Cubicin® – A Guide to Dosing

Cubicin

Indicated for the treatment of the following infection in adults[1] and paediatric patients (1 to 17 years of age)[5]:

- Complicated skin and soft tissue infections (cSSTI)

Indicated for the treatment of the following infections in adults:

- 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.
- *Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with cSSTI

Bactericidal activity[2] against a broad range of Gram-positive bacteria[3,4]

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)

Administered once daily

Recommendations[1]

Increases in plasma creatine phosphokinase (CPK) levels associated with musculoskeletal adverse events have been reported during Cubicin therapy

- Concomitant administration of Cubicin and other medicinal products associated with myopathy (e.g. statins, fibrates and cyclosporine) should be avoided, unless the benefit outweighs the risk
- CPK should be measured at baseline and at regular intervals (at least once weekly) during therapy in all patients
- More frequent monitoring of CPK levels (e.g. every 2–3 days at least during the first two weeks of treatment) should be carried out in patients who are at higher risk of developing myopathies:
    - Those with any degree of renal insufficiency (creatinine clearance <80 ml/min)
    - Patients taking other medicinal products known to be associated with myopathy

Cases of interference between Cubicin and particular reagents (recombinant thromboplastin) used in some coagulation assays (Prothrombin Time [PT]; International Normalized Ratio [INR])

have been reported. The interference leads to false results, with an apparent prolongation of PT and elevation of INR

- Drawing samples near the time of Cubicin trough plasma concentrations may minimize the potential for erroneous results

Results from the most recent study[5] in paediatric population indicated that compared with adults, children show progressively higher daptomycin clearance and higher volume of distribution with decreasing age.

- Hence, higher doses will be required in children and will vary by age groups in order to produce exposures equivalent to those seen for efficacy in adults
- In the paediatric population, daptomycin administered at doses of 5 mg/kg (12 to 17 years), 7 mg/kg (7 to 11 years), 9 mg/kg (2 to 6 years) and 10 mg/kg (1 to < 2 years) for up to 14 days was safe and effective in the treatment of cSSTI caused by Gram-positive pathogens

Because higher clearance of daptomycin was observed in previous single-dose paediatric PK studies[6,7,8] and in the most recent paediatric study described above[5]

- Age-adjusted daptomycin doses were given once daily up to 14 days in order to achieve exposures equivalent to those documented in adult cSSTI studies
- Dosing is age-dependent and weight-dependent
- Both safety and efficacy results are consistent with those from adult studies and with data from the literature

Cubicin 4 mg/kg

INDICATION

- cSSTI[1]

DOSAGE

Cubicin 4 mg/kg administered as a once-daily 2-minute i.v. injection or 30-minute i.v. infusion

Cubicin should be reconstituted to a 50 mg/ml solution with:

- 350 mg vial: 7 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)
- 500 mg vial: 10 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

Volume of Cubicin 50 mg/ml solution required:

- Volume in ml = Bodyweight (kg) x 4/50

This volume may be injected intravenously over 2 minutes or diluted with 0.9% sodium chloride (typical volume 50 ml) for infusion over 30 minutes

Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)
46	3.68	66	5.28	86	6.88	106	8.48
48	3.84	68	5.44	88	7.04	108	8.64
50	4.00	70	5.60	90	7.20	110	8.80
52	4.16	72	5.76	92	7.36	112	8.96
54	4.32	74	5.92	94	7.52	114	9.12
56	4.48	76	6.08	96	7.68	116	9.28
58	4.64	78	6.24	98	7.84	118	9.44
60	4.80	80	6.40	100	8.00	120	9.60
62	4.96	82	6.56	102	8.16	122	9.76
64	5.12	84	6.72	104	8.32	124	9.92

Cubicin 6 mg/kg

INDICATIONS

- RIE due to *Staphylococcus aureus*[1]
- *Staphylococcus aureus* bacteraemia when associated with RIE or with cSSTI[1]

DOSAGE

Cubicin 6 mg/kg administered as a once-daily 2-minute i.v. injection or 30-minute i.v. infusion

Cubicin should be reconstituted to a 50 mg/ml solution with:

- 350 mg vial: 7 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)
- 500 mg vial: 10 ml of 9 mg/ml (0.9%) sodium chloride solution (injection or infusion)

Volume of Cubicin 50 mg/ml solution required:

- Volume in ml = Bodyweight (kg) x 6/50

This volume may be injected intravenously over 2 minutes or diluted with 0.9% sodium chloride (typical volume 50 ml) for infusion over 30 minutes

Weight (kg)	Dose (ml)		Weight (kg)	Dose (ml)
46	5.52		66	7.92
48	5.76		68	8.16
50	6.00		70	8.40
52	6.24		72	8.64
54	6.48		74	8.88
56	6.72		76	9.12
58	6.96		78	9.36
60	7.20		80	9.60
62	7.44		82	9.84
64	7.68			

Cubicin Dosing in Paediatric Population for cSSTI

DOSAGE

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

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

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

Dose Adjustment in Renal Impairment in Adults

Indication for use	Creatinine clearance	Dose recommednation	Comments
cSSTI without *S. aureus* bacteraemia	≥30 ml/min	4 mg/kg once daily	
	<30 ml/min	4 mg/kg every 48 hours	(1,2)
RIE or cSSTI associated with *S. aureus* bacteraemia	≥30 ml/min	6 mg/kg once daily	
	<30 ml/min	6 mg/kg every 48 hours	(1.2)

(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
(2) The same dose adjustments, which are based on pharmacokinetic data in volunteers including PK modelling results, are recommended for patients on haemodialysis (HD) or continuous ambulatory peritoneal dialysis. Whenever possible, Cubicin should be administered following the completion of dialysis on dialysis days

Response to treatment, renal function and plasma CPK should be closely monitored in all patients with renal Impairment

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Cubicin.

REFERENCES: 1. Cubicin EU SmPC. **2.** Raja A *et al.* Daptomycin. *Nat Rev Drug Discov*. 2003;2:943–944. **3.** Rybak MJ *et al. In vitro* activities of daptomycin, vancomycin, linezolid and quinupristan-dalfopristan against staphylococci and enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother.* 2000;44:1062–1066. **4.** Tedesco KL and Rybak MJ. Daptomycin. *Pharmacotherapy.* 2004;24:41–57. **5** Study DAP-PEDS-07-03 **6**. Study DAP-PEDS-05-01. **7**. Study DAP-PEDS-07-02. **8.** Study DAP-PEDS-09-01

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions for CUBICIN at ADR Reporting at: www.medicinesauthority.gov.mt/adrportal.

Adverse events should also be reported to Merck Sharp & Dohme Cyprus Ltd by calling **800 7 4433** or at **malta_info@merck.com**.