510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K180936

B. Purpose for Submission:

To obtain a substantial equivalence determination for telavancin at concentrations of 0.002 – 32 µg/mL for susceptibility testing of Gram positive aerobic microorganisms with ETEST.

C. Measurand:

Telavancin 0.002 – 32 µg/mL

D. Type of Test:

Quantitative AST growth-based detection

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

ETEST Telavancin (TLA) (0.002 – 32 µg/mL)

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY – Manual Antimicrobial Test Systems

4. Panel:

   83 –Microbiology

H. Intended Use:

1. Intended use(s):

   ETEST is a quantitative technique for determination of antimicrobial susceptibility of 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.

   Telavancin has been shown to be active against the Gram positive aerobic microorganisms listed below according to the FDA label for this antimicrobial agent.

   Active both in vitro and in clinical infections:
   Staphylococcus aureus (including methicillin-resistant isolates)
   Enterococcus faecalis (vancomycin-susceptible isolates only)

2. Indication(s) for use:

   Same as the Intended Use

3. Special conditions for use statement(s):

   For prescription use only

   Limitations:

- *Due to the lack of an intermediate category and the observed trending for Telavancin, testing of S. aureus and E. faecalis have resulted in major discrepancies for isolates that are otherwise within essential agreement with the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for S. aureus when the ETEST TLA MIC is 0.25 µg/mL and 0.5 µg/mL for E. faecalis.*

4. Special instrument requirements:

   N/A

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 three letter code designating the identity of the antibiotic and is calibrated with MIC values in terms of µg/mL. On the reverse, 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.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ETEST Ceftaroline

2. Predicate 510(k) number(s):

   K151873

3. Comparison with predicate:

Table 1. Comparison with the Predicate Device

Similarities		
Item	**Device K180936 ETEST Telavancin**	**Predicate K151873 ETEST Ceftaroline**
Intended Use	ETEST is a quantitative technique for determination of antimicrobial susceptibility of 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 microorganism as tested on agar media using overnight incubation.	Same
Antimicrobial Concentration Range	0.002 – 32 µg/mL	Same
Test Design	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.	Same
Inoculation	Isolated colonies from culture	Same
Result	MIC	Same

Differences		
Item	**Device K180936 ETEST Telavancin**	**Predicate K151873 ETEST Ceftaroline**
Claimed organisms	*S. aureus* (including MRSA), *E. faecalis* (vancomycin-susceptible only)	*S. agalactiae, S. pneumoniae, H. influenza*
Antimicrobial Agent	Telavancin	Ceftaroline
Incubation	35°± 2° C for 16–20 hours	35°± 2° C for 20–24 hours

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

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA

CLSI M07-A10, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, January 2015.

CLSI M100-S26, Performance Standards for Antimicrobial Susceptibility Testing; Volume 36, No. 1, January 2016.

L. Test Principle:

The ETEST consists of a thin, inert, nonporous plastic strip that is used to determine the antimicrobial susceptibility of bacteria. One side of the strip carries the minimum inhibitory concentration (MIC) reading scale expressed in µg/mL. The other side of the strip contains a predefined continuous gradient of antibiotic concentrations.

When the strip is applied to an inoculated agar surface, the preformed antibiotic gradient immediately transfers into the agar matrix, then forming a stable, continuous and exponential gradient of antibiotic concentrations directly underneath the strip. Bacteria growth becomes visible during incubation, and a symmetrical inhibition ellipse centered along the strip appears. After incubation, the MIC value is read from the scale in terms of µg/mL at complete inhibition of bacterial growth, where the pointed end of the ellipse 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.

The MIC gradient on ETEST Telavancin ranges from 0.002 to 32 µg/mL.

M. Performance Characteristics:

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   A reproducibility study was conducted at three external sites using 10 isolates of Gram positive organisms that were consistent with the intended use. Testing was performed on three separate days and in triplicate for a total of 270 data points among the sites. The isolates tested included five *S. aureus* and five *E. faecalis* isolates.

   The mode MIC was determined and the reproducibility was calculated based on MIC values that fell within ± one doubling dilution from the mode MIC value. All results were on-scale and within ± 1 doubling dilution of the mode MIC value for telavancin. The overall reproducibility was 100.0%.

   b. Linearity/assay reportable range:

Not applicable

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

Inoculum Density Check. Inoculum density checks were performed for all quality control and reproducibility organism suspensions and for 10% of the suspensions prepared for susceptibility testing of the fresh clinical isolates. The mean inoculum density was acceptable at 4.40 X 10^5 CFU/mL.

