**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Cubicin 350 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 or water for injections.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A pale yellow to light brown lyophilised powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).
- Complicated skin and soft-tissue infections (cSSTI).
- 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.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or 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

Posology
- cSSTI without concurrent *Staphylococcus aureus* bacteraemia: The recommended dose is 4 mg/kg administered once every 24 hours for 7-14 days or until the infection is resolved (see section 5.1).
- cSSTI with concurrent *Staphylococcus aureus* bacteraemia: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. 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 right-sided infective endocarditis due to *Staphylococcus aureus*: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. The duration of therapy should be in accordance with available official recommendations.

Renal insufficiency
Daptomycin is eliminated primarily by the kidney.

Due to limited clinical experience (see table and footnotes below) Cubicin should only be used in patients with any degree of renal insufficiency (Cr Cl < 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment and renal function should be closely monitored in all patients with some degree of renal insufficiency (see also sections 4.4 and 5.2).

Dose adjustments in patients with renal insufficiency by indication and creatinine clearance

| Indication for use (1) | Creatinine clearance (1) | Dose recommendation (1) | Comments |
|---|---|---|---|
| cSSTI without *S. aureus* bacteraemia | ≥ 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 *S. aureus* bacteraemia | ≥ 50 ml/min | 6 mg/kg once daily | (3) |

(1) The safety and efficacy of the dose interval adjustment has not been clinically evaluated and the recommendation is based on pharmacokinetic modelling data (see sections 4.4 and 5.2).

(2) The same dose adjustments, which are also based solely on modelling are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, Cubicin should be administered following the completion of dialysis on dialysis days (see section 5.2).

(3) There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with S*taphylococcus aureus* bacteraemia who have a creatinine clearance < 50 ml/min. There are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteraemia whose creatinine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min.

Hepatic insufficiency
No dose adjustment is necessary when administering Cubicin to patients with mild or moderate hepatic insufficiency (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic insufficiency (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 insufficiency (see above and section 4.4). However, there are limited data on the safety and efficacy of daptomycin in patients aged > 65 years and caution should be exercised if Cubicin is given to such patients.

Children and adolescents (< 18 years old)
Due to the lack of data on safety and efficacy Cubicin is not recommended for use in children and adolescents (< 18 years of age). See also section 5.2.

Method of administration
Cubicin is given by intravenous infusion (see section 6.6) and administered over a 30 minute period.

## 4.3 Contraindications

Hypersensitivity to the active substance or excipient.

## 4.4 Special warnings and precautions for use

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.

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

Clinical data on the use of Cubicin to treat RIE due to *Staphylococcus aureus* are limited to 19 patients (see "Information from clinical trials" in section 5.1).

The efficacy of Cubicin in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated.

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

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).

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 also 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.
- 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.
- 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 insufficiency (creatinine clearance < 30 ml/min; see also section 4.2) and patients taking other medications known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
- Cubicin should not be administered to patients who are taking other medications 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).

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

Dose adjustment is needed for patients with cSSTI without bacteraemia whose creatinine clearance is < 30 ml/min (see sections 4.2 and 5.2). The safety and efficacy of the dose interval adjustment guidelines provided in section 4.2 are based on pharmacokinetic modelling and have not been clinically evaluated. In addition there are no data to support the use of 6 mg/kg daptomycin once daily in patients with RIE or with cSSTI associated with bacteraemia whose creatinine clearance is < 50 ml/min. 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 insufficiency (creatinine clearance < 80 ml/min) before commencing therapy with Cubicin. Regular monitoring of renal function is advised (see also 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 also section 4.5).

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).

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

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or shortly following treatment.

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

Daptomycin undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. *In vitro* studies have determined that daptomycin does not inhibit or induce the activities of clinically significant human CYP isoforms (1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-related drug interactions are to be expected.

There is limited experience regarding concomitant administration of daptomycin with other medicinal products that may trigger myopathy. However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in patients taking one of these medications at the same time as Cubicin. It is recommended that other medications 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 an apparent prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking daptomycin, consideration should be given to a possible in vitro interaction with the laboratory test. The possibility of erroneous results may be minimised by drawing samples for PT or INR testing near the time of trough plasma concentrations of daptomycin.

## 4.6 Pregnancy and lactation

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

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

It is not known whether daptomycin is excreted in human milk. Therefore, breastfeeding should be discontinued during treatment with 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 Undesirable effects

Clinical Studies
In clinical studies, 2,011 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. 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.

For subjects who received Cubicin, the adverse reactions that were most frequently reported during therapy plus follow-up were: headache, nausea, vomiting, diarrhoea, fungal infections, rash, infusion site reaction, increased Creatine phosphokinase (CPK) and abnormal liver enzymes; Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase.

