ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cubicin 350 mg powder for solution for injection or infusion
Cubicin 500 mg powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Cubicin 500 mg powder for solution for injection or infusion
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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cubicin is indicated for the treatment of the following infections (see sections 4.4 and 5.1).
- Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus.* It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- Adult and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated with cSSTI.

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

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

4.2 Posology and method of administration

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

Posology

Adults

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

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

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

Renal impairment

Daptomycin is eliminated primarily by the kidney.

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

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

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

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

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

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

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

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

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

Paediatric patients below the age of one year should not be given Cubicin due to the risk of potential effects on muscular, neuromuscular and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs (see section 5.3).

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

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

Enterococcal infections
There is insufficient evidence to be able to draw any conclusions regarding the possible clinical efficacy of Cubicin against infections due to enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*. In addition, dose regimens of daptomycin that might be appropriate for the treatment of enterococcal infections, with or without bacteraemia, have not been identified. Failures with daptomycin in the treatment of enterococcal infections that were mostly accompanied by bacteraemia have been reported. In some instances treatment failure has been associated with the selection of organisms with reduced susceptibility or frank resistance to daptomycin (see section 5.1).

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

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

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

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