



A guide to dosing

CUBICIN

- ▶ Indicated for the treatment of the following infections in adults:¹
 - Complicated skin and soft tissue infections (cSSTIs)
 - Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*
 - *Staphylococcus aureus* bacteraemia when associated with RIE or with cSSTI
- ▶ Bactericidal activity² against a broad range of Gram-positive bacteria^{3,4}
- ▶ Administered once daily



 **CUBICIN**[®]
daptomycin

DOSE ADJUSTMENT IN RENAL INSUFFICIENCY

Indication for use	Creatinine clearance	Dose recommendation	Comments
cSSTI without <i>S. aureus</i> 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 <i>S. aureus</i> 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 insufficiency

RECOMMENDATIONS¹

- ▶ 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 ciclosporin) 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 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



CUBICIN[®] 4 mg/kg

INDICATIONS

- ▶ cSSTIs¹
- ▶ cSSTI with bacteraemia (see 6 mg/kg dose)

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:

$$\text{Volume in ml} = \text{Bodyweight (kg)} \times 4/50$$

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

DOSAGE RECOMMENDATIONS

CUBICIN

4mg/kg

Patient weight (kg)

Volume of Cubicin 50 mg/ml
solution required (ml)

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



CUBICIN[®] 6 mg/kg

INDICATIONS

- ▶ RIE due to *Staphylococcus aureus*¹
- ▶ *Staphylococcus aureus* bacteraemia when associated with RIE or with cSSTI¹

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:

$$\text{Volume in ml} = \text{Bodyweight (kg)} \times 6/50$$

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

DOSAGE RECOMMENDATIONS

CUBICIN

6mg/kg

Patient weight (kg)

Volume of Cubicin 50 mg/ml
solution required (ml)

46
48
50
52
54
56
58

5.52
5.76
6.00
6.24
6.48
6.72
6.96

60
62
64
66
68
70
72
74
76
78
80
82

7.20
7.44
7.68
7.92
8.16
8.40
8.64
8.88
9.12
9.36
9.60
9.84

Cubicin® (Daptomycin) (powder for concentrate for solution for infusion/powder for solution for injection or infusion)

