, bloating and distension<br>Dyspepsia, glossitis |
| Hepatobiliary disorders | *Common:*<br><br><br><br>*Rare:* | Liver function tests abnormal[2] (increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP))<br>Jaundice |
| Skin and subcutaneous tissue disorders | *Common:*<br>*Uncommon:*<br>*Not known*:* | Rash, pruritus<br>Urticaria<br>Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)**, vesiculobullous rash with or without mucous membrane involvement (SJS or TEN)** |
| Musculoskeletal and connective tissue disorders | *Common:*<br><br>*Uncommon:*<br><br><br>*Not known*:* | Limb pain, serum creatine phosphokinase (CPK)[2] increased<br>Myositis, increased myoglobin, muscular weakness, muscle pain, arthralgia, serum lactate dehydrogenase (LDH) increased, muscle cramps<br>Rhabdomyolysis[3] ** |
| Renal and urinary disorders | *Uncommon:*<br><br>*Not known*:* | Renal impairment, including renal failure and renal insufficiency, serum creatinine increased<br>Tubulointerstitial nephritis (TIN)** |

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Reproductive system and breast disorders | *Uncommon:* | Vaginitis |
| General disorders and administration site conditions | *Common:*<br>*Uncommon:* | Infusion site reactions, pyrexia, asthenia<br>Fatigue, pain |

* Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

** See section 4.4.

[1] While the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, to date the reporting rate of spontaneous reports is very low (< 1/10,000).

[2] In some cases of myopathy involving raised CPK and muscle symptoms, the patients also presented with elevated transaminases. These transaminase increases were likely to be related to the skeletal muscle effects. The majority of transaminase elevations were of Grade 1-3 toxicity and resolved upon discontinuation of treatment.

[3] When clinical information on the patients was available to make a judgement, approximately 50 % of the cases occurred in patients with pre-existing renal impairment, or in those receiving concomitant medicinal products known to cause rhabdomyolysis.

The safety data for the administration of daptomycin via 2-minute intravenous injection are derived from two pharmacokinetic studies in healthy adult volunteers. Based on these study results, both methods of daptomycin administration, the 2-minute intravenous injection and the 30-minute intravenous infusion, had a similar safety and tolerability profile. There was no relevant difference in local tolerability or in the nature and frequency of adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

In the event of overdose, supportive care is advised. Daptomycin is slowly cleared from the body by haemodialysis (approximately 15 % of the administered dose is removed over 4 hours) or by peritoneal dialysis (approximately 11 % of the administered dose is removed over 48 hours).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Other antibacterials, ATC code: J01XX09

Mechanism of action
Daptomycin is a cyclic lipopeptide natural product that is active against Gram positive bacteria only.

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

PK/PD relationship
Daptomycin exhibits rapid, concentration dependent bactericidal activity against Gram positive organisms *in vitro* and in *in vivo* animal models. In animal models AUC/MIC and $C_{max}$/MIC correlate with efficacy and predicted bacterial kill *in vivo* at single doses equivalent to human adult doses of 4 mg/kg and 6 mg/kg once daily.

Mechanisms of resistance
Strains with decreased susceptibility to daptomycin have been reported especially during the treatment of patients with difficult-to-treat infections and/or following administration for prolonged periods. In particular, there have been reports of treatment failures in patients infected with *Staphylococcus aureus, Enterococcus faecalis or Enterococcus faecium,* including bacteraemic patients, that have been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin during therapy.

The mechanism(s) of daptomycin resistance is (are) not fully understood.

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

*Susceptibility*
The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought

when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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

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

Clinical efficacy in adults

In two adult clinical trials in complicated skin and soft tissues infections, 36 % of patients treated with Cubicin met the criteria for systemic inflammatory response syndrome (SIRS). The most common type of infection treated was wound infection (38 % of patients), while 21 % had major abscesses. These limitations of the patients population treated should be taken into account when deciding to use Cubicin.

