

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k102535

B. Purpose for Submission:

To obtain a substantial equivalence determination for Etest® strip for determining susceptibility of Gram positive organisms to telavancin

C. Measurand:

Telavancin concentrations of 0.002 – 32 µg/mL and 0.016 – 256 µg/mL

D. Type of Test:

Antimicrobial Susceptibility Test (AST) Growth Based Detection Method

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

Etest® Telavancin for Antimicrobial Susceptibility Testing

G. Regulatory Information:

1. Regulation section:

866.1640 Antimicrobial Susceptibility Test (AST) Powder

2. Classification:

II

3. Product code:

JWY - Manual Antimicrobial Susceptibility Test Systems

4. Panel:

83, Microbiology

H. Intended Use:

1. Intended use(s):

Etest® is a quantitative technique for determination of antimicrobial susceptibility of both non-fastidious Gram-negative and Gram positive aerobic bacteria such as *Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus* and *Enterococcus* species and fastidious bacteria, such as anaerobes, *N. gonorrhoeae*, *S. pneumoniae*, *Streptococcus* and *Haemophilus* species. The system comprises a predefined antibiotic gradient which is used to determine the Minimum Inhibitory Concentration (MIC) in µg/mL of different antimicrobial agents against microorganisms as tested on agar media using overnight incubation.

2. Indication(s) for use:

Etest® is a quantitative technique for determination of antimicrobial susceptibility of both non-fastidious Gram-negative and Gram positive aerobic bacteria such as *Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus* and *Enterococcus* species and fastidious bacteria, such as anaerobes, *N. gonorrhoeae*, *S. pneumoniae*, *Streptococcus* and *Haemophilus* species. The system comprises a predefined antibiotic gradient which is used to determine the Minimum Inhibitory Concentration (MIC) in µg/mL of different antimicrobial agents against microorganisms as tested on agar media using overnight incubation.

This 510(k) submission is for Etest® Telavancin for MIC determination across concentrations of 0.002 – 32 µg/mL and 0.016 – 256 µg/mL with *Staphylococcus aureus* (including methicillin-resistant isolates), *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group.

3. Special conditions for use statement(s):

For prescription use

4. Special instrument requirements:

Manual readings only

I. Device Description:

Etest® consists of a thin, inert and non-porous plastic strip, 5mm wide and 60 mm

long. One side of the strip carries a two-letter code designating the identity of the antibiotic and is calibrated with MIC values in terms of µg/mL. A predefined exponential gradient of the dried and stabilized antibiotic covers a continuous concentration range across 15 two-fold dilutions of a conventional MIC method.

The MIC interpretive criteria for telavancin are as follows:

Organism	Susceptibility Interpretive Criteria (MIC* in µg/mL):		
	S	I	R
<i>Staphylococcus aureus</i>	≤ 1	-	=
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 1	-	=
<i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group	≤ 0.12	-	=

*Currently there are no intermediate or resistant interpretive criteria for telavancin. The absence of resistant strains precludes defining any results categories other than "susceptible." For strains yielding results suggestive of a "non-susceptible" category, organism identification and antimicrobial susceptibility test results should be confirmed. Subsequently, the isolates should be saved and submitted to a reference laboratory that will confirm results using a reference dilution method.

*S = Susceptible: Attainable levels in blood or tissue on usual usage, including oral administration when applicable.

I = Intermediate: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated (e.g. quinolones and B-lactams in urine), or when a higher than normal dosage of drug can be used (e.g. B-lactams). The "intermediate" category also includes a "buffer zone" which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

R = Resistant to usually achievable systemic concentrations.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Etest®
2. Predicate 510(k) number(s): _____
k913459
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Incubation Temperature	35°	Same
Inoculation	Isolated colonies from culture used	Same
Result	MIC	MIC
Incubation Atmosphere	Aerobic and microaerophilic	Aerobic and microaerophilic

Differences		
Item	Device	Predicate
Antibiotic	Telavancin	Other antibiotics

K. Standard/Guidance Document Referenced (if applicable):

1. Guidance for Industry and FDA- Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; August 28, 2009.
2. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacterial That Grow Aerobically, Approved Standard- 8th Edition, Document M07-A8
3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing Approved Standard-, 19th Informational Supplement, Document M100-S19