Purity Check. All clinical, challenge and reproducibility test suspensions were subcultured to assure purity.

Growth or Device Failure. There were no growth or device failures during the course of the study.

Quality Control Testing. Organisms recommended by both FDA and the CLSI were tested with telavancin at three sites. The QC organisms tested included *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. These QC strains were tested a minimum of 20 times per site by both the ETEST and the reference method. The results demonstrate that the telavancin ETEST can produce quality control results in the recommended range > 95% of the time. See Table 2 below for a summary of the QC results.

Table 2. Quality Control Data for Telavancin

QC organism	Telavancin expected range (µg/mL)	Concentration (µg/mL)	Reference	ETEST
S. aureus ATCC 29213	0.03 – 0.12	0.016	-	-
		0.03	60	6
		0.06	20	71
		0.12	1	4
		0.25	-	-
E. faecalis ATCC 29212	0.03 – 0.12	0.016	-	-
		0.03	-	-
		0.06	75	41
		0.12	6	40
		0.25	-	-

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:

Results obtained with ETEST telavancin were compared to results obtained with the CLSI broth microdilution reference panel. The CLSI panel was prepared and interpreted in accordance with the CLSI Standard: CLSI Document M07-A10, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition, Vol. 35, No. 2; January 2015. The testing conditions for the reference method consisted of the following:

- Medium – Cation-adjusted Mueller Hinton Broth with appropriate dilutions of antimicrobial solution added
- Inoculum – Direct colony suspension to achieve a turbidity equivalent to a 0.5 McFarland standard
- Incubation 35 °C in ambient air; 16-20 hours for all organisms

Clinical testing was performed at three sites using a total of 561 clinical isolates (31 vancomycin-resistant *E. faecalis* isolates, 228 vancomycin-susceptible *E. faecalis* isolates, and 302 *S. aureus* isolates). Of the clinical isolates, 462 were fresh isolates (82.4%) and 99 were stock isolates (17.6%). Clinical isolates were tested using both ETEST and the reference method.

A total of 104 challenge isolates were also tested by ETEST and the reference method (seven vancomycin-resistant *E. faecalis* isolates, 23 vancomycin-susceptible *E. faecalis* isolates, and 74 *S. aureus* isolates). Testing of challenge isolates was conducted at a single site.

Combined clinical and challenge isolates (665 including vancomycin-resistant *E. faecalis*) included: 38 vancomycin-resistant *E. faecalis* isolates, 251 vancomycin-susceptible *E. faecalis* isolates, and 376 *S. aureus* isolates. Of the 376 *S. aureus* isolates tested, 181 isolates were methicillin-resistant (MRSA) and 189 were methicillin-susceptible. Of the 376 S. aureus isolates tested, the methicillin-resistance status was unavailable at the time of testing for 6 isolates.

For *S. aureus,* the combined results from clinical and challenge testing demonstrated a combined EA of 98.4% and CA of 97.9% (Table 3). Eight major errors were identified resulting in an overall major error rate of 2.2%. There were no very major errors. Results were acceptable.

For vancomycin-susceptible *E. faecalis*, the combined results from clinical and challenge testing demonstrated a combined EA of 91.6% and CA of 97.6% (Table 3).

Six major errors were identified resulting in an overall major error rate of 2.4%. There were no very major errors. Results were acceptable. The 31 vancomycin-resistant *E. faecalis* isolates that were tested were also identified as non-susceptible to telavancin by the ETEST. This organism is not an indication for telavancin, however, they were included in the study to evaluate the ability of the ETEST to evaluate resistance.

The overall EA and CA of the Telavancin ETEST was acceptable. However, given the lack of an intermediate interpretive criteria breakpoint and the observed trending (see below) towards higher MIC value by ETEST compared to the reference method, the following limitation was included in the labeling to instruct users to retest using an alternative method for *S. aureus* isolates that result with an MIC of 0.25 µg/mL and 0.5 µg/mL for *E. faecalis*.

Due to the lack of an intermediate category and the observed trending for Telavancin, testing of S. aureus and E. faecalis have resulted in major discrepancies for isolates that are otherwise within essential agreement with the reference method. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for S. aureus when the ETEST® TLA MIC is 0.25 µg/mL and 0.5 µg/mL for E. faecalis.

Table 3 . Performance of Clinical and Challenge Isolates, Telavancin ETEST.

