Food and Drug Administration
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www.fda.gov

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K191953

B Applicant

bioMérieux SA

C Proprietary and Established Names

ETEST Imipenem/Relebactam (IPR) (0.002/4-32/4 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 decision for ETEST Imipenem/Relebactam (IPR) at concentrations of 0.002/4 – 32 µg/mL for susceptibility testing of gram negative aerobic microorganisms

B Measurand:
Imipenem/Relebactam 0.002/4 -32/4 µg/mL. The relebactam concentration is fixed at 4 µg/mL.

C Type of Test:
Quantitative AST 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 determination of antimicrobial susceptibility of non-fastidious Gram-negative and Gram-ositive aerobic bacteria and fastidious bacteria. The system comprises a predefined greadient which is used to determine the Minimum Inhibitory Concentration (MIC, in ug/mL) of different antimicrobial agents against microorganisms tested on agar media after overnight incubation.

Imipenem/Relebactam has been shown to be active against the Gram-negative aerobic microorganisms listed below according to the FDA label for this antimicrobial agent.

ETEST IPR can be used to determine the MIC of Imipenem/Relebactam against the following microorganisms:

Active both in vitro and in clinical infections:

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae
Pseudomonas aeruginosa

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The ability of ETEST Imipenem/Relebactam to detect resistant isolates is unknown for *Citrobacter freundii, Klebsiella aerogenes, Enterobacter cloacae/Enterobacter cloacae* complex and *Klebsiella oxytoca* because an insufficient number of resistant strains were available at the time of comparative testing. Isolates yielding Imipenem/Relebactam results suggestive of a resistant category should be submitted to a reference laboratory for further testing.

Perform an alternative method of testing for isolates of *Morganella morganii, Citrobacter koseri, Serratia marcescens, Providencia rettgeri* and *Providencia stuartii*.

D Special Instrument Requirements:

Not Applicable

Device/System Characteristics:

A 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. 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.

B Principle of Operation:

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 Imipenem/Relebactam ranges from 0.002/4 to 32/4 µg/mL. The relebactam concentration is fixed at 4 µg/mL in this combination.

IV 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):

Device & Predicate Device(s):	**Device: K191953**	**Predicate: K183031**
Device Trade Name	**ETEST Imipenem/Relebactam (IPR) (0.002/4 – 32/4 µg/mL)**	**ETEST Meropenem/Vaborbactam (0.004/8 – 64/8 µg/mL)**
General Device Characteristic Similarities		

Device & Predicate Device(s):	**Device: K191953**	**Predicate: K183031**
Intended Use/Indications for 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 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	A predefined exponential gradient of the dried and stabilized antibiotic covers a continuous concentration range across two-fold dilutions of a conventional MIC method.	Same
Inoculation	Isolated colonies from subculture	Same
Incubation	35º ± 2º C for 16 – 20 hours	Same
Result	MIC	Same
General Device Characteristic Differences		
Antimicrobial Agent	Imipenem/Relebactam	Meropenem/Vaborbactam
Drug Concentration Range	0.002/4 – 32/4 µg/mL	0.004/8 – 64/8 µg/mL

V Standards/Guidance Documents Referenced:

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

CLSI M02-A12, Performance Standards for Antimicrobial Disk Susceptibility Test; Approved Standard, January 2015.

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

CLSI M100-28th ed., Performance Standards for Antimicrobial Susceptibility Testing (January 2018).

VI Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   A reproducibility study was performed at three external sites using ten isolates of Gram-negative organisms that were consistent with the intended use. The isolates tested included: *E. cloacae* (1 isolate), *E. coli* (2 isolates), *K. oxytoca* (1 isolate), *K. pneumoniae* (2 isolates) and *P. aeruginosa* (4 isolates). The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ± one doubling dilution of the mode MIC value.