L. Test Principle:

The Etest® gradient technology is based on a combination of the concepts of dilution and diffusion test methods for susceptibility testing. Etest® directly quantifies antimicrobial susceptibility in terms of discrete MIC values. When the Etest® strip is applied to an inoculated agar plate, the antibiotic is immediately released from the plastic surface into the agar. A predefined, continuous gradient of antibiotic concentrations is created and maintained directly underneath the strip. After incubation whereby bacterial growth becomes visible, a symmetrical inhibition ellipse centered along the strip will be seen. The MIC value in µg/mL is read where the ellipse edge intersects the strip. Since Etest® generates MIC values which fall between two-fold dilutions for interpretation; the MIC value read must be recorded to the next two-fold dilution.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A reproducibility study was conducted at three study sites. Twenty five *Staphylococcus* species (10 *S. aureus*, 4 *S. epidermidis*, 4 *S. haemolyticus*, 5 *E. faecalis*, and 1 Coagulase Negative Staphylococci) and Thirty three *Streptococcus* species (14 *S. pyogenes* Gr A, 1 *S. milleri*, 6 *S. viridans*, 2 Beta hemolytic *Streptococcus* spp., *Streptococcus* Gr C, 6 *S. agalactiae* Gr B, and 3 *S. viridans*) were tested at each site. Reference method plates were read visually in accordance with CLSI standard. Reproducibility was calculated as the percent of results for the combined sites which were within +/- one doubling dilution of the mode MIC value for all sites.

For reproducibility calculations, off-scale values are handled in two ways; “best case” and “worst case” scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value. There were no off-scale results in this study, only one value for overall reproducibility is reported.

The overall reproducibility was 100% for all organisms with on-scale results tested by Etest at 3 sites. These results met the acceptance criteria and are acceptable.

b. *Linearity/assay reportable range:*

Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The recommended QC isolates were tested a sufficient number of times with acceptable results with the reference method. The Etest® results demonstrate that the system can produce QC results in the recommended range.

Telavancin quality control data from combined sites is shown below. For *S. pneumoniae*, the data is from 3 testing sites. For *S. aureus* and *E. faecalis*, the data is from 4 testing sites because of the addition of a fourth site to test additional fresh isolates. At least 20 test results per QC organism at each site were available, except for site 4 which had 10 results. This number of QC runs is acceptable, given that this site was added later to test additional fresh isolates. Telavancin Etest quality control data for *Streptococcus* species were

compared to two reference methods, broth microdilution and agar dilution.

QC Organism	MIC range (µg/mL)	MIC value (µg/mL)	Reference Frequency	Etest Frequency
<i>S. aureus</i> ATCC 29213	0.125 - 1	0.06	0	0
		0.125	57	59
		0.25	10	11
		0.5	3	0
		1	0	0
		2		
<i>E. faecalis</i> ATCC 29212	0.125-0.5	0.06		
		0.125	16	52
		0.25	51	17
		0.5	4	2
		1		

QC Organism	MIC range (µg/mL)	MIC value (µg/mL)	Broth Micro Dilution Reference Frequency	Agar Dilution Frequency	Etest Frequency
<i>S. pneumoniae</i> ATCC 49619	0.004 – 0.032	0.002			
		0.004			
		0.008	10	25	4
		0.016	36	13	73
		0.032	18	0	0
		0.064			

All QC values were in the expected range.

Inoculum density checks showed acceptable results for QC organisms, as well as a select number of challenge and clinical isolates. The results were based on colony count values representing 20 tests for each QC organism and 38 tests for selected challenge and clinical isolates. All results were within the expected range.

d. *Detection limit:*

Not Applicable

e. *Analytical specificity:*

Not Applicable

f. *Assay cut-off:*

Not Applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

CLSI recommended reference methods were used to determine susceptibility. Clinical testing was performed at four sites for Staphylococci and Enterococci and at three sites for Streptococci. Etest and CLSI reference broth microdilution results were compared based on the guidelines provided in the AST Guidance Document. Essential agreement (EA) is when the Etest agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the Etest result interpretation agrees exactly with the reference panel result interpretation based on interpretive criteria. The %EA and %CA results were acceptable.

According the approved drug label for telavancin, only a susceptible interpretive category is defined. There are no intermediate or resistance interpretive categories. In this study, two isolates were noted to have MICs outside the susceptible category. There were 2 cases in this study in which Etest results gave a categorical interpretation that was not in agreement with the reference broth dilution MIC. The MIC results were for the two isolates were as follows:

For *E. faecalis* (Vancomycin-Susceptible), the telavancin MIC was 0.5 µg/mL (Susceptible) by Etest and 2 µg/mL (non-susceptible) by broth microdilution reference. This was considered a Very Major Error.

Fore *S. aureus* (Methicillin-Resistant), the telavancin MIC was 1.5 µg/mL (non-susceptible) by Etest. Triplicate testing by broth microdilution showed the MIC as 0.5, 0.5 and 1 µg/mL (Susceptible). This was considered a Major Error.

Labeling will recommend that isolates yielding a “non-susceptible” category should be submitted to a reference laboratory for further testing.

A total of 462 Gram positive aerobic organisms (challenge and clinical isolates) were evaluated at four clinical study sites (n=462). A total of 355 *Streptococcus* spp. (challenge and clinical isolates) were evaluated at 3 clinical study sties.

The performance evaluation summary of essential and category agreement results for challenge and clinical strains is shown in the tables below.