In a randomised controlled open-label study in 235 adult patients with *Staphylococcus aureus* bacteraemia (i.e. at least one positive blood culture of *Staphylococcus aureus* prior to receiving the first dose) 19 of 120 patients treated with Cubicin met the criteria for RIE. Of these 19 patients 11 were infected with methicillin-susceptible and 8 with methicillin-resistant *Staphylococcus aureus*. The success rates in RIE patients are shown in the table below.

| **Population** | **Daptomycin** | **Comparator** | **Differences in Success** |
|---|---|---|---|
| | **n/N (%)** | **n/N (%)** | **Rates (95 % CI)** |
| ITT (intention to treat) Population | | | |
| RIE | 8/19 (42.1 %) | 7/16 (43.8 %) | -1.6 % (-34.6, 31.3) |
| PP (per protocol) Population | | | |
| RIE | 6/12 (50.0 %) | 4/8 (50.0 %) | 0.0 % (-44.7, 44.7) |

Failure of treatment due to persisting or relapsing *Staphylococcus aureus* infections was observed in 19/120 (15.8 %) patients treated with Cubicin, 9/53 (16.7 %) patients treated with vancomycin and 2/62 (3.2 %) patients treated with an anti-staphylococcal semi-synthetic penicillin. Among these failures six patients treated with Cubicin and one patient treated with vancomycin were infected with *Staphylococcus aureus* that developed increasing MICs of daptomycin on or following therapy (see “Mechanisms of resistance” above). Most patients who failed due to persisting or relapsing *Staphylococcus aureus* infection had deep-seated infection and did not receive necessary surgical intervention.

Clinical efficacy in paediatric patients

The safety and efficacy of daptomycin was evaluated in paediatric patients aged 1 to 17 years (Study DAP-PEDS-07-03) with cSSTI caused by Gram positive pathogens. Patients were enrolled in a stepwise approach into well-defined age groups and given age-dependent doses once daily for 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 comparator (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 intravenous 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.

Summary of sponsor-defined clinical outcome at TOC:

| | **Clinical Success in Paediatric cSSTI** | | |
|---|---|---|---|
| | **Daptomycin n/N (%)** | **Comparator n/N (%)** | **% difference** |
| 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 (ME) | 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* (see table below; ME population); response rates were > 94 % for both treatment arms across these common pathogens.

Summary of overall therapeutic response by type of baseline pathogen (ME population):

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

[a] Subjects achieving clinical success (Clinical Response of "Cure" or "Improved") and microbiological success (pathogen–level response of "Eradicated" or "Presumed Eradicated") are classified as overall therapeutic success.

The safety and efficacy of daptomycin was evaluated in paediatric patients aged 1 to 17 years (Study DAP-PEDBAC-11-02) with bacteraemia caused by *Staphylococcus aureus*. Patients were randomised in a 2:1 ratio into the following age groups and given age-dependent doses once daily for up to 42 days, as follows:

- Age group 1 (n=21): 12 to 17 years treated with daptomycin dosed at 7 mg/kg or SOC comparator;
- Age group 2 (n=28): 7 to 11 years treated with daptomycin dosed at 9 mg/kg or SOC;
- Age group 3 (n=32): 1 to 6 years treated with daptomycin dosed at 12 mg/kg or SOC;

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

A total of 81 subjects were treated in the study, including 55 subjects who received daptomycin and 26 subjects who received standard-of-care. No patients 1 to <2 years of age were enrolled in the study. In all populations the clinical success rates were comparable in the daptomycin versus the SOC treatment arm.

Summary of Blinded Evaluator defined clinical outcome at TOC:

| | Clinical Success in Paediatric SAB | | |
|---|---|---|---|
| | **Daptomycin n/N (%)** | **Comparator n/N (%)** | **% difference** |
| Modified intent-to-treat (MITT) | 46/52 (88.5 %) | 19/24 (79.2 %) | 9.3 % |
| Microbiologically modified intent-to-treat (mMITT) | 45/51 (88.2 %) | 17/22 (77.3 %) | 11.0 % |
| Clinically evaluable (CE) | 36/40 (90.0 %) | 9/12 (75.0 %) | 15.0 % |

The microbiological outcome at TOC for the daptomycin and SOC treatment arms for infections caused by MRSA and MSSA are presented in the table below (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

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

Daptomycin administered as a 2-minute intravenous injection also exhibited dose proportional pharmacokinetics in the approved therapeutic dose range of 4 to 6 mg/kg. Comparable exposure (AUC and $C_{max}$) was demonstrated in healthy adult subjects following administration of daptomycin as a 30-minute intravenous infusion or as a 2-minute intravenous injection.