   The majority of data points were on-scale and within ± one doubling dilution of the mode MIC value. One isolate provided off-scale results. The data was analyzed taking into consideration best case and worst case scenarios as described in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems*.

   The reproducibility was acceptable at 100% for best case results and 99.6% for worst case results.

2. Linearity:

   Not Applicable

3. Analytical Specificity/Interference:

   Not Applicable

4. Assay Reportable Range:

   0.002/4 – 32/4 µg/mL

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

Inoculum Density Check: Inoculum density checks were performed on quality control strains, strains used for reproducibility testing and for at least 10% of the clinical isolates. The inoculum density testing verified the appropriate organism concentrations.

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

Growth or Device Failure: There were no device failures in the ETEST Imipenem/Relebactam clinical trial. All clinical and challenge isolates grew in the ETEST Imipenem/Relabactam test system.

Quality Control Testing. The QC strain recommended by the CLSI for testing the combination of imipenem/relebactam (*K. pneumoniae* ATCC BAA 1705) was tested at four sites for a minimum of 20 times at each site by both the ETEST and the reference method. The results demonstrate that the imipenem/relebactam ETEST can produce quality control results for *K. pneumoniae* ATCC BAA 1705 in the recommended range >95% of the time (Table 1).

In addition to testing *K. pneumoniae* ATCC BAA 1705, the following additional "auxiliary" quality control strains were tested at four sites for a minimum of 20 times at each site by both the ETEST and the reference method: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 35218. Even though these auxiliary QC strains generally are not relevant for verification of the activity of the relebactam component of imipenem/relebactam combination, they do provide verification of the activity of the imipenem component of the drug (Table 2).

QC Strain Integrity Check: Additional QC testing was performed to confirm the integrity of the quality control strains *K. pneumoniae* ATCC 1705, *E. coli* ATCC 35318 and *K. pneumoniae* ATCC 700603 as recommended by the CLSI. All results were acceptable.

Table 1: Quality Control Summary for Imipenem/Relebactam with the CLSI-Recommended QC Strain.

QC Organism	Imipenem/ Relebactam Expected Range (µg/mL)	Concentration (µg/mL)	Reference	ETEST
K. pneumoniae ATCC BAA-1705	0.032 - 0.25	<0.032		
		0.032		
		0.064	7	
		0.125	60	52
		0.25	17	32
		>0.25		

Table 2: Quality Control Summary for Imipenem/Relebactam with Auxiliary QC Strains

QC Organism	Imipenem/ Relebactam Expected Range (µg/mL)	Concentration (µg/mL)	Reference	ETEST
E. coli ATCC 25922	0.064 – 0.25	<0.064		
		0.064		
		0.125	75	59
		0.25	9	25
		>0.25		
K. pneumoniae ATCC 700603	0.032 – 0.25	<0.032		
		0.032		
		0.064	6	
		0.125	69	66
		0.25	8	18
		>0.25	1	
P. aeruginosa ATCC 27853	0.25 - 1	<0.125		
		0.125		
		0.25	46	4
		0.5	38	79
		1		1
		>1		
E. coli ATCC 35218	0.064 – 0.25	<0.064		
		0.064		
		0.125	75	29
		0.25	9	55
		>0.25		

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 were compared to results obtained with the CLSI broth microdilution reference panel. The CLSI panel was prepared and interpreted according to CLSI recommendations outlined in the CLSI Standard: CLSI Document M07-A10. 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 suspension equivalent to a 0.5 McFarland standard suspension
- Incubation 35 °C in ambient air; 16-20 hours for all organisms

Plate inoculation was performed using an optional inoculator and strip applicator. To address the use of the optional inoculator and strip applicator the sponsor included the following footnote to the Performance Characteristics Table:

The optional inoculator and ETEST strip applicator were used for plate inoculation and applying ETEST strips onto agar media. In the studies, swabs and the Inoculator RETRO C80 were used for plate inoculation/streaking and forceps and the Vacuum Pen NEMA C88 were used for ETEST® strip application.

