510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250274

B Applicant

bioMérieux, SA

C Proprietary and Established Names

ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 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 a special design and formulation of imipenem/relebactam at concentrations of 0.008/4-128/4 µg/mL for susceptibility testing of the following microorganisms: *Pseudomonas aeruginosa*.

B Measurand:

Imipenem/relebactam 0.008/4-128/4 µg/mL

C Type of Test:

Quantitative Antimicrobial Susceptibility Test growth-based detection

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

ETEST is a manual, quantitative technique for the 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.

Testing with ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) is indicated for *Pseudomonas aeruginosa*, as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC).

The ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) demonstrated acceptable performance with the following microorganism:

Pseudomonas aeruginosa

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Manual reading only

IV Device/System Characteristics:

A Device Description:

ETEST is a thin, inert and non-porous plastic strip carrying the MIC reading scale in µg/mL on one side and a predefined antibiotic gradient on the other side.

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

The ETEST 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 exponential gradient of antibiotic concentrations.

ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) with a concentration range of 0.008/4-128/4 µg/mL is specially designed and formulated for testing *P. aeruginosa*.

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 Meropenem/Vaborbactam (MEV) (0.004/8-64/8 µg/mL)

B Predicate 510(k) Number(s):

K183031

C Comparison with Predicate(s):

Table 1: Predicate Comparison

Device & Predicate Device(s):	**Device K250274**	**Predicate K183031**
Device Trade Name	ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL)	ETEST Meropenem/Vaborbactam (MEV) (0.004-64/8 µg/mL)
General Device Characteristic Similarities		
Intended Use	ETEST is a manual, quantitative technique for the 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	Same

Device & Predicate Device(s):	Device K250274	Predicate K183031
	microorganisms tested on agar media after overnight incubation.	
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
Inoculation	Isolated colonies from culture in a suspension equivalent to 0.5 McFarland. Inoculum is applied to agar with swab manually or with rotation plate for even distribution of inoculum.	Same
Incubation	35º±2º C for 16 – 20 hours	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC test strip.	Same
Results	MIC (µg/mL)	Same
General Device Characteristic Differences		
Antimicrobial Agent	Imipenem/relebactam	Meropenem/ vaborbactam
Drug concentration Range	0.008/4-128/4 µg/mL	0.004/8-64/8 µg/mL
Indication for Use/Claimed Organisms	*Pseudomonas aeruginosa*	*Enterobacter cloacae* complex *Escherichia coli* *Klebsiella pneumoniae* *Citrobacter freundii* *Citrobacter koseri* *Klebsiella aerogenes* *Klebsiella oxytoca* *Morganella morganii*

Device & Predicate Device(s):	Device K250274	Predicate K183031
		Providencia spp. *Serratia marcescens*

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 M07 12th Edition, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically* (March 2024)
- CLSI M100 34th ed. *Performance Standards for Antimicrobial Susceptibility Testing* (February 2024)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using 10 on-scale *P. aeruginosa* isolates. Each isolate was tested in triplicate over three days for a total of 270 data points. The mode MIC value 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. All MIC results were on scale. The testing resulted in overall reproducibility of greater than 95%. The results are acceptable.

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:
   Inoculums were prepared to achieve turbidity equivalent to a 0.5 McFarland standard. Colony counts were performed periodically at each site for all QC replicates, from at least one replicate of each reproducibility isolate on each of the three days of testing, and from a minimum of 10% of the clinical strains tested. The inoculum densities were acceptable.

Purity Check:
Verification of isolate purity was conducted on all clinical, challenge, QC, and reproducibility organism suspensions for each ETEST and from each growth control well of the broth microdilution reference panel. All organism suspensions for both the broth microdilution reference panels and ETEST were pure.

Growth or Device Failure:
No device failures occurred in the ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) clinical study.

Quality Control Testing:
Even though IRPA is specially formulated for testing *P. aeruginosa*, other quality control (QC) strains were also tested. One CLSI recommended QC strain (*K. pneumoniae* ATCC BAA-1705) and one CLSI QC strain (*P. aeruginosa* ATCC 27853) were tested at least 20 times per site at four sites using both ETEST and broth microdilution (BMD) reference methods. One CLSI QC strain (*E. coli* ATCC 25922) was tested at least 20 times per site at four sites for verification broth microdilution (BMD) reference results only. The results are summarized in **Table 2**.

