Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K192050

B Applicant

bioMérieux SA

C Proprietary and Established Names

ETEST Eravacycline (ERV) (0.002 - 32 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for eravacycline at concentrations of 0.002 – 32 µg/mL for susceptibility testing of Gram-negative and Gram-positive aerobic organisms with ETEST.

B Measurand:

Eravacycline 0.002 – 32 µg/mL

C Type of Test:

Quantitative Antimicrobial Susceptibility Test growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

ETEST is a manual, quantitative technique for determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. 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 tested on agar media using overnight incubation.

Eravacycline has been shown to be active against most isolates of the microorganisms listed below according to the FDA label for this antimicrobial agent.

ETEST ERV can be used to determine the MIC of Eravacycline against the following microorganisms:

Active both *in vitro* and in clinical infections:

Gram-negative:
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae

Gram-positive:
Enterococcus faecalis
Enterococcus faecium

In vitro data are available for the following microorganisms, but clinical significance is unknown:

Citrobacter koseri
Klebsiella aerogenes

B Indication(s) for Use:

Same as Intended Use

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only
- The ability of ETEST Eravacycline to detect the following non-susceptible *Enterobacteriaceae* isolates is unknown because non-susceptible isolates were not available at the time of comparative testing: *Citrobacter koseri*.
- Due to the lack of an intermediate interpretive category for Eravacycline, results obtained with *E. cloacae* and *K. pneumoniae* and *E. faecium* showed potential for very major errors compared to the reference method and results obtained with *E. faecalis* showed potential for major and very major errors. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for:

E. cloacae when ETEST MIC is 0.5 µg/mL (Susceptible)
K. pneumoniae when ETEST MIC is 0.25 or 0.5 µg/mL (Susceptible)

E. faecium when ETEST MIC is 0.064 µg/mL (Susceptible)
E. faecalis when ETEST MIC is 0.064 (Susceptible) or 0.125 µg/mL (non-Susceptible).

D Special Instrument Requirements:
Manual reading only

IV Device/System Characteristics:

A Device Description:

The ETEST gradient technology is based on a combination of the concepts of dilution and diffusion principles for susceptibility testing.

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 has the minimum inhibitory concentration (MIC) reading scale expressed in µg/mL. The other side of the strip contains a predefined continuous exponential 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. Bacterial growth becomes visible during incubation, and a symmetrical inhibition ellipse centered along the strip appears. 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.

ETEST Eravacycline contains a range of eravacycline from 0.002 to 32 µg/mL.

B Principle of Operation:

When the ETEST 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
ETEST Telavancin (TLA) (0.002-32 µg/mL)

B Predicate 510(k) Number(s):
K180936

C Comparison with Predicate(s):

Device & Predicate Device(s):	**ETEST Eravacycline** (device) **K192050**	**ETEST Telavancin** (predicate) **K180936**
Device Trade Name	ETEST Eravacycline	ETEST Telavancin
General Device Characteristic Similarities		
Intended Use	ETEST is a manual, quantitative technique for determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-positive aerobic bacteria and fastidious bacteria. 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 tested on agar media after overnight incubation.	Same
Test Design	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
Antimicrobial Concentration Range	0.002 – 32 µg/mL	Same
Inoculum	Isolated colonies from culture	Same
Incubation	35º ± 2º C for 16 – 20 hours	Same
Result	MIC in µg/mL	Same
General Device Characteristic Differences		
Claimed Organisms	Gram-negative: *Citrobacter freundii* *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae*	*Staphylococcus aureus* (including methicillin-resistant isolates) *Enterococcus faecalis* (vancomycin-susceptible isolates only)

	Gram-positive: *Enterococcus faecalis* *Enterococcus faecium*	
Antibiotic	Eravacycline	Telavancin

VI Standards/Guidance Documents Referenced:

- Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.
- CLSI document M07, 11th ed., "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, 2018".
- CLSI M100, 28th ed., "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Eighth Informational Supplement, January 2018".

VII Performance Characteristics:

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites over three days using a ten-organism panel that included seven *Enterobacteriaceae* isolates [*C. freundii* (1), *E. cloacae* (1), *E. coli* (3), *K. oxytoca* (1), *K. pneumoniae* (1)] and three *Enterococcus* isolates [*E. faecalis* (2), *E. faecium* (1)]. The mode of MIC values was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode.

   The overall reproducibility results were acceptable at > 95%.