Clinical testing was performed at four sites with both ETEST Imipenem/Relebactam and the reference method using a total of 420 *Enterobacteriaceae* isolates including the following indicated for use species: *C. freundii* (30 isolates), *E. cloacae* (20 isolates), *E. cloacae* complex (70 isolates), *E. coli* (152 isolates), *K. aerogenes* (30 isolates), *K. oxytoca* (30 isolates) and *K. pneumoniae* (88 isolates). Of these 241 were fresh isolates (57.4%), 72 were recent isolates (17.1%), and 107 were stock isolates (25.5%). The percentage of fresh/recent isolates considered to be "contemporary" is unknown.

A total of 154 isolates of *P. aeruginosa* were tested with ETEST Imipenem/Relebactam and the reference method using 93 fresh isolates (60.4%), 21 recent isolates (13.6%) and 40 stock isolates (26.0%). The percentage of fresh/recent isolates considered to be "contemporary" is unknown.

A total of 78 challenge isolates were tested at a single site using ETEST Imipenem/Relebactam and the reference method including the following indicated for use species: *E. cloacae* (13 isolates), *E. coli* (13 isolates), *K. oxytoca* (2 isolates), *K. pneumoniae* (29 isolates) and *P. aeruginosa* (21 isolates).

Results of comparative testing with clinical and challenge isolates combined demonstrated an EA of 95.8% and CA of 98.1% for *Enterobacteriaceae* which was considered acceptable (Table 3). One very major discrepancy was observed among 44 *Enterobacteriaceae* resistant isolates and was considered a random error. The sponsor provided the following footnote to the performance table to address the very major error:

The percentage of very major errors of 2.3% (1/44 resistant Enterobacteriaceae isolates) was only due to one Very Major Error with an E. coli isolate. Repeat testing of both ETEST Imipenem/Relebactam and the reference method with this isolate showed acceptable category agreement between the two tests.

For *P. aeruginosa*, results of comparative testing with clinical and challenge isolates demonstrated EA and CA of 96.0% which was considered acceptable (Table 3). There were no major or very major discrepancies with *P. aeruginosa*.

Table 3. Performance of ETEST Imipenem/Relebactam

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Enterobacteriaceae[a]													
Clinical	420	402	95.7	398	380	95.5	416	99.0	32	385	3	0	1[b]
Challenge	57	55	96.5	51	49	96.1	52	91.2	12	43	5	0	0
Total	477	457	95.8	449	429	95.5	468	98.1	44	428	8	0	1[b]
Pseudomonas aeruginosa													
Clinical	154	147	95.5	152	145	95.4	147	95.5	9	139	4	3	0
Challenge	21	21	100.0	13	13	100.0	21	100.0	10	11	0	0	0
Total	175	168	96.0	165	158	95.8	168	96.0	19	150	4	3	0

[a] Includes isolates of *C. freundii, E. cloacae*/*E. cloacae* complex, *E. coli, K. aerogenes, K. oxytoca* and *K. pneumoniae*

[b] Considered a random error

EA – Essential Agreement (± 1 dilution)
CA – Category Agreement
Eval – Evaluable isolates
R – Resistant isolates
S – Susceptible 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 Imipenem/Relebactam are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both ETEST Imipenem/Relebactam 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 Imipenem/Relebactam.

An insufficient number of resistant strains were evaluated for the following species: *C. freundii, E. cloacae and E. cloacae complex, K. aerogenes* and *K. oxytoca*. The sponsor included the following limitation in the device labeling:

The ability of ETEST Imipenem/Relebactam to detect resistant isolates is unknown for Citrobacter freundii, Klebsiella aerogenes, Enterobacter cloacae/Enterobacter cloacae complex and Klebsiella oxytoca because an insufficient number of resistant strains were available at the time of comparative testing. Isolates yielding Imipenem/Relebactam results suggestive of a resistant category should be submitted to a reference laboratory for further testing.

