Antibiotic Susceptibility Testing with Cubicin® (daptomycin)
ANTIBIOTIC SUSCEPTIBILITY TESTING WITH CUBICIN® (DAPTOMYCIN)

Introduction

- Cubicin® (daptomycin) is a cyclic lipopeptide antibiotic against Gram-positive bacteria, approved for:
  - Complicated skin and soft tissue infections (cSSTIs)¹
  - *Staphylococcus aureus* bacteraemia when associated with right-sided infective endocarditis or cSSTI
  - Right-sided infective endocarditis due to *S. aureus*¹

- Daptomycin has one characteristic that affects susceptibility testing:
  - It requires appropriate concentrations of free Ca²⁺ ions for accurate assessment of its activity *in vitro*²⁻⁴

Effect of Ca²⁺ on susceptibility testing

- Daptomycin activity is dependent on the presence of physiological Ca²⁺ concentrations²⁻⁴

- Other divalent and monovalent cations have negligible effects on activity²,⁵,⁶

- A Ca²⁺ 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 Ca²⁺ in human plasma (1.15–1.31 mM)⁷,⁸

- Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardization of test media to 50 µg/ml Ca²⁺
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 Ca<sup>2+</sup>  
- MIC determination using broths other than Mueller–Hinton broth has not been validated |

| Etest* | - Daptomycin Etest strips (bioMerieux SA), which contain a constant Ca<sup>2+</sup> level throughout the daptomycin gradient, are also a recommended method  
- Ca<sup>2+</sup> content in the agar is also essential and should be in the range of 25–30 µg/ml  
- The daptomycin Etest strips are suitable for use on Mueller–Hinton agar (BBL™ Mueller–Hinton agar is recommended because the Ca<sup>2+</sup> concentration is consistently within the required range) |

**Automated and semi-automated systems**

| Automated and semi-automated systems | - Development of daptomycin panels and cards for bioMerieux VITEK 1 and VITEK 2; BD Phoenix and Trek SensiTitre 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 Ca<sup>2+</sup> concentrations that is also appropriate for daptomycin testing. Supplementing agar with Ca<sup>2+</sup> is problematic  
- The variability in Ca<sup>2+</sup> 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 criteria**<sup>10</sup> (www.escmid.org)

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<thead>
<tr>
<th>Staphylococcus spp.</th>
<th>Susceptible</th>
<th>Resistant</th>
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<tbody>
<tr>
<td>≤1 µg/ml</td>
<td>&gt;1 µg/ml</td>
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<tr>
<th>Streptococcus spp. Groups A, B, C and G (excluding S. pneumoniae)</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<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*
Suspected adverse reactions and medication errors associated with the use of Cubicin® should be reported to:

Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D’Argens, Gzira GZR 1368, or at:

&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.

SmPC for full reconstitution and dilution instructions. LEGAL CATEGORY:

Susceptibility to Cubicin®

- Of 2,977 European Gram-positive clinical isolates tested in a 2011 European surveillance programme, 99.9% were susceptible to Cubicin®.

Further information

Please contact your local Novartis Office: Novartis Pharma Services Inc.
Representative Office Malta +356 21222872 or +356 22983217

References

1. Cubicin® EU SmPC.