The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to Common = ≥ 1/100, < 1/10; Uncommon = > 1/1,000, < 1/100; Rare = > 1/10,000, < 1/1,000, Very rare = ≤ 1/10,000:

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

*Infections and Infestations*
Common: Fungal infections
Uncommon: Urinary tract infection

*Blood and lymphatic system disorders*
Uncommon: Thrombocythaemia, anaemia, eosinophilia

*Metabolism and nutrition disorders*
Uncommon: Anorexia, hyperglycaemia

*Psychiatric disorders*
Uncommon: Anxiety, insomnia

*Nervous system disorders*
Common: Headache
Uncommon: Dizziness, paraesthesiae, taste disorder

*Cardiac disorders*
Uncommon: Supraventricular tachycardia, extrasystole

*Vascular disorders*
Uncommon: Flushes, hypertension, hypotension

*Gastrointestinal disorders*
Common: Nausea, vomiting, diarrhoea
Uncommon: Constipation, abdominal pain, dyspepsia, glossitis

*Hepatobiliary disorders*
Uncommon: Jaundice

*Skin and subcutaneous tissue disorders*
Common: Rash
Uncommon: Pruritis, urticaria

*Musculoskeletal, connective tissue and bone disorders*
Uncommon: Myositis, muscle weakness, muscle pain, arthralgia

*Renal and urinary disorders*
Uncommon: Renal insufficiency, including renal impairment and renal failure

*Reproductive system and breast disorders*
Uncommon: Vaginitis

*General disorders and administration site conditions*
Common: Infusion site reactions
Uncommon: Pyrexia, weakness, fatigue, pain

*Investigations*
Common: Liver function tests abnormal (increased AST, ALT and alkaline phosphatase), increased CPK
Uncommon: Electrolyte imbalance, increased serum creatinine, increased myoglobin, Lactic dehydrogenase (LDH) increased

Post-Marketing
Adverse reactions that have been reported Post-Marketing that are not listed above are:

*Immune system disorders*
Hypersensitivity, manifested by isolated spontaneous reports including, but not limited to; pulmonary eosinophilia, vesicobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling.
Anaphylaxis
Infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste.

*Musculoskeletal, connective tissue and bone disorders*
Rhabdomyolysis
When clinical information on the patients was available to make a judgement, approximately 50% of the cases occurred in patients with pre-existing renal insufficiency, or in those receiving concomitant medications known to cause rhabdomyolysis.

*Nervous system disorders*
Peripheral neuropathy

Investigations
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.

### 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

Mode 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 sensitive Gram positive organisms *in vitro*. In animal models AUC/MIC and $C_{max}$/MIC correlate with efficacy and predicted bacterial kill *in vivo* at single doses equivalent to human 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 of resistance to daptomycin has not yet been identified.

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.

Information from clinical trials

In two 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 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.

## 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 for up to 14 days in healthy volunteers. Steady-state concentrations are achieved by the third daily dose.

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

Distribution
The steady state volume of distribution of daptomycin was approximately 0.1 l/kg in healthy adult volunteers, consistent with distribution primarily within the extracellular space. Tissue distribution studies in animals have shown that daptomycin preferentially distributes into highly vascularised tissues and to a lesser degree penetrates 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 volunteers and patients treated with daptomycin, protein binding averaged about 90% including subjects with renal insufficiency.

Metabolism
*In vitro* studies have demonstrated that there is no or limited liver microsomal mediated metabolism of daptomycin in humans and that CYP450 involvement in daptomycin metabolism is minimal. Analysis of plasma samples from subjects who received a 6 mg/kg dose of daptomycin did not show any trace of metabolism, suggesting little to no systemic metabolism.

Furthermore, no metabolites have been observed in plasma following administration of radiolabeled drug to humans based on total radiolabel and microbiologically active concentrations. Of the four minor metabolites detected in urine, two are Phase I oxidative metabolites present in low concentrations.

Elimination
Daptomycin is excreted primarily by the kidneys. Concomitant administration of probenecid and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting minimal to no active tubular secretion of daptomycin.

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

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

Special populations

*Elderly*
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 insufficiency.

*Children and adolescents (< 18 years of age)*
Pharmacokinetic profiles were obtained following single intravenous administration of daptomycin 4 mg/kg in paediatric patients with proven or suspected Gram-positive infection, divided into three age groups (2-6 years, 7-11 years and 12-17 years). The pharmacokinetics of daptomycin following a single 4 mg/kg dose in adolescents aged 12-17 years are generally similar to those of healthy adult subjects with normal renal function with trends towards lower AUC and $C_{max}$ in adolescents. In the younger age groups (2-6 years and 7-11 years), exposure ($C_{max}$ and AUC) and elimination half-life for the same mg/kg dose were reduced compared with adolescents.

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

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

*Renal insufficiency*
Following administration of a single 4 mg/kg or 6 mg/kg dose of daptomycin to subjects with various degrees of renal insufficiency, daptomycin clearance (CL) was reduced and systemic exposure (AUC) was increased. In subjects with severe renal insufficiency (CLcr < 30 ml/min) and end-stage renal disease, exposure (AUC) and elimination half life were increased between 2-3-fold relative to healthy subjects. See section 4.2 regarding the need for dose adjustment.

*Hepatic insufficiency*
The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic insufficiency (Child-Pugh B classification of hepatic insufficiency) 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 insufficiency. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency (Child-Pugh C classification) have not been evaluated.

## 5.3 Preclinical safety data

In studies of clinically-relevant duration (14-28 days), 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 for patients with normal renal function. 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 6 mg/kg once daily in patients with normal renal function.

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.

Reproductive toxicity testing showed no evidence of effects on fertility, embryofetal, 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. The combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section 6.6) at 25°C should not exceed 12 hours (or 24 at 2°C - 8°C).

