Cubicin® – A Guide to Dosing

Cubicin (Daptomycin) powder for solution for injection or infusion

Indications (see Annex 2 for SmPC) [Ref. 5.3.5.1: P017]:

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

Bactericidal activity [Ref. 5.4: 04J2D7] against a broad range of Gram-positive bacteria [Ref. 5.4: 04J2D8] [Ref. 5.4: 04J2DC]

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 (see Annex 2 for SmPC)

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 studies [Ref. 5.3.5.1: P017] [Ref. 5.3.5.1: 04L997] in paediatric populations 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 has a positive risk-benefit profile in the treatment of cSSTI caused by Gram-positive pathogens
- In the paediatric population, daptomycin administered at doses of 7 mg/kg (12 to 17 years), 9 mg/kg (7 to 11 years), or 12 mg/kg (1 to 6 years) for up to 42 days has a positive risk-benefit profile in the treatment of *Staphylococcus aureus* bacteremia associated with cSSTI.

Because higher clearance of daptomycin was observed in previous single-dose paediatric PK studies [Ref. 5.3.3.2: 04FTKP] [Ref. 5.3.3.2: 04FVHB] [Ref. 5.3.3.2: 04FVN7] and in the most recent paediatric studies described above [Ref. 5.3.5.1: P017] [Ref. 5.3.5.1: 04L997].

- 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
- Age-adjusted daptomycin doses were given once daily up to 42 days in order to achieve exposures equivalent to those documented in adult SAB study.
- 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 in adult patients without *Staphylococcus aureus* bacteremia (see Annex 2 for SmPC)

DOSAGE

Cubicin 4 mg/kg administered as a once-daily 2-minute intravenous (IV) injection or 30-minute IV 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

Dose Adjustment for Renal Impairment in Adults

Indication for use	Creatinine clearance	Dose recommendation	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)

(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 adult 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**.**

Cubicin 6 mg/kg

INDICATIONS

- RIE due to *Staphylococcus aureus* in adult patients (see Annex 2 for SmPC)
- *Staphylococcus aureus* bacteraemia when associated with RIE or with cSSTI in adult patients (see Annex 2 for SmPC)

DOSAGE

Cubicin 6 mg/kg administered as a once-daily 2-minute IV injection or 30-minute IV 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)	Weight (kg)	Dose (ml)	Weight (kg)	Dose (ml)
46	5.52	66	7.92	86	10.32	106	12.72
48	5.76	68	8.16	88	10.56	108	12.96
50	6.00	70	8.40	90	10.80	110	13.20
52	6.24	72	8.64	92	11.04	112	13.44
54	6.48	74	8.88	94	11.28	114	13.68
56	6.72	76	9.12	96	11.52	116	13.92
58	6.96	78	9.36	98	11.76	118	14.16
60	7.20	80	9.60	100	12.00	120	14.40
62	7.44	82	9.84	102	12.24	122	14.64
64	7.68	84	10.08	104	12.48	124	14.88

Dose Adjustment in Renal Impairment in Adults

Indication for use	Creatinine clearance	Dose recommendation	Comments
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 adult 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.

Cubicin Dosing in Paediatric Patients for Treatment of cSSTI, without *Staphylococcus aureus* bacteremia

DOSAGE

In the treatment of paediatric patients (1 to 17 years of age) with complicated skin and soft-tissue infections (cSSTI) without associated *S. aureus* bacteremia, Cubicin is given by intravenous (IV) infusion over a 30 or 60-minute period depending on the age of the patient (see also dosing and administration section for Pediatric Patients in the SmPC in Annex 2).

Ages	Daptomycin Dose	Infusion Time	Treatment Duration
12 to 17 years	5 mg/kg once daily	30 minutes	Up to 14 days
7 to 11 years	7 mg/kg once daily	30 minutes	
2 to 6 years	9 mg/kg once daily	60 minutes	
1 to <2 years	10 mg/kg once daily	60 minutes	

Cubicin Dosing in Paediatric Patients for Treatment of *Staphylococcus aureus* bacteremia, when associated with cSSTI

DOSAGE

In the treatment of paediatric patients (1 to 17 years of age) with *S. aureus* bacteremia when associated with complicated skin and soft-tissue infections (cSSTI), Cubicin is given by intravenous (IV) infusion over a 30 or 60-minute period depending on the age of the patient (see also dosing and administration section for Pediatric Patients in the SmPC in Annex 2):

Ages	Daptomycin Dose	Infusion Time	Treatment Duration
12 to 17 years	7 mg/kg once daily	30 minutes	Up to 42 days
7 to 11 years	9 mg/kg once daily	30 minutes	
1 to 6 years	12 mg/kg once daily	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. The dosage regimen for CUBICIN in paediatric patients with renal impairment has not been established.

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

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 (daptomycin) 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**.

REFERENCES

[Ref. 5.3.3.2: 04FTKP]	Clinical Study Report, Multicenter Study: An Evaluation of the Pharmacokinetics of a Single Dose Of Daptomycin (4 mg/kg) in Pediatric Patients Aged Two to Seventeen Years Who Are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-Positive Infection (Protocol 028).
[Ref. 5.3.3.2: 04FVHB]	Clinical Study Report, Multicenter Study: An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged Two to Six Years Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection (Protocol 023).
[Ref. 5.3.3.2: 04FVN7]	Clinical Study Report, Multicenter Study: An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged 3 Months to Twenty-four Months Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Bacterial Infection (Protocol 018).
[Ref. 5.3.5.1: 04L997]	Clinical Study Report, Multicenter Study: A Comparative Evaluation of the Safety and Efficacy of Daptomycin Versus Standard of Care in Pediatric Subjects One - Seventeen Years of Age with Bacteremia Caused by Staphylococcus aureus (Protocol 005).
[Ref. 5.3.5.1: P017]	Clinical Study Report: An Evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Pediatric Subjects Aged one to Seventeen Years with Complicated Skin and Skin Structure Infections Caused by Gram-positive Pathogens (Protocol 017).

[Ref. 5.4: 04GRR4] Humphries RM, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. Clin Microbiol Rev. 2013 Oct;26(4):759-80.

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[Ref. 5.4: 04J50J] bioMerieux. Etest Customer Information Sheet: Etest Daptomycin (DPC) – technical variables that may cause discrepancies in MIC results [Internet]. France: bioMerieux; 2012. Available from: https://kaldur.landspitali.is/gaeda/gnhsykla.nsf/5e27f2e5a88c898e00256500003c98c2/2030bf44cbec6e0e00256f23003f2169/$FILE/Etest_Daptomycin_MIC_variables.pdf

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