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

Table 2: Quality Control Test Results for ETEST Imipenem/Relebactam

QC Organism	Expected Range (µg/mL)	Concentration µg/mL	Reference BMD (All Sites)	ETEST (All Sites)
Klebsiella pneumoniae ATCC BAA-1705	0.03/4 – 0.25/4	<0.03		
		0.03		
		0.06	3	38
		0.125	63	45
		0.25	16	
		>0.25	1	
Pseudomonas aeruginosa ATCC 27853	0.25/4 – 1/4	<0.25		
		0.25	63	58
		0.5	18	25
		1	2	
		>1		
Escherichia coli ATCC 25922	0.06/4 – 0.5/4	<0.06		N/A
		0.06	1	
		0.125	65	
		0.25	15	
		0.5	2	
		>0.5		

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Results obtained with ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel, prepared and interpreted according to recommendations outlined in CLSI M07 *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically* 11th ed., contained two-fold serial dilutions of imipenem/relebactam with a concentration range of 0.008/4 – 128/4 µg/mL. At the end of incubation, the MIC value obtained from the ETEST (determined based on 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: 35º C ± 2º C for 16-20 hours in aerobic conditions

   Clinical testing was performed at three external sites (two US sites and one OUS site) with both ETEST imipenem/relebactam and the reference method with a total of 360 *P. aeruginosa* clinical isolates. The clinical testing included 48.9% contemporary (176/360; isolated no longer than 6 months prior to testing) and 51.1% stock (184/360; no time limit on time from isolation prior to testing) clinical isolates. A total of 77 *P. aeruginosa* challenge isolates were also evaluated at one internal site using ETEST imipenem/relebactam and the reference method.

   In total, the comparative study included 437 *P. aeruginosa* clinical and challenge isolates.

   The performance of the 437 clinical and challenge isolates is summarized in **Table 3**.

Table 3: Performance of ETEST Imipenem/Relebactam with Clinical and Challenge Isolates

	Tot	No. EA	EA %	Eval Tot	No. Eval EA	Eval EA %	No. CA	CA %	No. R	No. S	min	maj	vmj
***Pseudomonas aeruginosa* (Breakpoints (µg/mL): S≤2/4, I 4/4, R≥8/4)**													
Clinical	360	351	97.5	355	346	97.5	327	90.8	27	296	30	3	0
Challenge	77	76	98.7	52	51	98.1	71	92.2	36	33	6	0	0
Total	437	427	**97.7**	407	397	97.5	398	**91.1**	63	329	36	3	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable MIC results
S – Susceptible
min – minor discrepancies
maj – manor discrepancies
vmj – very major discrepancies
R – resistant

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

ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) performance for all *P. aeruginosa* isolates (clinical and challenge) is acceptable with an EA of 97.7% and CA of 91.1%. There were three major errors among 329 susceptible isolates (3/329 = 0.9%) which is acceptable. There were no very major errors.

Testing/Reporting Non-Indicated Species
For this review, the interpretative criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and Cosmetic Act, the following statement is added in the precautions section of 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 labelling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

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, the NEMA C88 vacuum pen or the automatic Applicator SIMPLEX C76.

The ETEST studies for imipenem/relebactam 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:

In the ETEST Imipenem/Relebactam clinical studies, swabs were used for plate inoculation/streaking and forceps were used for ETEST strip application. Testing with the optional Inoculator RETRO C80, Vacuum Pen NEMA C88, and Applicator SIMPLEX C76 was not evaluated during the clinical studies.

MIC Trending Analysis
Using the combined clinical and challenge data, an analysis of trending was conducted for *P. aeruginosa* isolates. Results are to determine if species-related trends were observed (**Table 4**). This trending calculation considers MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method irrespective of whether the device MIC values are on-scale or not. Results that are not clearly at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Species for which the difference between the percentage of isolates with higher vs. lower readings was ≥ 30% and for which the confidence interval was determined to be statistically

significant were considered to show evidence of trending. Trending that provides higher or lower MIC values compared to the reference is addressed in labeling.

No significant trending was observed for *P. aeruginosa* overall with ETEST imipenem/relebactam when compared to the reference method (**Table 4**).

Table 4. Trending Observed with ETEST Imipenem/Relebactam

Organism Name	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No.	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
P. aeruginosa	407	99, (24.3)	245	63, (15.5)	-9%, (-14%, -3%)	No

Resistant Isolates:
A total of 437 clinical and challenge isolates were tested for *P. aeruginosa* and 63 (14.4%) resistant isolates were available for testing which is acceptable.

Resistance Mechanism Characterization
Challenge isolates of *P. aeruginosa* harboring various molecular mechanisms of resistance were evaluated with ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL). The following mechanisms were evaluated: CARB, FOX, GES, GIM, IMP, KPC, NDM, OXA, PDC, PER, PME, SHV, SPM, TEM, VEB, and VIM alleles.

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 recognized susceptibility interpretive criteria for imipenem/relebactam are listed in **Table 5**.

Table 5. FDA Identified Interpretive Criteria for Imipenem/Relebactam

	Minimum Inhibitory Concentration (µg/mL)[a]		
Organism	**S**	**I**	**R**
Pseudomonas aeruginosa	≤2/4	4/4	≥8/4

[a] FDA STIC Webpage

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 bioMérieux ETEST Imipenem/Relebactam *P. aeruginosa* (IRPA) (0.008/4-128/4 µg/mL) when revised breakpoints for imipenem/relebactam 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 ETEST imipenem/relebactam 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.