From a microbiological point of view the product should be used immediately. 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 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator at 2°C - 8°C.
For storage conditions of the reconstituted diluted medicinal product see section 6.3.

## 6.5 Nature and contents of container

Single use 10 ml type 1 clear glass vials with type 1 rubber stoppers and aluminium closures with yellow plastic flip off caps.

## 6.6 Special precautions for disposal and other handling

A 50 mg/ml concentration is obtained by reconstituting with 7 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, or water for injections.

Aseptic technique should be used to reconstitute lyophilised Cubicin. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. 7 ml of either sodium chloride 9 mg/ml solution for injection or water for injections should be slowly injected through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes. 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. Reconstitution is typically complete within 15 minutes.

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.

The reconstituted solution should then be diluted with sodium chloride intravenous infusion (typical volume 50 ml) and infused over 30 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.

Cubicin vials are for single-use only.

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

# 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

# 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/328/001

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

19 January 2006

## 10. DATE OF REVISION OF THE TEXT

## 1. NAME OF THE MEDICINAL PRODUCT

Cubicin 500 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg daptomycin.

One ml provides 50 mg of daptomycin after reconstitution with 10 ml of sodium chloride 9 mg/ml (0.9%) solution or water for injections.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

A pale yellow to light brown lyophilised powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1).
- Complicated skin and soft-tissue infections (cSSTI).
- 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.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or 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

Posology
- cSSTI without concurrent *Staphylococcus aureus* bacteraemia: The recommended dose is 4 mg/kg administered once every 24 hours for 7-14 days or until the infection is resolved (see section 5.1).
- cSSTI with concurrent *Staphylococcus aureus* bacteraemia: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. 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 right-sided infective endocarditis due to *Staphylococcus aureus*: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. The duration of therapy should be in accordance with available official recommendations.

Renal insufficiency
Daptomycin is eliminated primarily by the kidney.

Due to limited clinical experience (see table and footnotes below) Cubicin should only be used in patients with any degree of renal insufficiency (Cr Cl < 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment and renal function should be closely monitored in all patients with some degree of renal insufficiency) (see also sections 4.4 and 5.2).

Dose adjustments in patients with renal insufficiency by indication and creatinine clearance

| Indication for use (1) | Creatinine clearance (1) | Dose recommendation (1) | Comments |
|---|---|---|---|
| cSSTI without *S. aureus* bacteraemia | ≥ 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 *S. aureus* bacteraemia | ≥ 50 ml/min | 6 mg/kg once daily | (3) |

(1) The safety and efficacy of the dose interval adjustment has not been clinically evaluated and the recommendation is based on pharmacokinetic modelling data (see sections 4.4 and 5.2).

(2) The same dose adjustments, which are also based solely on modelling are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, Cubicin should be administered following the completion of dialysis on dialysis days (see section 5.2).

(3) There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with S*taphylococcus aureus* bacteraemia who have a creatinine clearance < 50 ml/min. There are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with *Staphylococcus aureus* bacteraemia whose creatinine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min.

Hepatic insufficiency
No dose adjustment is necessary when administering Cubicin to patients with mild or moderate hepatic insufficiency (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic insufficiency (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 insufficiency (see above and section 4.4). However, there are limited data on the safety and efficacy of daptomycin in patients aged > 65 years and caution should be exercised if Cubicin is given to such patients.

Children and adolescents (< 18 years old)
Due to the lack of data on safety and efficacy Cubicin is not recommended for use in children and adolescents (< 18 years of age). See also section 5.2.

Method of administration
Cubicin is given by intravenous infusion (see section 6.6) and administered over a 30 minute period.

## 4.3 Contraindications

Hypersensitivity to the active substance or excipient.

## 4.4 Special warnings and precautions for use

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.

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

Clinical data on the use of Cubicin to treat RIE due to *Staphylococcus aureus* are limited to 19 patients (see "Information from clinical trials" in section 5.1).

The efficacy of Cubicin in patients with prosthetic valve infections or with left-sided infective endocarditis due to *Staphylococcus aureus* has not been demonstrated.

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

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 for 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).

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 also 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.
- 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.
- 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 insufficiency (creatinine clearance < 30 ml/min; see also section 4.2) and patients taking other medications known to be associated with myopathy (e.g. HMG-CoA reductase inhibitors, fibrates and ciclosporin).
- Cubicin should not be administered to patients who are taking other medications 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).

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

Dose adjustment is needed for patients with cSSTI without bacteraemia whose creatinine clearance is < 30 ml/min (see sections 4.2 and 5.2). The safety and efficacy of the dose interval adjustment guidelines provided in section 4.2 are based on pharmacokinetic modelling and have not been clinically evaluated. In addition there are no data to support the use of 6 mg/kg daptomycin once daily in patients with RIE or with cSSTI associated with bacteraemia whose creatinine clearance is < 50 ml/min. 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 insufficiency (creatinine clearance < 80 ml/min) before commencing therapy with Cubicin. Regular monitoring of renal function is advised (see also 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 also section 4.5).

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).

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

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or shortly following treatment.

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

Daptomycin undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. *In vitro* studies have determined that daptomycin does not inhibit or induce the activities of clinically significant human CYP isoforms (1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-related drug interactions are to be expected.