2. Linearity:

   Not applicable

3. Analytical Specificity/Interference:

   Not applicable

4. Assay Reportable Range:

   Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Inoculum Density Check. Inoculum density checks were performed for all quality control and for 10% of the suspensions prepared for susceptibility testing of the contemporary clinical isolates. Inoculum density checks were also performed on reproducibility organism

suspensions. However, the result of one colony count was missing for one of the 27 replicates of *Enterobacter cloacae*. This missing value was accepted.

The overall mean inoculum densities (CFU/mL) for isolates tested with the reference method ranged from 3.57×10^5 to 5.72×10^5. The overall mean inoculum densities for isolates tested with the ETEST ranged from 6.43×10^7 to 1.72×10^8.

The inoculum densities were acceptable.

Purity Check. Verification of isolate purity was conducted on all clinical, challenge and reproducibility organism suspensions for each ETEST and from each growth control well of the broth microdilution (BMD) reference panel.

Growth or Device Failure. No device failures occurred in the ETEST Eravacycline clinical trial.

Quality Control Testing. The CLSI recommended QC strains (*E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212 and *P. aeruginosa* ATCC 27853) were tested at least 20 times per site at four sites using both ETEST and BMD reference methods. The results are summarized in **Table 1**.

The Quality Control results were within the recommended range > 95% of the time which is acceptable.

Table 1. ETEST Eravacycline QC Results

QC Organism	Eravacycline Expected Range	Eravacycline MIC (µg/mL)	Reference (BMD) Results	ETEST Results
E. coli ATCC 25922	0.03 – 0.12 µg/mL	<0.03		
		0.03		
		0.06	51	
		0.12	30	79
		>0.12		2[1]
E. faecalis ATCC 29212	0.016 – 0.06 µg/mL	<0.016		
		0.016		
		0.03	61	33
		0.06	20	48
		>0.06		
P. aeruginosa ATCC 27853	2 - 16 µg/mL	<2		
		2		
		4	60	39
		8	18	41
		16	2	
		>16	1[2]	1[1,2]

1 Out-of-range ETEST results from three different sites. Every QC result was in range on subsequent days of testing so comparative study data was not excluded from analysis.

2 Two out-of-range reference results and one out-of-range ETEST result from a single day at a single site. Per the AST Special Controls Guidance, data obtained from clinical isolates tested that day were excluded from analysis and were repeated.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Results obtained with ETEST Eravacycline were compared to results obtained with the CLSI broth microdilution (BMD) reference panel. The reference panel, prepared and interpreted according to recommendations outlined in the CLSI M07 11th ed., contained two-fold serial dilutions of eravacycline with a concentration range of 0.002 – 32 μg/mL. At the end of incubation, the MIC value obtained from the ETEST (where the complete inhibition of growth intersects the strip) was compared to MIC results obtained with the reference method. The testing conditions for ETEST consisted of the following:

- Inoculum: Direct colony suspension to achieve a suspension equivalent to a 0.5 McFarland standard suspension
- Medium: Cation-adjusted Mueller Hinton agar
- Incubation: 35° C ± 2 for 16-20 hours

Clinical testing for ETEST Eravacycline was evaluated at three external sites (two located within the United States and one located outside the United States). Each clinical isolate was tested one time by ETEST and BMD using the same initial standardized inoculum prepared in 0.85% saline. A total of 600 clinical isolates were tested which included 480 *Enterobacteriaceae* isolates [*C. freundii* (60), *C. koseri* (30), *E. cloacae* (60), *E. coli* (180), *K. aerogenes* (29), *K. oxytoca* (31), *K. pneumoniae* (90)] and 120 *Enterococcus* isolates [*E. faecalis* (60), *E. faecium* (60)]. Of the tested clinical isolates, 78.2% (469/600) were considered contemporary (i.e., tested within six months of the organism's original isolation from clinical culture) and 21.8% (131/600) were considered stock (i.e., no time limit on time from isolation prior to testing).

Challenge testing was performed at one internal site using ETEST and BMD. A total of 79 challenge isolates were tested which included 62 *Enterobacteriaceae* isolates [*C. freundii* (10), *E. cloacae* (12), *E. coli* (11), *K. aerogenes* (3), *K. oxytoca* (12), *K. pneumoniae* (14)] and 17 *Enterococcus* isolates [*E. faecalis* (14), *E. faecium* (3)].

In total, the comparative study included clinical and challenge isolates as follows: 542 *Enterobacteriaceae* [*C. freundii* (70), *C. koseri* (30), *E. cloacae* (72), *E. coli* (191), *K. aerogenes* (32), *K. oxytoca* (43), *K. pneumoniae* (104)] and 137 *Enterococcus* spp. [*E. faecalis* (74), *E. faecium* (63)]. Information on the numbers of each *Enterobacteriaceae* and *Enterococcus* species is included as a footnote to the performance table in the labeling.