PRESENTATION: Single-use vials containing 350mg daptomycin powder for concentrate for solution for infusion. Single use vials containing 500mg daptomycin powder for solution for injection or infusion. A pale yellow to light brown lyophilised powder. One ml provides 50mg of daptomycin after reconstitution with 7ml (350mg strength vial) or 10ml (500mg strength vial) sodium chloride 0.9% solution. Please refer to SmPC for full details regarding reconstitution and dilution of vials. **INDICATIONS:** Treatment of the following infections in adults caused by susceptible Gram positive pathogens: complicated skin and soft-tissue infections (cSSTI), right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*, and *S. aureus* bacteraemia (SAB) when associated with RIE or with cSSTI. 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 antibacterial susceptibility, expert advice and official guidance on the appropriate use of antibacterial agents. **DOSEAGE: Adults:** Cubicin is given either via a 30 minute infusion or by intravenous injection administered over 2 minutes once every 24 hours. There is no clinical experience in patients with the administration of daptomycin as an injection over 2 minutes. cSSTI without concurrent *S. aureus* bacteraemia: 4 mg/kg for 7-14 days or until the infection is resolved. cSSTI with concurrent *Staphylococcus aureus* bacteraemia: 6 mg/kg for a minimum of 14 days in accordance with the perceived risk of complications in the individual patient. Known or suspected right-sided infective endocarditis due to *S. aureus*: 6 mg/kg for a duration of therapy in accordance with available official recommendations. **Renal impairment:** Due to limited clinical experience Cubicin should only be used in patients with any degree of renal impairment (creatinine clearance CrCl < 80 ml/min) when 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. Dose adjustments are required in patients with renal impairment in accordance with indication for use and creatinine clearance: cSSTI without *S. aureus* bacteraemia: CrCl ≥30ml/min: 4mg/kg once every 24 hours, CrCl <30ml/min: 4mg/kg once every 48 hours, RIE or cSSTI associated with *S. aureus* bacteraemia: CrCl ≥30ml/min: 6mg/kg once every 24 hours, CrCl <30ml/min: 6 mg/kg once every 48 hours or in patients on haemodialysis. Patients on haemodialysis or continuous ambulatory peritoneal dialysis in cSSTI without *S. aureus* bacteraemia: 4mg/kg every 48 hours. RIE or cSSTI associated with *S. aureus* bacteraemia: 6 mg/kg every 48 hours. Administered following dialysis on dialysis days whenever possible. **The elderly:** As for adults, caution in patients >65 years. **Children and adolescents (< 18 years of age):** not recommended due to insufficient data. **Mild-moderate hepatic impairment:** no dose adjustment required. Severe hepatic impairment (Child-Pugh Class C): no data available, use with caution. No dose adjustment is required based on age, body mass index or gender alone. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or excipient. **WARNINGS/PRECAUTIONS:** If a focus of *S. aureus* infection other than cSSTI or RIE is identified after initiation of Cubicin, alternative antibacterial therapy with proven efficacy should be considered. Anaphylaxis/hypersensitivity reactions have been reported with Cubicin. Cubicin is not effective in pneumonia. The efficacy of Cubicin in patients with prosthetic valve infections or with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. Patients with deep-seated infections should receive any required surgical interventions without delay. **Enterococcal Infections:** There is insufficient evidence to be able to draw conclusions regarding the possible clinical efficacy of Cubicin against infections due to enterococci. In addition, dose regimens of Cubicin that might be appropriate for the treatment of enterococcal infections, with or without bacteraemia, have not been identified. Reports of failures of Cubicin in the treatment of enterococcal infections were mostly accompanied by bacteraemia, where some treatment failures were associated with selection of organisms with reduced susceptibility or frank resistance to daptomycin. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with Cubicin. **Drug / Laboratory Test Interactions:** False prolongation of the prothrombin time and elevation of international normalised ratio have been observed when certain recombinant thromboplastin reagents are utilised for the assay. **Creatine phosphokinase (CPK) and myopathy:** Increases in plasma CPK levels associated with muscular pains and/or weakness and cases of myositis, myoglobinaemia and rhabdomyolysis have been reported during therapy with Cubicin, and 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 who received comparators (0.5%). CPK levels should be measured at baseline and at least once weekly. Patients with CPK > 5 times upper limit normal at baseline and other patients at higher risk of developing myopathy should be monitored more frequently (eg every 2-3 days, at least during the first two weeks of treatment). Cubicin should only be administered to those patients taking other medication associated with myopathy if the benefit to the patient outweighs the risk. Patients should be reviewed regularly for signs or symptoms of myopathy. Patients developing 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 CPK levels reach > 5 times upper limit normal. **Peripheral neuropathy:** Patients developing signs or symptoms should be investigated and consideration given to discontinuing treatment. **Eosinophilic Pneumonia:** Eosinophilic pneumonia has been reported in patients receiving Cubicin. Patients who develop these symptoms and signs while receiving Cubicin should undergo prompt medical evaluation, including, if appropriate, bronchoalveolar lavage to exclude other causes. Cubicin should be discontinued immediately and treatment with systemic steroids should be initiated when appropriate. Renal