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

Distribution
The volume of distribution at steady state of daptomycin in healthy adult subjects was approximately 0.1 l/kg and was independent of dose. Tissue distribution studies in rats showed that daptomycin appears to only minimally penetrate the blood-brain barrier and the placental barrier following single and multiple doses.

Daptomycin is reversibly bound to human plasma proteins in a concentration independent manner. In healthy adult volunteers and adult patients treated with daptomycin, protein binding averaged about 90 % including subjects with renal impairment.

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

After infusion of 14C-daptomycin in healthy adults, the plasma radioactivity was similar to the concentration determined by microbiological assay. Inactive metabolites were detected in urine, as determined by the difference in total radioactive concentrations and microbiologically active concentrations. In a separate study, no metabolites were observed in plasma, and minor amounts of three oxidative metabolites and one unidentified compound were detected in urine. The site of metabolism has not been identified.

Elimination
Daptomycin is excreted primarily by the kidneys. Concomitant administration of probenecid

and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting minimal to no active tubular secretion of daptomycin.

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

In a mass balance study using radiolabelled material, 78 % of the administered dose was recovered from the urine based on total radioactivity, whilst urinary recovery of unchanged daptomycin was approximately 50 % of the dose. About 5 % of the administered radiolabel was excreted in the faeces.

Special populations

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

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

*Children and adolescents (1 to 17 years of age)*
The pharmacokinetics of daptomycin in paediatric subjects was evaluated in 3 single-dose pharmacokinetic studies. After a single 4 mg/kg dose of Cubicin, total clearance normalised by weight and elimination half-life of daptomycin in adolescents (12-17 years of age) with Gram-positive infection were similar to adults. After a single 4 mg/kg dose of 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 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 children 13-24 months of age were similar to children 2-6 years of age who received a single 4-10 mg/kg dose. The results of these studies show that exposures (AUC) in paediatric patients across all doses are generally lower than those in adults at comparable doses.

*Paediatric patients with cSSTI*
A Phase 4 study (DAP-PEDS-07-03) was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years old, inclusive) with cSSTI caused by Gram-positive pathogens. Daptomycin pharmacokinetics in patients in this study are summarised in Table 2. Following administration of multiple doses, daptomycin exposure was similar across different age groups after dose adjustment based on body weight and age. Plasma exposures achieved with these doses were consistent with those achieved in the adult cSSTI study (following 4 mg/kg once daily in adults).

**Table 2Mean (Standard Deviation) of Daptomycin Pharmacokinetics in Paediatric cSSTI 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 |
| AUC0-24hr (µg×hr/ml) | 387 (81) | 438 | 439 (102) | 466 |
| $C_{max}$ (µg/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

*Paediatric patients with SAB*
A Phase 4 study (DAP-PEDBAC-11-02) was conducted to assess safety, efficacy, and pharmacokinetics of daptomycin in paediatric patients (1 to 17 years old, inclusive) with SAB. Daptomycin pharmacokinetics inpatients in this study are summarised in Table 3. Following administration of multiple doses, daptomycin exposure was similar across different age groups after dose adjustment based on body weight and age. Plasma exposures achieved with these doses were consistent with those achieved in the adult SAB study (following 6 mg/kg once daily in adults).

**Table 3Mean (Standard Deviation) of Daptomycin Pharmacokinetics in Paediatric SAB Patients (1 to 17 Years of Age) in Study DAP-PEDBAC-11-02**

| Age Range | 12-17 years (N=13) | 7-11 years (N=19) | 1 to 6 years (N=19)* |
|---|---|---|---|
| Dose Infusion Time | 7 mg/kg 30 minutes | 9 mg/kg 30 minutes | 12 mg/kg 60 minutes |
| AUC0-24hr (µg×hr/ml) | 656 (334) | 579 (116) | 620 (109) |
| $C_{max}$ (µg/ml) | 104 (35.5) | 104 (14.5) | 106 (12.8) |
| Apparent $t_{1/2}$ (hr) | 7.5 (2.3) | 6.0 (0.8) | 5.1 (0.6) |
| CL/wt (ml/hr/kg) | 12.4 (3.9) | 15.9 (2.8) | 19.9 (3.4) |