At the time of comparative testing, non-susceptible isolates were not available for *Citrobacter koseri*. This is addressed with the following statement included in the Limitations section of the device labeling:

> *The ability of ETEST Eravacycline to detect the following non-susceptible Enterobacteriaceae isolates is unknown because non-susceptible isolates were not available at the time of comparative testing: Citrobacter koseri.*

To address testing of non-indicated species, the following statement is included in the Precautions section of the device labeling:

> *Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, the safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well-controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Overall Performance

ETEST Eravacycline performance observed for clinical challenge isolates is provided in **Table 2**.

Table 2: Performance of Clinical and Challenge Isolates

Eravacycline	Total	EA N	EA %	Eval. Total	Eval. EA N	Eval. EA %	CA N	CA %	#NS	min	maj	vmj
***Enterobacteriaceae* (all)**												
Clinical	480	477	99.4	480	477	99.4	472	98.3	70	n/a	4	4
Challenge	62	62	100	62	62	100	59	95.2	22	n/a	2	1
Combined	542	539	99.4	542	539	99.4	531	98.0	92	n/a	6	5
Enterococcus faecalis* and *Enterococcus faecium												
Clinical	120	120	100	120	120	100	113	94.2	8	n/a	4	3
Challenge	17	17	100	14	14	100	14	100	1	n/a	0	0
Combined	137	137	100	134	134	100	130	94.9	9	n/a	4	3

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
NS – Non-susceptible isolates
min – minor errors
maj – major errors
vmj – very major errors

n/a – Not applicable due to only a susceptible interpretive criterion for eravacycline

Essential Agreement (EA) is when the ETEST result agrees exactly or within one doubling dilution of the reference broth microdilution result. Category Agreement (CA) is when the ETEST result interpretation agrees exactly with the reference broth microdilution result interpretation.

ETEST Eravacycline performance for all *Enterobacteriaceae* isolates (clinical and challenge) is acceptable with 99.4% EA and 98.0% CA. There were six major errors (6/450 = 1.3%) and five very major errors (5/92 = 5.4%). Due to the lack of an intermediate interpretive criteria

(eravacycline has only a “susceptible” category), further analysis of the errors was performed and adjustments were made by considering the MIC values of the errors compared to the reference MIC value. Four of the five very major errors had an MIC value that was one doubling dilution from the reference and thus in essential agreement. Therefore, the adjusted very major error rate is 1.1% (1/92) which is acceptable. To address the adjustment of the very major errors, the following statement is included as a footnote to the performance table in the device labeling:

> *The overall categorical very major error rate for eravacycline when testing Enterobacteriaceae clinical and challenge isolates is 5.4% (5/92). Based on the essential agreement and lack of an intermediate breakpoint for eravacycline, the overall adjusted very major error rate for Enterobacteriaceae clinical and challenge isolates is 1.1% (1/92).*

When evaluating individual species, the major error rate of *C. freundii* was 7.0% (4/53). All major error MIC values were in essential agreement with the reference resulting in an adjusted major error of zero. This error adjustment is acceptable as there was evidence of trending towards higher MIC values, which is consistent with the type of error (see below). This is addressed in a trending footnote to the performance table in the device labeling.

When evaluating *E. cloacae*, the very major error rate was 11.5% (3/29). All very major error MIC values were in essential agreement with the reference. However, adjustment of the very major error is inappropriate since there was no evidence of trending that is consistent with this type of error (see below). When evaluating *K. pneumoniae*, the very major error rate was 5.9% (2/34). One of the two *K. pneumoniae* very major errors had an MIC value that was in essential agreement with the reference. Therefore, the adjusted very major error rate is at 2.9% (1/34).

To mitigate the potential for occurrence of these errors, the following statement was included in the Limitations section of the device labeling:

> *Due to the lack of an intermediate interpretive category for Eravacycline, results obtained with E. cloacae and K. pneumoniae and E. faecium showed potential for very major errors compared to the reference method and results obtained with E. faecalis showed potential for major and very major errors. If critical to patient care, testing should be repeated using an alternative testing/reference method prior to reporting results for:*
>
> *E. cloacae when ETEST MIC is 0.5 µg/mL (Susceptible)*
> *K. pneumoniae when ETEST MIC is 0.25 or 0.5 µg/mL (Susceptible)*
>
> *E. faecium when ETEST MIC is 0.064 µg/mL (Susceptible)*
> *E. faecalis when ETEST MIC is 0.064 (Susceptible) or 0.125 µg/mL (non-Susceptible).*