There is limited experience regarding concomitant administration of daptomycin with other medicinal products that may trigger myopathy. However, some cases of marked rises in CPK levels and cases of rhabdomyolysis occurred in patients taking one of these medications at the same time as Cubicin. It is recommended that other medications 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 an apparent prolongation of PT and elevation of INR. If unexplained abnormalities of PT/INR are observed in patients taking daptomycin, consideration should be given to a possible in vitro interaction with the laboratory test. The possibility of erroneous results may be minimised by drawing samples for PT or INR testing near the time of trough plasma concentrations of daptomycin.

## 4.6 Pregnancy and lactation

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

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

It is not known whether daptomycin is excreted in human milk. Therefore, breastfeeding should be discontinued during treatment with 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 Undesirable effects

Clinical Studies
In clinical studies, 2,011 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. 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.

For subjects who received Cubicin, the adverse reactions that were most frequently reported during therapy plus follow-up were: headache, nausea, vomiting, diarrhoea, fungal infections, rash, infusion site reaction, increased Creatine phosphokinase (CPK) and abnormal liver enzymes; Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase.

The following adverse reactions were reported during therapy and during follow-up with frequencies corresponding to Common = ≥ 1/100, < 1/10; Uncommon = > 1/1,000, < 1/100; Rare = > 1/10,000, < 1/1,000, Very rare = ≤ 1/10,000:

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

*Infections and Infestations*
Common: Fungal infections
Uncommon: Urinary tract infection

*Blood and lymphatic system disorders*
Uncommon: Thrombocythaemia, anaemia, eosinophilia

*Metabolism and nutrition disorders*
Uncommon: Anorexia, hyperglycaemia

*Psychiatric disorders*
Uncommon: Anxiety, insomnia

*Nervous system disorders*
Common: Headache
Uncommon: Dizziness, paraesthesiae, taste disorder

*Cardiac disorders*
Uncommon: Supraventricular tachycardia, extrasystole

*Vascular disorders*
Uncommon: Flushes, hypertension, hypotension

*Gastrointestinal disorders*
Common: Nausea, vomiting, diarrhoea
Uncommon: Constipation, abdominal pain, dyspepsia, glossitis

*Hepatobiliary disorders*
Uncommon: Jaundice

*Skin and subcutaneous tissue disorders*
Common: Rash
Uncommon: Pruritis, urticaria

*Musculoskeletal, connective tissue and bone disorders*
Uncommon: Myositis, muscle weakness, muscle pain, arthralgia

*Renal and urinary disorders*
Uncommon: Renal insufficiency, including renal impairment and renal failure

*Reproductive system and breast disorders*
Uncommon: Vaginitis

*General disorders and administration site conditions*
Common: Infusion site reactions
Uncommon: Pyrexia, weakness, fatigue, pain

*Investigations*
Common: Liver function tests abnormal (increased AST, ALT and alkaline phosphatase), increased CPK
Uncommon: Electrolyte imbalance, increased serum creatinine, increased myoglobin, Lactic dehydrogenase (LDH) increased

Post-Marketing
Adverse reactions that have been reported Post-Marketing that are not listed above are:

*Immune system disorders*
Hypersensitivity, manifested by isolated spontaneous reports including, but not limited to; pulmonary eosinophilia, vesicobullous rash with mucous membrane involvement and sensation of oropharyngeal swelling.
Anaphylaxis
Infusion reactions including the following symptoms: tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope and metallic taste.

*Musculoskeletal, connective tissue and bone disorders*
Rhabdomyolysis
When clinical information on the patients was available to make a judgement, approximately 50% of the cases occurred in patients with pre-existing renal insufficiency, or in those receiving concomitant medications known to cause rhabdomyolysis.

*Nervous system disorders*
Peripheral neuropathy

Investigations
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.

### 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

Mode 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 sensitive Gram positive organisms *in vitro*. In animal models AUC/MIC and $C_{max}$/MIC correlate with efficacy and predicted bacterial kill *in vivo* at single doses equivalent to human 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 of resistance to daptomycin has not yet been identified.

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.

Information from clinical trials

In two 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 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.

## 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 for up to 14 days in healthy volunteers. Steady-state concentrations are achieved by the third daily dose.

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

Distribution
The steady state volume of distribution of daptomycin was approximately 0.1 l/kg in healthy adult volunteers, consistent with distribution primarily within the extracellular space. Tissue distribution studies in animals have shown that daptomycin preferentially distributes into highly vascularised tissues and to a lesser degree penetrates 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 volunteers and patients treated with daptomycin, protein binding averaged about 90% including subjects with renal insufficiency.

Metabolism
*In vitro* studies have demonstrated that there is no or limited liver microsomal mediated metabolism of daptomycin in humans and that CYP450 involvement in daptomycin metabolism is minimal. Analysis of plasma samples from subjects who received a 6 mg/kg dose of daptomycin did not show any trace of metabolism, suggesting little to no systemic metabolism.

Furthermore, no metabolites have been observed in plasma following administration of radiolabeled drug to humans based on total radiolabel and microbiologically active concentrations. Of the four minor metabolites detected in urine, two are Phase I oxidative metabolites present in low concentrations.

Elimination
Daptomycin is excreted primarily by the kidneys. Concomitant administration of probenecid and daptomycin has no effect on daptomycin pharmacokinetics in humans suggesting minimal to no active tubular secretion of daptomycin.

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

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

Special populations

*Elderly*
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 insufficiency.

