

Antibiotic Susceptibility Testing with Cubicin® (daptomycin)

Introduction

Cubicin (daptomycin) is a cyclic lipopeptide antibiotic against Gram-positive bacteria, approved for the following indications (see Annex 2 for SmPC) [Ref. 5.3.5.1: P017]:

- 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.
 - Paediatric patients below the age of one (1) 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

Daptomycin has one characteristic that affects susceptibility testing:

- It requires appropriate concentrations of free calcium (Ca^{2+}) ions for accurate assessment of its activity *in vitro* [Ref. 5.4: 04J4XD, 04J4XC, 04J50P]

Effect of Calcium (Ca^{2+}) on susceptibility testing

Daptomycin activity is dependent on the presence of physiological calcium (Ca^{2+}) concentrations [Ref. 5.4: 04J4XD, 04J4XC, 04J50P]

Other divalent and monovalent cations have negligible effects on activity [Ref. 5.4: 04J4XD]

A Ca^{2+} concentration of 50 $\mu\text{g}/\text{ml}$ (1.25 mmol/L) in growth media provides optimal determination of daptomycin minimum inhibitory concentration (MIC) and correlates with physiological levels of free Ca^{2+} in human plasma (1.15–1.31 mmol/L) [Ref. 5.4: 04J50Q, 04J4X9]

Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardization of test media to 50 $\mu\text{g}/\text{ml}$ Ca^{2+} (1.25 mmol/L). [Ref. 5.4: 04J4X9, 04J50J, 04NNDL]

Summary of daptomycin susceptibility testing methods

Recommended methods for daptomycin susceptibility testing

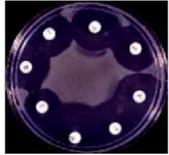
<p>Broth microdilution (BMD)</p>  <p>✓</p>	<ul style="list-style-type: none"> ▪ BMD is the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended method for determining MIC and susceptibility of pathogens to daptomycin [Ref. 5.4: 04NNDL] , [Ref. 5.4: 04J50L] ▪ Follow CLSI-approved method using Mueller–Hinton broth (with or without 2–5% lysed horse blood) adjusted to 50 µg/ml Ca²⁺ (1.25 mmol/L) [Ref. 5.4: 04J50L], [Ref. 5.4: 04GRR4] ▪ MIC determination using broths other than Mueller–Hinton broth has not been validated [Ref. 5.4: 04NNDL]
<p>E test*</p>  <p>✓</p>	<ul style="list-style-type: none"> ▪ Daptomycin E test strips (bioMerieux SA), which contain a constant Ca²⁺ level throughout the daptomycin gradient, are also a recommended method [Ref. 5.4: 04J50J] ▪ Ca²⁺ content in the agar is also essential and should be in the range of 25–40 µg/ml (0.62-1 mmol/L) [Ref. 5.4: 04J50J] ▪ The daptomycin E test strips are suitable for use on Mueller–Hinton agar plates. [Ref. 5.4: 04J50J]

*FOR FURTHER INFORMATION AND LOCAL DISTRIBUTOR CONTACT DETAILS GO TO WWW.BIOMERIEUX-DIAGNOSTICS.COM/ETEST

Automated and semi-automated systems

<p>Automated and semi-automated systems</p> <p>?</p>	<ul style="list-style-type: none"> ▪ Development of daptomycin panels and cards for BioMerieux ViTeK 1 and VITEK 2, BD Phoenix and Trek SensiTitre is complete [Ref. 5.4: 04NNDL] ▪ Contact your local representative/customer services of the system manufacturer to obtain these systems and software updates as appropriate ▪ Other systems are in development
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Non-recommended methods for susceptibility testing

<p>Agar dilution</p> 	<ul style="list-style-type: none"> This method is not recommended because there is no agar with consistent Ca²⁺ concentrations that is also appropriate for daptomycin testing. Supplementing agar with Ca²⁺ is problematic [Ref. 5.4: 04GRR4],[Ref. 5.4: 04NNDL] The variability in Ca²⁺ concentrations of agar between different batches and manufacturers makes this method unpredictable [Ref. 5.4: 04GRR4]
<p>Disk diffusion</p> 	<ul style="list-style-type: none"> A 30 µg disk was withdrawn from the US market due to problems in distinguishing resistant isolates from susceptible strains [Ref. 5.4: 04GRR4] This method is currently not recommended [Ref. 5.4: 04GRR4]