Gram-Positive Organisms

Clinical data

Organism group	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#NS	#vmj	#maj	#min
<i>S. aureus</i> MR	135	133	98.5	135	133	98.5	135	100	0	0	0	0
<i>S. aureus</i> MS	65	65	100	65	65	100	65	100	0	0	0	0
<i>S. epidermidis</i> MR	33	32	97.0	33	32	97.0	33	100	0	0	0	0
<i>S. epidermidis</i> MS	22	22	100	22	22	100	22	100	0	0	0	0
Coag neg staph MR	30	30	100	30	30	100	30	100	0	0	0	0
Coag neg staph MS	25	25	100	25	25	100	25	100	0	0	0	0
<i>S. haemolyticus</i> MR	6	6	100	6	6	100	6	100	0	0	0	0
<i>E. faecalis</i> VS	65	63	97	65	63	97	64	98	1	1	0	0
<i>E. faecium</i> VS	15	14	93.3	15	14	93.3	15	100	0	0	0	0
Total	396	390	98.5	396	390	98.5	395	99.7	1	1	0	0

Challenge

<i>S. aureus</i> MR	21	20	95.2	21	20	95.2	20	95.2	0	0	1	0
<i>S. aureus</i> MS	9	9	100.0	9	9	100.0	9	100	0	0	0	0
<i>S. epidermidis</i> MR	6	6	100.0	6	6	100.0	6	100	0	0	0	0
<i>S. epidermidis</i> MS	3	3	100.0	3	3	100.0	3	100	0	0	0	0
Coag neg staph MR	10	10	100.0	10	10	100.0	10	100	0	0	0	0
Coag neg staph MS	9	9	100.0	9	9	100.0	9	100	0	0	0	0
<i>S. haemolyticus</i> MR	2	2	100.0	2	2	100.0	2	100	0	0	0	0
<i>E. faecalis</i> VS	6	6	100.0	6	6	100.0	6	100	0	0	0	0
Total	66	65	98.5	66	65	98.5	65	98.5	0	0	1	0

Clinical and Challenge Combined

All Organisms	462	455	98.5	462	455	98.5	460	99.6	1	1	1	0
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Streptococci

Clinical data

Organism group	Total Tested	#EA	%EA Total	Total Evaluable	#EA of Evaluable	%EA Evaluable	#CA	%CA	#NS	#vmj	#maj	#min
<i>S. pyogenes</i> gr A	155	151	97.4	155	151	97.4	155	100	0	0	0	0
<i>S. agalactiae</i> gr B	55	55	100	55	55	100	55	100	0	0	0	0
β - <i>Streptococcus</i> gr C	14	14	100	14	14	100	14	100	0	0	0	0
β - <i>Streptococcus</i> gr G	14	14	100	14	14	100	14	100	1	0	0	0
β - <i>Streptococcus</i> spp.	10	10	100	10	10	100	10	100	1	0	0	0
<i>S. viridans</i>	41	41	100	41	41	100	41	100	0	0	0	0
<i>S. milleri</i>	12	12	100	12	12	100	12	100	0	0	0	0
Total	301	297	98.7	301	297	98.7	301	100	2	0	0	0

Challenge

<i>S. pyogenes</i> gr A	24	24	100	24	24	100	24	100	0	0	0	0
<i>S. agalactiae</i> gr B	5	5	100	5	5	100	5	100	0	0	0	0
β - <i>Streptococcus</i> gr C	5	5	100	5	5	100	5	100	0	0	0	0
β - <i>Streptococcus</i> gr G	5	5	100	5	5	100	5	100	0	0	0	0
β - <i>Streptococcus</i> spp.	1	1	100	1	1	100	1	100	0	0	0	0
<i>S. viridans</i>	9	8	88.9	9	8	88.9	9	100	0	0	0	0
<i>S. anginosus</i>	2	1	50.0	2	1	50.0	2	100	0	0	0	0
<i>S. intermedius</i>	3	3	100	3	3	100	3	100	0	0	0	0
Total	54	52	96.3	54	52	96.3	54	100	0	0	0	0

Clinical and Challenge Combined

All Organisms	355	349	98.3	355	349	98.3	355	100	2	0	0	0
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b. *Matrix comparison:*

Not Applicable

3. Clinical studies:

a. *Clinical Sensitivity:*

Not Applicable

b. *Clinical specificity:*

Not Applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

MIC Interpretive Standards (µg/mL)

	<i>Susceptible</i>
<i>Staphylococcus aureus</i>	≤ 1
<i>Enterococcus faecalis</i>	≤ 1
<i>Streptococcus spp.</i>	≤ 0.12

The current absence of data for resistant isolates precluded defining any results other than “susceptible”. Isolates yielding MIC results suggestive of a “non-susceptible” category should be submitted to a reference laboratory for further testing.

N. Proposed Labeling:

The expected value range, interpretive criteria and QC ranges are in the package insert. The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.