*Children and adolescents (< 18 years of age)*
Pharmacokinetic profiles were obtained following single intravenous administration of daptomycin 4 mg/kg in paediatric patients with proven or suspected Gram-positive infection, divided into three age groups (2-6 years, 7-11 years and 12-17 years). The pharmacokinetics of daptomycin following a single 4 mg/kg dose in adolescents aged 12-17 years are generally similar to those of healthy adult subjects with normal renal function with trends towards lower AUC and $C_{max}$ in adolescents. In the younger age groups (2-6 years and 7-11 years), exposure ($C_{max}$ and AUC) and elimination half-life for the same mg/kg dose were reduced compared with adolescents.

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

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

*Renal insufficiency*
Following administration of a single 4 mg/kg or 6 mg/kg dose of daptomycin to subjects with various degrees of renal insufficiency, daptomycin clearance (CL) was reduced and systemic exposure (AUC) was increased. In subjects with severe renal insufficiency (CLcr < 30 ml/min) and end-stage renal disease, exposure (AUC) and elimination half life were increased between 2-3-fold relative to healthy subjects. See section 4.2 regarding the need for dose adjustment.

*Hepatic insufficiency*
The pharmacokinetics of daptomycin is not altered in subjects with moderate hepatic insufficiency (Child-Pugh B classification of hepatic insufficiency) 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 insufficiency. The pharmacokinetics of daptomycin in patients with severe hepatic insufficiency (Child-Pugh C classification) have not been evaluated.

## 5.3 Preclinical safety data

In studies of clinically-relevant duration (14-28 days), 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 for patients with normal renal function. 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 6 mg/kg once daily in patients with normal renal function.

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.

Reproductive toxicity testing showed no evidence of effects on fertility, embryofetal, 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. The combined storage time (reconstituted solution in vial and diluted solution in infusion bag; see section 6.6) at 25°C should not exceed 12 hours (or 24 at 2°C - 8°C).

From a microbiological point of view the product should be used immediately. 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 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store in a refrigerator at 2°C - 8°C.

For storage conditions of the reconstituted diluted medicinal product see section 6.3.

### 6.5 Nature and contents of container

Single use 10 ml type 1 clear glass vials with type 1 rubber stoppers and aluminium closures with blue plastic flip off caps.

### 6.6 Special precautions for disposal and other handling

A 50 mg/ml concentration is obtained by reconstituting with 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, or water for injections.

Aseptic technique should be used to reconstitute lyophilised Cubicin. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. 10 ml of either sodium chloride 9 mg/ml solution for injection or water for injections should be slowly injected through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes. 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. Reconstitution is typically complete within 15 minutes.

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.

The reconstituted solution should then be diluted with sodium chloride intravenous infusion (typical volume 50 ml) and infused over 30 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.

Cubicin vials are for single-use only.

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

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/328/002

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

19 January 2006

## 10. DATE OF REVISION OF THE TEXT

# ANNEX II

## A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

## B. CONDITIONS OF THE MARKETING AUTHORISATION

## A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharmaceuticals UK Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

## B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

*Pharmacovigilance system*
The MAH must ensure that the system of pharmacovigilance, as described in the amended version dated 4th December 06 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

*Risk Management Plan*
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2.1 dated 18th July 07 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Cubicin 350 mg powder for concentrate for solution for infusion
daptomycin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 350 mg daptomycin.

**3. LIST OF EXCIPIENTS**

Sodium hydroxide

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use for directions on reconstitution.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP
Read the leaflet for the shelf life of the reconstituted product

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/328/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cubicin 350 mg powder for concentrate for solution for infusion
daptomycin

For intravenous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 350 mg daptomycin.

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Cubicin 500 mg powder for concentrate for solution for infusion
daptomycin

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 500 mg daptomycin.

**3. LIST OF EXCIPIENTS**

Sodium hydroxide

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use for directions on reconstitution.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP
Read the leaflet for the shelf life of the reconstituted product

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/328/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cubicin 500 mg powder for concentrate for solution for infusion
daptomycin

For intravenous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 500 mg daptomycin.

## 6. OTHER

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Cubicin 350 mg powder for concentrate for solution for infusion**
**daptomycin**

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

**In this leaflet**:


## 1. WHAT CUBICIN IS AND WHAT IT IS USED FOR

The active substance in Cubicin powder for concentrate for solution for infusion is daptomycin. Daptomycin is an antibiotic that can stop the growth of certain bacteria. Cubicin is used in adults to treat infections of the skin and the tissues below the skin. It is also used in adults to treat infections in the tissues that line the inside of the heart (including heart valves) which are caused by a bacterium called *Staphyloccocus aureus* and to treat infections in the blood caused by the same bacterium when associated with skin or heart infection.

Depending on the type of infection(s) that you have, your doctor may also prescribe other antibiotics while you are receiving treatment with Cubicin.

## 2. BEFORE YOU ARE GIVEN CUBICIN

**You should not be given Cubicin**
If you are allergic (hypersensitive) to daptomycin or to sodium hydroxide.
If this applies to you, tell your doctor or nurse. If you think you may be allergic, ask your doctor or nurse for advice.

