Antibiotic Susceptibility Testing with CUBICIN® (daptomycin)
**Introduction**

Cubicin (daptomycin) is a cyclic lipopeptide antibiotic against Gram-positive bacteria only, approved for treatment of the following infections in adults:

- Complicated skin and soft-tissue infections (cSSTIs)
- *Staphylococcus aureus* bacteraemia when associated with right-sided infective endocarditis or cSSTI
- Right-sided infective endocarditis due to *S. aureus*

Cubicin is also indicated in paediatric patients aged 1 to 17 years for the treatment of complicated skin and soft tissue infections (cSSTI).

- 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.

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*.

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

Daptomycin activity is dependent on the presence of physiological Ca\(^{2+}\) concentrations.

- Other divalent and monovalent cations have negligible effects on activity.

A Ca\(^{2+}\) concentration of 50 μg/ml (1.1 mM) 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 mM).

Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardisation of test media to 50 μg/ml Ca\(^{2+}\).

**Susceptibility to Cubicin**

- Of 2,977 European Gram-positive clinical isolates tested in a 2011 European surveillance programme, 99.9% were susceptible to Cubicin.
Summary of daptomycin susceptibility testing methods

Recommended methods for daptomycin susceptibility testing

| Broth microdilution (BMD) | ▶ The 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
▶ Follow CLSI-approved method using Mueller–Hinton broth (with or without 2–5% lysed horse blood) adjusted to 50 μg/ml Ca²⁺
▶ MIC determination using broths other than Mueller–Hinton broth has not been validated |

| Etest* | ▶ Daptomycin Etest strips (bioMérieux SA), which contain a constant Ca²⁺ level throughout the daptomycin gradient, are also a recommended method
▶ Ca²⁺ content in the agar is also essential and should be in the range of 25–40 μg/ml
▶ The daptomycin Etest strips are suitable for use on Mueller–Hinton agar (BBL™ Mueller–Hinton agar is recommended because the Ca²⁺ concentration is consistently within the required range)⁹ |

Automated and semi-automated systems

| Automated and semi-automated systems | ▶ Development of daptomycin panels and cards for bioMérieux VITEK 1 and VITEK 2; BD Phoenix and Trek SensiTite is complete
▶ Contact your local representative/customer services of the system manufacturer to obtain these systems and software updates as appropriate
▶ Other systems are in development |

Non-recommended methods for susceptibility testing

| Agar dilution | ▶ 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
▶ The variability in Ca²⁺ concentrations of agar between different batches and manufacturers makes this method unpredictable |

| Disk diffusion | ▶ A 30 μg disk was withdrawn from the US market due to problems in distinguishing resistant isolates from susceptible strains
▶ This method is currently not recommended |

EUCAST-approved interpretive criteria¹⁰ ([www.escmid.org](http://www.escmid.org))

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<tr>
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<th>Susceptible</th>
<th>Resistant</th>
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<td><em>Staphylococcus</em> spp.</td>
<td>≤1 μg/ml</td>
<td>&gt;1 μg/ml</td>
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<tr>
<td><em>Streptococcus</em> spp. A, B, C and G (excluding <em>S. pneumoniae</em>)</td>
<td>≤1 μg/ml</td>
<td>&gt;1 μg/ml</td>
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*For further information and local distributor contact details go to www.biomerieux-diagnostics.com/etest*
Further information

Please contact your local Novartis office
see www.novartis.ie

References.

1. Cubicin SmPC.
12. Study DAP-PEDS-07-03.

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2.
Tel: +353 1 6764971. Fax: +353 1 6762517. Website: www.hpра.ie E-mail: medsafety@hpра.ie

Adverse events should also be reported to Novartis Ireland via telephone at (01) 2080612 or via e-mail at drugsafety.dublin@novartis.com

Novartis Ireland ltd. Vista Building, Elm park Business Park, Merrion Road, Dublin 4.

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