Pharmacokinetic parameter values estimated using a model-based approach with sparsely collected pharmacokinetic samples from individual patients in the study.
*Mean (Standard Deviation) calculated for patients 2 to 6 years of age, since no patients 1 to <2 years of age were enrolled in the study. Simulation using a population pharmacokinetic model demonstrated that the AUCss (area under the concentration-time curve at steady state) 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*
Relative to non-obese subjects daptomycin systemic exposure measured by AUC was about 28 % higher in moderately obese subjects (Body Mass Index of 25-40 $kg/m^2$) and 42 % higher in extremely obese subjects (Body Mass Index of > 40 $kg/m^2$). However, no dose adjustment is considered to be necessary based on obesity alone.

*Gender*
No clinically significant gender-related differences in daptomycin pharmacokinetics have

been observed.

*Race*
No clinically significant differences in daptomycin pharmacokinetics have been observed in Black or Japanese subjects relative to Caucasian subjects.

*Renal impairment*
Following administration of a single 4 mg/kg or 6 mg/kg intravenous dose of daptomycin over a 30-minute period to adult subjects with various degrees of renal impairment, total daptomycin clearance (CL) decreased and systemic exposure (AUC) increased as renal function (creatinine clearance) decreased.

Based on pharmacokinetic data and modelling, the daptomycin AUC during the first day after administration of a 6 mg/kg dose to adult patients on HD or CAPD was 2-fold higher than that observed in adult patients with normal renal function who received the same dose. On the second day after administration of a 6 mg/kg dose to HD and CAPD adult patients the daptomycin AUC was approximately 1.3-fold higher than that observed after a second 6 mg/kg dose in adult patients with normal renal function. On this basis, it is recommended that adult patients on HD or CAPD receive daptomycin once every 48 hours at the dose recommended for the type of infection being treated (see section 4.2).

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

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

## 5.3 Preclinical safety data

Daptomycin administration was associated with minimal to mild degenerative/regenerative changes in skeletal muscle in the rat and dog. Microscopic changes in skeletal muscle were minimal (approximately 0.05 % of myofibres affected) and at the higher doses were accompanied by elevations in CPK. No fibrosis or rhabdomyolysis was observed. Depending on the study duration, all muscle effects, including microscopic changes, were fully reversible within 1-3 months following cessation of dosing. No functional or pathological changes in smooth or cardiac muscle were observed.

The lowest observable effect level (LOEL) for myopathy in rats and dogs occurred at exposure levels of 0.8 to 2.3-fold the human therapeutic levels at 6 mg/kg (30-minute intravenous infusion) for patients with normal renal function. As the pharmacokinetics (see section 5.2) is comparable, the safety margins for both methods of administration are very similar.

A study in dogs demonstrated that skeletal myopathy was reduced upon once daily administration as compared to fractionated dosing at same total daily

dose, suggesting that myopathic effects in animals were primarily related to time between doses.

Effects on peripheral nerves were observed at higher doses than those associated with skeletal muscle effects in adult rats and dogs, and were primarily related to plasma $C_{max}$. Peripheral nerve changes were characterised by minimal to slight axonal degeneration and were frequently accompanied by functional changes. Reversal of both the microscopic and functional effects was complete within 6 months post-dose. Safety 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 on dosing with 30-minute intravenous infusion of 6 mg/kg once daily in patients with normal renal function.

The findings of *in vitro* and some *in vivo* studies designed to investigate the mechanism of daptomycin myotoxicity indicate that the plasma membrane of differentiated spontaneously contracting muscle cells is the target of toxicity. The specific cell surface component directly targeted has not been identified. Mitochondrial loss/damage was also observed; however the role and significance of this finding in the overall pathology are unknown. This finding was not associated with an effect on muscle contraction.

In contrast to adult dogs, juvenile dogs appeared to be more sensitive to peripheral nerve lesions as compared to skeletal myopathy. Juvenile dogs developed peripheral and spinal nerve lesions at doses lower than those associated with skeletal muscle toxicity.