impairment: Severe renal impairment may increase the risk of myopathy. Caution is advised when administering Cubicin to patients who already have some degree of renal impairment (creatinine clearance < 80 ml/min) before commencing therapy with Cubicin and regular monitoring of renal function is advised. Regular monitoring of renal function is also advised during concomitant administration of potentially nephrotoxic agents, regardless of the patient's pre-existing renal function. Please see Dosage and Administration section for more details, including dose adjustments. Caution is recommended in very obese patients (Body Mass Index (BMI) > 40 kg/m²), but no dose adjustment is required. Appropriate measures should be taken if superinfection occurs or if antibiotic-associated or pseudomembranous colitis are suspected. **Pregnancy and lactation:** Due to the lack of clinical data, Cubicin should not be administered in pregnancy unless the potential benefit outweighs the risk, and breastfeeding should be discontinued during treatment with Cubicin. **INTERACTIONS:** CYP450 related drug interactions are unlikely. The pharmacokinetics of aztreonam, warfarin and probenecid were not significantly altered in interaction studies with Cubicin. Small alterations in pharmacokinetics of daptomycin and tobramycin were observed with a Cubicin dose of 2 mg/kg. Caution is warranted when Cubicin is co-administered with tobramycin. Experience with concomitant administration of Cubicin with warfarin is limited. Anticoagulant activity in patients receiving Cubicin and warfarin should be monitored for the first several days after initiation of Cubicin. It is recommended that other medications associated with myopathy should, if possible, be temporarily discontinued during treatment with Cubicin unless the benefit of concomitant administration outweighs the risk, failing which CPK levels should be monitored more than once weekly and patients closely monitored for signs or symptoms of myopathy. Caution is advised when Cubicin is co-administered with any other medicinal product known to reduce renal filtration. If unexplained abnormalities or PT/INR assays are observed in patients on Cubicin, consideration should be given to a possible in vitro interaction with the laboratory test. **Incompatibilities:** glucose-containing solutions. Medicinal products other than those listed in the SmPC under *Instructions for use and Handling*. **ADVERSE REACTIONS:** The safety data for the administration of daptomycin via the 2-minute intravenous injection route are derived from two pharmacokinetic studies in healthy volunteers. Based on these study results, no relevant difference in local tolerability or in the nature and frequency of adverse events was observed. **Serious Undesirable Effects: Clinical trials & Post-marketing Reports:** *Uncommon* (≥0.1% to <1%): Fungaemia, thrombocytopenia, eosinophilia, hyperglycaemia, paraesthesia, tremor, supraventricular tachycardia, extrasystole, myositis, renal impairment, including renal insufficiency, renal failure and serum creatinine increased. *Rare* (≥1/10,000 to <1/1,000): jaundice. *Frequency not known:* eosinophilic pneumonia, peripheral neuropathy, 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 tachycardia, wheezing, pyrexia, rigors, systemic flushing, vertigo, syncope, metallic taste, rhabdomyolysis, peripheral neuropathy, *Clostridium difficile*-associated diarrhoea. **Common undesirable effects: Clinical trials & Postmarketing Reports:** *Common* (≥1% to <10%): headache, dizziness, nausea, vomiting, diarrhoea, constipation fungal infections, urinary tract infections, candida infection, rash, pruritus, infusion site reaction, pyrexia, asthenia, increased CPK and abnormal liver enzymes (AST, ALT and alkaline phosphatase), anaemia, anxiety, insomnia, hypotension, hypertension, gastrointestinal and abdominal pain, flatulence, bloating and distension, limb pain. **Other undesirable effects: Refer to Cubicin Summary of Product Characteristics for a detailed listing of all undesirable effects. Special Storage Instructions:** store unreconstituted vials in a refrigerator at 2-8°C. See SmPC for instructions for storage of reconstituted diluted medicinal product. **Special Precautions for disposal and other handling:** Preparation of the solution for infusion requires an additional dilution step. Please refer to SmPC section 6.6 *Special Precautions for disposal and other handling*. 30-minute intravenous infusion & 2-minute intravenous injection should be reconstituted with sodium chloride 0.9% solution for injections. 30-minute IV infusion should then be diluted with sodium chloride only. **Please refer to the SmPC for full reconstitution and dilution instructions.** **LEGAL CATEGORY:** POM. **MARKETING AUTHORISATION HOLDER:** Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom. **MARKETING AUTHORISATION NUMBER:** CUBICIN 350 mg powder for solution for injection or infusion EU/1/05/328/001 & EU/1/05/328/003; CUBICIN 500 mg powder for solution for injection or infusion EU/1/05/328/002 & EU/1/05/328/004. **Please refer to Summary of Product Characteristics (SmPC) before prescribing.** Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 124, Valletta, VLT 1000, Malta. Tel: +356 21222872, +356 22983217. 2013-MT-CUB-09-July-2013

Any suspected adverse reactions and medication errors can be reported via the National Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA or sent by e-mail to postlicensing.medicinesauthority@gov.mt

Healthcare professionals may also report any adverse events suspected to be associated with the use of Cubicin to Novartis Pharma Services Inc. Representative Office Malta by phone on 22983217 or 21222872, by fax on 22487219 or e-mail at drug_safety.malta@novartis.com

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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 quinupristin-dalfopristin 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.