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. NS	min	maj	vmj
***S. aureus* (MSSA)**												
Clinical	163	160	98.2	163	160	98.2	163	100	0	NA	0	0
Challenge	26	25	96.2	26	25	96.2	25	96.2	0	NA	1	0
Combined	189	185	97.9	189	185	97.9	188	99.5	0	NA	1	0
***S. aureus* (MRSA)**												
Clinical	139	137	98.6	139	137	98.6	137	98.6	3	NA	2	0
Challenge	42	42	100	42	42	100	41	97.6	2	NA	1	0
Combined	181	179	98.9	181	179	98.9	178	98.3	5	NA	3	0
***S. aureus* (all)**												
Clinical	302	297	98.3	302	297	98.3	300	99.3	3	NA	2	0
Challenge	74	73	98.6	74	73	98.6	68	91.9	2	NA	6	0
Combined	376	370	98.4	376	370	98.4	368	97.9	5	NA	8	0
***E. faecalis* (vancomycin-susceptible)**												
Clinical	228	208	91.2	228	208	91.6	245	97.6	0	NA	5	0
Challenge	23	22	95.7	23	22	95.7	22	95.7	0	NA	1	0
Combined	251	230	91.6	251	230	91.6	245	97.6	0	NA	6	0
***E. faecalis* (vancomycin-resistant)**												
Clinical	31	31	100	12	12	100	31	100	31	NA	0	0
Challenge	7	7	100	0	0	NA	7	100	7	NA	0	0
Combined	38	38	100	12	12	100	38	100	38	NA	0	0
***E. faecalis* (all)**												
Clinical	259	239	92.3	240	220	91.7	254	98.1	31	NA	5	0

Challenge	30	29	96.7	23	22	95.7	29	96.7	7	NA	1	0
Combined	289	268	92.7	263	242	92	283	97.9	38	NA	6	0
All organisms (excluding vancomycin-resistant *E. faecalis*)												
Clinical	530	505	95.3	530	505	95.3	523	98.7	3	NA	7	0
Challenge	97	95	97.9	97	95	97.9	90	92.8	2	NA	7	0
Combined	627	600	95.7	627	600	95.7	613	97.8	5	NA	14	0
All organisms (including vancomycin-resistant *E. faecalis*)												
Clinical	561	536	95.5	542	517	95.4	554	98.8	34	NA	7	0
Challenge	104	102	98.1	97	95	97.9	97	93.3	9	NA	7	0
Combined	665	638	95.9	639	612	95.8	651	97.9	43	NA	14	0

EA – Essential Agreement (+/- 1 dilution)
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

Essential Agreement (EA) occurs when the result of the reference method and that of ETEST Telavancin are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both ETEST Telavancin and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of ETEST Telavancin.

MIC Trending

An analysis was conducted to evaluate trending in MIC values. Trending was observed (Table 4) for each species tested for both *S. aureus* and *E. faecalis* tending to be in exact agreement or higher when compared to the reference method. The difference between higher and lower dilutions for *E. faecalis* was 72.11% and 63.83% for *S. aureus.* The following footnotes were included in the labeling to indicate this trending:

ETEST Telavancin MIC values tended to be in exact agreement or one doubling dilution higher when testing Staphylococcus aureus compared to the reference broth microdilution method.

ETEST Telavancin MIC values tended to be one doubling dilution higher when testing Enterococcus faecalis compared to the reference broth microdilution method.

Table 4. Trending for *S. aureus* and *E. faecalis* (vancomycin-susceptible)

Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
***E. faecalis*[a] (vancomycin-susceptible)**					
251	0	3	64	163	21
	(1.2%)		(25.5%)	(73.31%)	
***S. aureus*[b] (MSSA + MRSA)**					
376	0	3	130	237	6
	(0.8%)		(34.57%)	(64.63%)	

[a]Difference between the higher and lower dilutions for vancomycin-susceptible *E. faecalis* is: 72.11%; 95% C.I. (65.89% to 77.26%).
[b]Difference between the higher and lower dilutions for *S. aureus* (MSSA + MRSA) is: 63.83%; 95% C.I. (58.64% to 68.52%).

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):

No applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Table 5. Interpretive Criteria (Breakpoints) for Telavancin

Organism	Interpretive Criteria for Telavancin (MIC, µg/mL)		
	S	I	R
S. aureus (including MRSA)	≤ 0.12	NA	NA
E. faecalis (vancomycin-susceptible only)	≤ 0.25	NA	NA

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

O. Conclusion:

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