ETEST Eravacycline performance for all *E. faecalis* and *E. faecium* isolates (clinical and challenge) is acceptable with 100% EA and 94.9% CA. There were four major errors (4/128 = 3.1%) and three very major errors (3/9 = 33.3%). All errors had an MIC value that was in essential agreement with the reference. Therefore, the adjusted major and very major error is zero which is acceptable. To address the adjustment of the major and very major errors, the following statement is included as a footnote to the performance table in the device labeling:

The overall categorical major and very major error rates for eravacycline when testing Enterococcus spp. (E. faecalis and E. faecium) clinical and challenge isolates is 3.1% (4/128) and 33.3% (3/9), respectively. Based on the essential agreement and lack of an intermediate breakpoint for eravacycline, the overall adjusted major and very major error rates for testing Enterococcus spp. clinical and challenge isolates is zero.

Inoculator and ETEST Strip Applicator Options

Culture media plates for ETEST can be inoculated and streaked by swabs manually or with the RETRO C80 inoculator. ETEST strips can be applied onto inoculated media using forceps or the NEMA C88 vacuum pen.

The ETEST Eravacycline studies used manual inoculation with swabs and applied ETEST strips with forceps at all test sites. The following statement is included as a footnote to the performance table in the device labeling:

The optional inoculator and ETEST strip applicator were used for plate inoculation and applying ETEST strips onto agar media. In the ETEST Eravacycline clinical studies, swabs were used for plate inoculation/streaking and forceps were used for ETEST strip application.

Trending

A trending analysis was conducted using the combined data (clinical and challenge) for each organism species and group. This trending calculation analyzes device MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method. MIC values that are off-scale for both the reference and device are not considered in the trending analysis.

Trending results were stratified by species to determine if species-related trends were observed (**Table 3**). Species for which the difference between the percentage of isolates with higher versus lower MIC values was ≥30% and for which the confidence interval was determined to be statistically significant were considered to have evidence of trending and is addressed in labeling.

A trend toward higher MIC values was observed for *C. freundii, E. coli* and *K. aerogenes*. The following statement is included as a footnote to the performance table in the device labeling:

ETEST Eravacycline MIC values tended to be in exact agreement or at least one doubling dilution higher when testing C. freundii, E. coli and K. aerogenes compared to the CLSI reference broth microdilution method. Of these species, only C. freundii reported categorical errors (4/53 (7%) were major errors), all of which were within essential agreement of the reference method which is acceptable.

Table 3. Trending by Species (clinical and challenge isolates combined)

Organism	Total Evaluable for Trending	≥1 dil. Lower # (%)	Exact # (%)	≥1 dil. Higher # (%)	Percent Difference (95% CI)	Trending Noted
Citrobacter freundii	70	3	37	30	38.6% (25.28 to 50.27)	yes
Citrobacter koseri	30	0	24	6	20.0%	no
Enterobacter cloacae	72	5	51	16	15.3%	no
Escherichia coli	191	11	97	83	37.7% (29.65 to 45.22)	yes
Klebsiella aerogenes	32	0	16	16	50.0% (30.43 to 66.37)	yes
Klebsiella oxytoca	43	2	35	6	9.3%	no
Klebsiella pneumoniae	104	5	81	18	12.5%	no
Enterobacteriaceae (all)	542	26	341	175	27.5%	no
Enterococcus faecalis	74	9	54	11	2.7%	no
Enterococcus faecium	63	4	54	5	1.6%	no
Enterococcus spp. (all)	137	13	108	16	2.2%	no

Resistance Markers

Resistance markers for clinical isolates were identified by genotype sequencing. They consisted of β-lactamase genetic markers (*tem, cmy, oxa, ndm, ctx, kpc, act, shv, vim, ges, oxy, okp, imp, lap, mir*) and tetracycline-resistance genetic markers [*tet(A), tet(B) tet(D), tet(L), tet(M), tet(S*])*.*

2. Matrix Comparison:

Not applicable

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable

D Clinical Cut-Off:

Not applicable

E Expected Values/Reference Range:

The FDA-identified susceptibility interpretive criteria for eravacycline are listed in **Table 4**.

Table 4: FDA Identified Interpretive Criteria for Eravacycline (µg/mL)[a]

Organism	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤0.5	-	-
Enterococcus faecalis and *Enterococcus faecium*	≤0.06	-	-

[a]According to FDA STIC Website

VIII Proposed Labeling:

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

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a breakpoint change protocol that was reviewed and accepted by FDA. This protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate the ETEST Eravacycline when revised breakpoints for eravacycline are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, bioMérieux will update the eravacycline device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.