

NDA No. 21-572 SN007
Cubicin
Cubist Pharmaceuticals, Inc.

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Microbiology Portion of the Package Insert

Changes to the Microbiology Portion of the Package Insert by this Reviewer are indicated as follows: ***added text is italicized, bolded, and underlined*** while ~~deleted text is stricken through~~.

MICROBIOLOGY

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. Daptomycin is a natural product which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The *in vitro* spectrum of activity of daptomycin encompasses most clinically relevant Gram-positive pathogenic bacteria. Daptomycin retains potency against antibiotic resistant Gram-positive bacteria including isolates resistant to methicillin, vancomycin, and linezolid.

Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram-positive organisms *in vitro*. This has been demonstrated both by time-kill curves and by MBC/MIC ratios using broth dilution methodology.

In vitro studies have demonstrated additive or indifferent interactions of daptomycin with other antibiotics. Antagonism, as determined by kill curve studies, has not been observed. *In vitro* synergistic interactions occurred with aminoglycosides and β -lactam antibiotics against some isolates of staphylococci and enterococci, including some MRSA isolates.

Mechanism of Action

The mechanism of action of daptomycin is distinct from any other antibiotic. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death.

Resistance

Mechanisms of Resistance:

At this time, no mechanism of resistance to daptomycin has been identified. Currently, there are no known transferable elements that confer resistance to daptomycin.

Cross Resistance:

Cross-resistance has not been observed with any other class of antibiotic.

Other:

The emergence of resistance to daptomycin occurred in 2 of more than 1000 (<0.2%) infected subjects across the entire set of Phase 2 and 3 clinical trials. In one case, a resistant *S. aureus* was isolated from a patient in a Phase 2 study who received daptomycin at less than the protocol-specified dose for the initial 5 days of therapy. In the second case, a resistant *E. faecalis* was isolated from a patient with an infected chronic decubitus ulcer enrolled in a salvage trial.

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Daptomycin has been shown to be active against most isolates of the following microorganisms both *in vitro* and in clinical infections, as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative Gram-positive microorganisms:

Enterococcus faecalis (vancomycin-susceptible **strains isolates** only)
Staphylococcus aureus (including methicillin-resistant **strains isolates**)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. *equisimilis*
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. Greater than 90% of the following microorganisms demonstrate an *in vitro* MIC less than or equal to the susceptible breakpoint for daptomycin versus the bacterial genus. The efficacy of daptomycin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms:

Corynebacterium jeikeium
Enterococcus faecalis (vancomycin-resistant **strains isolates**)
Enterococcus faecium (including vancomycin-resistant **strains isolates**)
Staphylococcus epidermidis (including methicillin-resistant **strains isolates**)
Staphylococcus haemolyticus

Susceptibility Testing Methods

Susceptibility testing by dilution methods requires the use of daptomycin susceptibility powder. The testing also requires presence of physiological levels of free calcium ions (50 mg/L calcium chloride) in Mueller-Hinton broth medium. ~~and a minimum of 28 mg/L calcium chloride in Mueller-Hinton agar medium.~~

Dilution technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure^{2,3}. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of daptomycin powder. The MIC values should be interpreted according to the criteria in Table 3. **Agar dilution has not been validated for daptomycin.**

Diffusion technique

~~Quantitative methods that require measurement of zone diameters have not been shown to provide reproducible estimates of the susceptibility of bacteria to daptomycin[†].~~
The disk diffusion method does not reliably differentiate isolates with reduced susceptibility to daptomycin (MIC >2 µg/mL) from susceptible isolates (MIC < 1µg/mL). Therefore, disk diffusion testing is not recommended.

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Table 3. Susceptibility Interpretive Criteria for Daptomycin

| Pathogen | Minimal inhibitory concentration ($\mu\text{g/mL}$) ^a | | |
|--|--|-----|-----|
| | S | I | R |
| <i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin-resistant) | ≤ 1 | (b) | (b) |
| <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i> | ≤ 1 | (b) | (b) |
| <i>Enterococcus faecalis</i> (vancomycin-susceptible only) | ≤ 4 | (b) | (b) |

- a. The MIC interpretive criteria for *S. aureus* and *E. faecalis* are applicable only to tests performed by broth microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L; the MIC interpretive criteria for *Streptococcus* spp. other than *S. pneumoniae* are applicable only to tests performed by broth microdilution using Mueller-Hinton broth adjusted to a calcium content of 50 mg/L, supplemented with 2 to 5% lysed horse blood, inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.
- b. The current absence of data on daptomycin resistant ~~strains~~ isolates precludes defining any categories other than “Susceptible”. ~~Strains~~ Isolates yielding test results suggestive of a “non-susceptible” category should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the procedures. Standard daptomycin powder should provide the range of values noted in Table 4. Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant. [Agar dilution has not been validated for daptomycin.](#)

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Table 4. Acceptable Quality Control Ranges for Daptomycin to Be Used in Validation of Susceptibility Test Results

| QC Strain | Minimum Inhibitory Concentration <i>Range</i> (MIC in µg/mL) ^a |
|--|--|
| <i>Enterococcus faecalis</i> ATCC 29212 | 1-8 |
| <i>Staphylococcus aureus</i> ATCC 29213 | 0.25-1 |
| <i>Streptococcus pneumoniae</i> ATCC 49619 ^b | 0.06-0.5 ^c |

- Quality control ranges reflect MICs obtained when Mueller-Hinton broth is supplemented with calcium to a final concentration of 50 mg/L.
- This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.
- This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation adjusted Mueller-Hinton broth with 2-5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

REFERENCES

~~National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests; approved standard eighth edition. NCCLS document M2-A8, Villanova (PA). 2003 January.~~

Clinical Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically; approved standard-seventh edition. CLSI document M7-A7, Wayne (PA). 2006 January.

Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; sixteenth informational supplement. CLSI document M100-S16, Wayne (PA). 2006 January.

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/s/

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