The FDA approved drug label for imipenem/relebactam indicates that the drug is active *in vitro* against isolates of *C. koseri*. During the clinical study, 30 clinical isolates of *C. koseri* were tested with ETEST Imipenem/Relebactam, however, the EA obtained for this species

was not acceptable (86.7%). In addition, other members of the *Enterobacteriaceae* not listed as indicated species in the FDA approved drug label (*Morganella morganii, Citrobacter koseri, Serratia marcescens, Providencia rettgeri, Providencia stuartii*) were tested and showed unacceptable category agreement as compared to the reference method. The sponsor included the following limitation in the device labeling to address testing of these species:

> *Perform an alternative method of testing for isolates of Morganella morganii, Citrobacter koseri, Serratia marcescens, Providencia rettgeri and Providencia stuartii.*

To address testing and reporting of MIC results for non-indicated species the sponsor included the following statement 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 labelling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

MIC Trending Analysis

Using the combined clinical and challenge data an analysis of trending was conducted for both *Enterobacteriaceae* and *P. aeruginosa*. 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.

Trending results for indicated species and overall trending for indicated Enterobacteriaceae are shown in Table 4; results are stratified by species to determine if species-related trends were observed. 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.

A trend toward higher MIC reading was observed for *Enterobacteriaceae* and *P. aeruginosa* with ETEST Imipenem/Relebactam (Table 4). To address the observed trending, the sponsor included the following footnote to the performance table in the device labeling:

> *ETEST Imipenem/Relebactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing Enterobacteriaceae and P. aeruginosa compared to the reference broth microdilution method.*

Table 4. Trending for ETEST Imipenem/Relebactam

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
C. freundii	30	0	8 (26.7)	22 (73.3)	73.3	Yes
E. cloacae/E. cloacae complex	103	3 (2.9)	35 (34.0)	65 (63.1)	60.2	Yes
E. coli	148	7 (4.7)	63 (42.6)	78 (52.7)	48.0	Yes
K. aerogenes	30	11 (36.7)	14 (46.7)	5 (16.7)	-20.0	No
K. oxytoca	32	2 (6.3)	13 (40.6)	17 (53.1)	46.9	Yes
K. pneumoniae	111	33 (29.7)	43 (38.7)	35 (31.5)	1.8	No
Enterobacteriaceae	454	56 (12.3)	176 (38.8)	222 (48.9)	36.6	Yes
P. aeruginosa	165	12 (7.3)	77 (46.7)	76 (46.1)	38.8	Yes

Resistance Mechanism Characterization
Challenge isolates of *Enterobacteriaceae* and *P. aeruginosa* harboring various molecular mechanisms of resistance noted in the FDA drug label were evaluated with ETEST Imipenem/Relebactam. The following drug label listed mechanisms were evaluated: *KPC*, *TEM*, SHV, *CTX-M*, *CMY*, *DHA*, *ACT*, *PDC*, *GES*, and *VEB.*

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:

Table 5. FDA-Identified Interpretive Criteria for Imipenem/Relebactam

Organism	Interpretive Criteria for Imipenem/Relebactam MIC (µg/mL)[a]		
	S	I	R
Enterobacteriaceae [b]	≤1/4	2/4	≥4/4
P. aeruginosa	≤2/4	4/4	≥8/4

[a] FDA STIC Webpage
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm
[b] *C. freundii, E. cloacae, E. coli, K. aerogenes, K. oxytoca, K. pneumoniae*

VII Proposed Labeling:

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

VIII 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/development-resources/antibacterial-susceptibility-test-interpretive-criteria. The protocol outline the specific procedures and acceptance criteria that bioMérieux intends to use to evaluate ETEST Imipenem/Relebactam (IPR) (0.002/4 – 32/4) 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 imipenem/relebactam device label to include (1) the new breakpoint, (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.