**Take special care with Cubicin**
- If you have, or have previously had kidney problems. Your doctor may need to change the dose of Cubicin (see section 3 of this leaflet).
- Occasionally, patients receiving Cubicin may develop tender or aching muscles or muscle weakness (see section 4 of this leaflet for more information). If this happens tell your doctor. Your doctor will make sure you have a blood test and will advise whether or not to continue with Cubicin. The symptoms generally go away within a few days of stopping Cubicin.
- If you are very overweight. There is a possibility that your blood levels of Cubicin could be higher than those found in persons of average weight and you may need careful monitoring in case of side effects.

If any of these applies to you, tell your doctor or nurse before you are given Cubicin.

**Tell your doctor if you develop any of the following symptoms:**
- Any unusual tingling or numbness of the hands or feet, loss of feeling or difficulties with movements. If this happens, tell your doctor who will decide whether you should continue the treatment.
- Diarrhoea, especially if you notice blood.
- Cubicin may interfere with laboratory tests that measure how well your blood is clotting. The results can suggest poor blood clotting when, in fact, there is no problem. Therefore it is important that your doctor takes into account that you are receiving Cubicin. Please inform your doctor that you are on treatment with Cubicin.

Your doctor will perform blood tests to monitor the health of your muscles both before you start treatment and frequently during treatment with Cubicin.

**Use in children**
The use of Cubicin in children has not been studied and is therefore not recommended.

**Use in elderly**
People over the age of 65 can be given the same dose as other adults, provided their kidneys are working well.

**Taking other medicines**
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
It is particularly important that you mention the following:
- Medicines called statins or fibrates (to lower cholesterol) or ciclosporin. It is possible that the risk of side effects affecting the muscles may be higher when any of these medicines (and some others that can affect muscles) is taken during treatment with Cubicin. Your doctor may decide not to give you Cubicin or to stop the other medicine for a while.
- Pain killing medicines called non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (e.g. celecoxib). These could interfere with the effects of Cubicin in the kidney.

**Pregnancy and breast-feeding**
Cubicin is not usually given to pregnant women. Tell your doctor if you are pregnant, think you may be pregnant, or are planning to become pregnant.

Do not breast-feed if you are receiving Cubicin, because it may pass into your breast milk and could affect the baby.

**Driving and using machines**
Cubicin has no known effects on the ability to drive or use machines.

## 3. HOW CUBICIN IS GIVEN

Cubicin will usually be given to you by a doctor or a nurse.

The dose will depend on how much you weigh and the type of infection being treated. The usual dose for adults is 4 mg for every kilogram (kg) of body weight once daily for skin infections or 6 mg for every kg of body weight once daily for a heart infection or a blood infection associated with skin or heart infection. This dose is given directly into your blood stream (into a vein) over a period of about 30 minutes. The same dose is recommended in people aged over 65 years provided their kidneys are working well.

If your kidneys do not work well, you may receive Cubicin less often, e.g. once every other day. If you are receiving dialysis, and your next dose of Cubicin is due on a dialysis day, you will be usually given Cubicin after the dialysis session.

A course of treatment usually lasts for 1 to 2 weeks for skin infections. For blood or heart infections and skin infections your doctor will decide how long you should be treated.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Cubicin can cause side effects, although not everybody gets them.

**Some side effects are very rare** (reported in less than 1 in 10,000 patients given Cubicin)
A hypersensitivity reaction (serious allergic reaction including anaphylaxis) has been reported, in some cases during the infusion. This serious allergic reaction needs immediate medical attention. Tell your doctor or nurse straight away if you experience any of the following symptoms:
- Chest pain or tightness
- Rash with blistering, sometimes affecting the mouth and genitals
- Swelling around throat
- Rapid or weak pulse
- Wheezing
- Fever
- Shivering or trembling
- Hot flushes
- Dizziness
- Fainting
- Metallic taste

Tell your doctor if you experience unexplained muscle pain, tenderness, or weakness. In very rare cases (reported in less than 1 in every 10,000 patients), muscle problems can be serious, including muscle breakdown (rhabdomyolysis), which can result in kidney damage.

Cubicin may also cause other side effects:

**Some side effects are common** (reported in more than 1 in 100 patients given Cubicin)
- Fungal infections such as thrush,
- Headache,
- Diarrhoea, felling sick (nausea) or being sick (vomiting),
- Skin rash,
- Pain, itchiness or redness at the site of infusion,
- Blood testing showing higher levels of liver enzymes or creatine phosphokinase (CPK).

**Some side effects are uncommon** (reported in more than 1 in 1,000 but less than 1 in 100 patients given Cubicin)
- Urinary tract infection,
- Blood disorders (e.g increased number of small blood particles called platelets, which may increase the tendency for blood clotting, decreased number of red blood cells, known as anaemia, or higher levels of certain types of white blood cells),
- Decreased appetite,
- Dizziness, anxiety, difficulty in sleeping, tingling or numbness of the hands or feet, taste disturbance,
- Changes in heart rhythm, flushes, high or low blood pressure,
- Constipation, abdominal pain, indigestion, inflammation of the tongue,
- Yellowing of the skin and eyes,
- Itchy rash of skin,
- Muscle pain or weakness, joint pain,
- kidney problems,
- Inflammation and irritation of the vagina,
- General pain or weakness, fever, tiredness,

- Blood test showing increased levels of blood sugar, serum creatinine, myoglobin, or lactic dehydrogenase (LDH), or imbalance of salts.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

## 5. HOW TO STORE CUBICIN

Your doctor, nurse or pharmacist knows how to store Cubicin properly.