In neonatal dogs, daptomycin caused marked clinical signs of twitching, muscle rigidity in the limbs, and impaired use of limbs, which resulted in decreases in body weight and overall body condition at doses ≥ 50 mg/kg/day and necessitated early discontinuation of treatment in these dose groups. At lower dose levels (25 mg/kg/day), mild and reversible clinical signs of twitching and one incidence of muscle rigidity were observed without any effects on body weight. There was no histopathological correlation in the peripheral and central nervous system tissue, or in the skeletal muscle, at any dose level, and the mechanism and clinical relevance for the adverse clinical signs are therefore unknown.

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

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium hydroxide

## 6.2 Incompatibilities

Cubicin is not physically or chemically compatible with glucose-containing solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

3 years

After reconstitution: Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25 °C and up to 48 hours at 2 °C – 8 °C. Chemical and physical stability of the diluted solution in infusion bags is established as 12 hours at 25 °C or 24 hours at 2 °C – 8 °C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section 6.6) at 25 °C must not exceed 12 hours (or 24 at 2 °C – 8 °C).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial (see section 6.6) at 25 °C must not exceed 12 hours (or 48 at 2 °C – 8 °C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. If not used immediately, in-use storage times are the responsibility of the user and would not normally be longer than 24 hours at 2 °C – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
For storage conditions after reconstitution and after reconstitution and dilution of the medicinal product see section 6.3.

## 6.5 Nature and contents of container

Cubicin 350 mg powder for solution for injection or infusion
Single use 10 ml type I clear glass vials with type I rubber stoppers and aluminium closures with yellow plastic flip off caps.
Available in packs containing 1 vial or 5 vials. Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

In adults, daptomycin may be administered intravenously as an infusion over 30 minutes or as an injection over 2 minutes. Daptomycin should not be administered as a 2-minute injection to paediatric patients. Paediatric patients 7 to 17 years old should receive daptomycin infused over 30 minutes. In paediatric patients under 7 years old receiving a 9-12 mg/kg dose, daptomycin should be administered over 60 minutes (see sections 4.2 and 5.2). Preparation of the solution for infusion requires an additional dilution step as detailed below.

Cubicin given as 30 or 60-minute intravenous infusion
A 50 mg/ml concentration of Cubicin 350 mg powder for infusion is obtained by reconstituting the lyophilised product with 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.

The lyophilised product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

*Cubicin 350 mg powder for solution for injection or infusion*
To prepare Cubicin for intravenous infusion, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute or dilute lyophilised Cubicin.
For Reconstitution:

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards

the wall of the vial.

2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Cubicin range in colour from pale yellow to light brown.
5. The reconstituted solution should then be diluted with sodium chloride 9 mg/ml (0.9 %) (typical volume 50 ml).

<u>For Dilution:</u>

1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/ml) from the vial using a new sterile needle that is 21 gauge or smaller in diameter by inverting the vial in order to allow the solution to drain towards the stopper. Using a syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove the required solution from the inverted vial.
2. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
3. Transfer the required reconstituted dose into 50 ml sodium chloride 9 mg/ml (0.9 %).
4. The reconstituted and diluted solution should then be infused intravenously over 30 or 60 minutes as directed in section 4.2.

The following have been shown to be compatible when added to Cubicin containing infusion solutions: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin and lidocaine.

<u>Cubicin given as 2-minute intravenous injection (adult patients only)</u>
Water should not be used for reconstitution of Cubicin for intravenous injection. Cubicin should only be reconstituted with sodium chloride 9 mg/ml (0.9 %).

A 50 mg/ml concentration of Cubicin 350 mg powder for injection is obtained by reconstituting the lyophilised product with 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection.

The lyophilised product takes approximately 15 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

*Cubicin 350 mg powder for solution for injection or infusion*

To prepare Cubicin for intravenous injection, please adhere to the following instructions:

Aseptic technique should be used throughout to reconstitute lyophilised Cubicin.

1. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface. Draw 7 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection into a syringe using a sterile transfer needle that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Cubicin range in colour from pale yellow to light brown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin/ml) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous injection.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
9. The reconstituted solution should then be injected intravenously slowly over 2 minutes as directed in section 4.2.

Cubicin vials are for single-use only.

From a microbiological point of view, the product should be used immediately after reconstitution (see section 6.3).

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

## 7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

Cubicin 350 mg powder for solution for injection or infusion
PLGB 53095/0013

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

## 10 DATE OF REVISION OF THE TEXT

11/11/2021