EUCAST-approved interpretive criteria [Ref. 5.4: 04J50L] (www.escmid.org)

	Susceptible (mg/L)	Resistant (mg/L)
<i>Staphylococcus</i> spp.	≤1	>1
<i>Streptococcus</i> spp. Groups A, B, C and G (excluding <i>S.pneumoniae</i>)	≤1	>1

Susceptibility to Cubicin

Of 2,977 European Gram-positive clinical isolates tested in a 2011 European surveillance programme, 99.9% were susceptible to Cubicin. [Ref. 5.4: 04J3WL]

Further information

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.
- [Ref. 5.4: 04J2D7] Kirkpatrick P, Raja A, LaBonte J, Lebbos J. Daptomycin. *Nat Rev Drug Discov.* 2003 Dec;2(12):943-4.
- [Ref. 5.4: 04J2D8] Rybak MJ, Hershberger E, Moldovan T, Grucz RG. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against Staphylococci and Enterococci, including vancomycin-intermediate and -resistant strains. *Antimicrob Agents Chemother.* 2000 Apr;44(4):1062-6.
- [Ref. 5.4: 04J2DC] Tedesco KL, Rybak MJ. Daptomycin. *Pharmacotherapy.* 2004 Jan;24(1):41-57.
- [Ref. 5.4: 04J3WL] Sader HS, Flamm RK, Jones RN. Antimicrobial activity of daptomycin tested against Gram-positive pathogens collected in Europe, Latin America, and selected countries in the Asia-Pacific Region (2011). *Diagn Microbiol Infect Dis.* 2013 Apr;75(4):417-22.
- [Ref. 5.4: 04J4X9] Wise R, Andrews JM, Ashby JP. Activity of daptomycin against Gram-positive pathogens: a comparison with other agents and the determination of a tentative breakpoint. *J Antimicrob Chemother.* 2001 Oct;48(4):563-7.
- [Ref. 5.4: 04J4XC] Fuchs PC, Barry AL, Brown SD. Daptomycin susceptibility tests: interpretive criteria, quality control, and effect of calcium on in vitro tests. *Diagn Microbiol Infect Dis.* 2000 Sep;38(1):51-8.
- [Ref. 5.4: 04J4XD] Eliopoulos GM, Willey S, Reiszner E, Spitzer PG, Caputo G, Moellering RC Jr. In vitro and in vivo activity of LY 146032, a new cyclic lipopeptide antibiotic. *Antimicrob Agents*

- Chemother. 1986 Oct;30(4):532-5.
- [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/5e27f2e5a88c898e0025650003c98c2/2030bf44cbec6e0e00256f23003f2169/\\$FILE/Etest_Daptomycin_MIC_variables.pdf](https://kaldur.landspitali.is/gaeda/gnhsykla.nsf/5e27f2e5a88c898e0025650003c98c2/2030bf44cbec6e0e00256f23003f2169/$FILE/Etest_Daptomycin_MIC_variables.pdf)
- [Ref. 5.4: 04J50L] European Committee on Antimicrobial Susceptibility Testing (EUCAST). European Committee on Antimicrobial Susceptibility Testing: breakpoint tables for interpretation of MICs and zone diameters version 6.0 [Internet]. Basel: EUCAST; 2016. Available from: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf
- [Ref. 5.4: 04J50P] Fuchs PC, Barry AL, Brown SD. Evaluation of daptomycin susceptibility testing by Etest and the effect of different batches of media. J Antimicrob Chemother. 2001 Oct;48(4):557-61.
- [Ref. 5.4: 04J50Q] Barry AL, Fuchs PC, Brown SD. In vitro activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers. Antimicrob Agents Chemother. 2001 Jun;45(6):1919-22.
- [Ref. 5.4: 04NNDL] Koeth LM, Thorne GM. Daptomycin in vitro susceptibility methodology: a review of methods, including determination of calcium in testing media. Clin. Microbiol. Newsl. 2010 Nov 1;32(21):161-9.