## 6. FURTHER INFORMATION

**What Cubicin contains**
- The active substance is daptomycin.
- The other ingredient is sodium hydroxide.

**What Cubicin looks like and contents of the pack**
Cubicin is supplied as a pale yellow to light brown powder in a glass vial. It is mixed with a solvent to form a liquid before it is administered.

Cubicin is available in packs containing 1 vial.

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**Manufacturer**
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Novartis Pharmaceuticals UK Ltd.
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**This leaflet was last approved in**

**INFORMATION FOR THE HEALTHCARE PROFESSIONALS**

Important: Please refer to the Summary of Product Characteristics before prescribing.

Instructions for use and handling

350 mg presentation: a 50 mg/ml concentration can be achieved by reconstituting with 7 ml of 0.9% sodium chloride intravenous infusion.

Vials of 350 mg/vial can also be reconstituted with sterile water for injections. Cubicin (daptomycin) is not physically or chemically compatible with glucose-containing solutions.

Aseptic technique should be used to reconstitute lyophilised Cubicin. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. 7 ml of either sodium chloride 9 mg/ml solution for injection or water for injections should be slowly injected through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes. 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. Reconstitution is typically complete within 15 minutes.

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.

The reconstituted solution should then be diluted with sodium chloride intravenous infusion (typical volume 50 ml) and infused over 30 minutes.

Chemical and physical in-use stability on the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours if stored under refrigeration (2 to 8°C). The combined time (vial and infusion bag) at 25°C should not exceed 12 hours (24 hours if refrigerated).

Stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 24 hours if stored under refrigeration at 2 to 8°C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

Cubicin is not physically or chemically compatible with glucose-containing solutions.
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.

This medicinal product must not be mixed with other medicinal products except those mentioned above.

Cubicin vials are for single-use only. Any unused portion remaining in the vial should be discarded.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Cubicin 500 mg powder for concentrate for solution for infusion**
**daptomycin**

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

**In this leaflet**:


## 1. WHAT CUBICIN IS AND WHAT IT IS USED FOR

The active substance in Cubicin powder for concentrate for solution for infusion is daptomycin. Daptomycin is an antibiotic that can stop the growth of certain bacteria. Cubicin is used in adults to treat infections of the skin and the tissues below the skin. It is also used in adults to treat infections in the tissues that line the inside of the heart (including heart valves) which are caused by a bacterium called *Staphyloccocus aureus* and to treat infections in the blood caused by the same bacterium when associated with skin or heart infection.

Depending on the type of infection(s) that you have, your doctor may also prescribe other antibiotics while you are receiving treatment with Cubicin.

## 2. BEFORE YOU ARE GIVEN CUBICIN

**You should not be given Cubicin**
If you are allergic (hypersensitive) to daptomycin or to sodium hydroxide.
If this applies to you, tell your doctor or nurse. If you think you may be allergic, ask your doctor or nurse for advice.

**Take special care with Cubicin**
- If you have, or have previously had kidney problems. Your doctor may need to change the dose of Cubicin (see section 3 of this leaflet).
- Occasionally, patients receiving Cubicin may develop tender or aching muscles or muscle weakness (see section 4 of this leaflet for more information). If this happens tell your doctor. Your doctor will make sure you have a blood test and will advise whether or not to continue with Cubicin. The symptoms generally go away within a few days of stopping Cubicin.
- If you are very overweight. There is a possibility that your blood levels of Cubicin could be higher than those found in persons of average weight and you may need careful monitoring in case of side effects.

If any of these applies to you, tell your doctor or nurse before you are given Cubicin.

**Tell your doctor if you develop any of the following symptoms:**
- Any unusual tingling or numbness of the hands or feet, loss of feeling or difficulties with movements. If this happens, tell your doctor who will decide whether you should continue the treatment.
- Diarrhoea, especially if you notice blood.
- Cubicin may interfere with laboratory tests that measure how well your blood is clotting. The results can suggest poor blood clotting when, in fact, there is no problem. Therefore it is important that your doctor takes into account that you are receiving Cubicin. Please inform your doctor that you are on treatment with Cubicin.

Your doctor will perform blood tests to monitor the health of your muscles both before you start treatment and frequently during treatment with Cubicin.

**Use in children**
The use of Cubicin in children has not been studied and is therefore not recommended.

**Use in elderly**
People over the age of 65 can be given the same dose as other adults, provided their kidneys are working well.

**Taking other medicines**
Please tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
It is particularly important that you mention the following:
- Medicines called statins or fibrates (to lower cholesterol) or ciclosporin. It is possible that the risk of side effects affecting the muscles may be higher when any of these medicines (and some others that can affect muscles) is taken during treatment with Cubicin. Your doctor may decide not to give you Cubicin or to stop the other medicine for a while.
- Pain killing medicines called non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (e.g. celecoxib). These could interfere with the effects of Cubicin in the kidney.

**Pregnancy and breast-feeding**
Cubicin is not usually given to pregnant women. Tell your doctor if you are pregnant, think you may be pregnant, or are planning to become pregnant.

Do not breast-feed if you are receiving Cubicin, because it may pass into your breast milk and could affect the baby.

**Driving and using machines**
Cubicin has no known effects on the ability to drive or use machines.

## 3. HOW CUBICIN IS GIVEN

Cubicin will usually be given to you by a doctor or a nurse.

The dose will depend on how much you weigh and the type of infection being treated. The usual dose for adults is 4 mg for every kilogram (kg) of body weight once daily for skin infections or 6 mg for every kg of body weight once daily for a heart infection or a blood infection associated with skin or heart infection. This dose is given directly into your blood stream (into a vein) over a period of about 30 minutes. The same dose is recommended in people aged over 65 years provided their kidneys are working well.

If your kidneys do not work well, you may receive Cubicin less often, e.g. once every other day. If you are receiving dialysis, and your next dose of Cubicin is due on a dialysis day, you will be usually given Cubicin after the dialysis session.

A course of treatment usually lasts for 1 to 2 weeks for skin infections. For blood or heart infections and skin infections your doctor will decide how long you should be treated.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Cubicin can cause side effects, although not everybody gets them.

**Some side effects are very rare** (reported in less than 1 in 10,000 patients given Cubicin)
A hypersensitivity reaction (serious allergic reaction including anaphylaxis) has been reported, in some cases during the infusion. This serious allergic reaction needs immediate medical attention. Tell your doctor or nurse straight away if you experience any of the following symptoms:
- Chest pain or tightness
- Rash with blistering, sometimes affecting the mouth and genitals
- Swelling around throat
- Rapid or weak pulse
- Wheezing
- Fever
- Shivering or trembling
- Hot flushes
- Dizziness
- Fainting
- Metallic taste

Tell your doctor if you experience unexplained muscle pain, tenderness, or weakness. In very rare cases (reported in less than 1 in every 10,000 patients), muscle problems can be serious, including muscle breakdown (rhabdomyolysis), which can result in kidney damage.

Cubicin may also cause other side effects:

**Some side effects are common** (reported in more than 1 in 100 patients given Cubicin)
- Fungal infections such as thrush,
- Headache,
- Diarrhoea, felling sick (nausea) or being sick (vomiting),
- Skin rash,
- Pain, itchiness or redness at the site of infusion,
- Blood testing showing higher levels of liver enzymes or creatine phosphokinase (CPK).

**Some side effects are uncommon** (reported in more than 1 in 1,000 but less than 1 in 100 patients given Cubicin)
- Urinary tract infection,
- Blood disorders (e.g increased number of small blood particles called platelets, which may increase the tendency for blood clotting, decreased number of red blood cells, known as anaemia, or higher levels of certain types of white blood cells),
- Decreased appetite,
- Dizziness, anxiety, difficulty in sleeping, tingling or numbness of the hands or feet, taste disturbance,
- Changes in heart rhythm, flushes, high or low blood pressure,
- Constipation, abdominal pain, indigestion, inflammation of the tongue,
- Yellowing of the skin and eyes,
- Itchy rash of skin,
- Muscle pain or weakness, joint pain,
- kidney problems,
- Inflammation and irritation of the vagina,
- General pain or weakness, fever, tiredness,

- Blood test showing increased levels of blood sugar, serum creatinine, myoglobin, or lactic dehydrogenase (LDH), or imbalance of salts.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

## 5. HOW TO STORE CUBICIN

Your doctor, nurse or pharmacist knows how to store Cubicin properly.

## 6. FURTHER INFORMATION

**What Cubicin contains**
- The active substance is daptomycin.
- The other ingredient is sodium hydroxide.

**What Cubicin looks like and contents of the pack**
Cubicin is supplied as a pale yellow to light brown powder in a glass vial. It is mixed with a solvent to form a liquid before it is administered.

Cubicin is available in packs containing 1 vial.

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**Manufacturer**
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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**This leaflet was last approved in**

**INFORMATION FOR THE HEALTHCARE PROFESSIONALS**

Important: Please refer to the Summary of Product Characteristics before prescribing.

Instructions for use and handling

500 mg presentation: a 50 mg/ml concentration can be achieved by reconstituting with 10 ml of 0.9% sodium chloride intravenous infusion.

Vials of 500 mg/vial can also be reconstituted with sterile water for injections. Cubicin (daptomycin) is not physically or chemically compatible with glucose-containing solutions.

Aseptic technique should be used to reconstitute lyophilised Cubicin. The polypropylene flip off cap should be removed to expose the central portions of the rubber stopper. 10 ml of either sodium chloride 9 mg/ml solution for injection or water for injections should be slowly injected through the centre of the rubber stopper into the vial pointing the needle towards the wall of the vial. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes. 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. Reconstitution is typically complete within 15 minutes.

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.

The reconstituted solution should then be diluted with sodium chloride intravenous infusion (typical volume 50 ml) and infused over 30 minutes.

Chemical and physical in-use stability on the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours if stored under refrigeration (2 to 8°C). The combined time (vial and infusion bag) at 25°C should not exceed 12 hours (24 hours if refrigerated).

Stability of the diluted solution in infusion bags is established as 12 hours at 25°C or 24 hours if stored under refrigeration at 2 to 8°C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

Cubicin is not physically or chemically compatible with glucose-containing solutions.
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.

This medicinal product must not be mixed with other medicinal products except those mentioned above.

Cubicin vials are for single-use only. Any unused portion remaining in the vial should be discarded.