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

K191809

B Applicant

Liofilchem s. r. l.

C Proprietary and Established Names

MTS Imipenem-relebactam 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 determination for Imipenem/relebactam at concentrations of 0.002/4 – 32/4 µg/mL for susceptibility testing of non-fastidious Gram-negative organisms

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 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:

MTS (MIC Test Strip) Imipenem-relebactam 0.002/4 – 32/4 µg/mL is a quantitative method intended for the in vitro determination of antimicrobial susceptibility of bacteria. MTS consists of specialized paper impregnated with a pre-defined concentration gradient of an antimicrobial agent, which is used to determine the minimum inhibitory concentration (MIC) in µg/mL of antimicrobial agents against bacteria as tested on agar media using overnight incubation and manual reading procedures.

The MTS Imipenem-relebactam at concentrations of 0.002/4 – 32/4 µg/mL should be interpreted at 16-20 hours of incubation.

Imipenem-relebactam has been shown to be active both clinically and in vitro against these bacterial species according to the FDA drug approved label:

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

Imipenem-relebactam has been shown to be active in vitro only against the non-fastidious bacteria listed below according to the FDA drug approved label:

Citrobacter koseri

C Special Conditions for Use Statement(s):

- Rx - For Prescription Use Only

- The ability of the MTS Imipenem-relebactam to detect resistant isolates with the following drug/bacterial species combinations is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing.

  Imipenem-relebactam: *Citrobacter koseri*

- Due to a limited number of isolates for testing, performance for *E. asburiae* could not be adequately evaluated. Therefore, an alternative test should be performed for imipenem/relebactam when *E. asburiae* is isolated.

- Due to low essential and categorical agreement for *P. mirabilis*, an alternative test should be performed for the imipenem/relebactam when *P. mirabilis* is isolated.

D Special Instrument Requirements:

Manual reading only

IV Device/System Characteristics:

A Device Description:

The MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of Imipenem/relebactam across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the imipenem/relebactam code (I/R) and the MIC reading scale in µg/mL. MIC values are determined by identifying the drug concentration at which growth of the ellipse ends.

B Principle of Operation:

MTS are made of specialized paper impregnated with a predefined concentration gradient of antibiotic, across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. When the MIC Test Strip is applied onto an inoculated agar surface, the preformed exponential gradient of antimicrobial agent is immediately transferred to the agar matrix. After 16-20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read directly from the scale in terms of µg/mL at the point where the edge of the inhibition ellipse intersects the strip MIC Test Strip.

Growth along the entire gradient (i.e., no inhibition ellipse) indicates that the MIC value is greater than or equal to (≥) the highest value on the scale. An inhibition ellipse that intersects below the lower end of the scale is read as less than (<) the lowest value. An MIC of 0.125 µg/mL is considered to be the same as 0.12 µg/mL for reporting purposes.

An MTS MIC value which falls between standard two-fold dilutions must be rounded up to the next standard upper two-fold value before categorization.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Liofilchem MIC Test Strip (MTS)-Vancomycin 0.016 -256 ug/mL

B Predicate 510(k) Number(s):

K153687

C Comparison with Predicate(s):

Table 1: Comparison with the Predicate

Device & Predicate Device(s):	**Device: K191809**	**Predicate: K153687**
Device Trade Name	**Liofilchem MTS, Imipenem/relebactam**	**Liofilchem MTS, Vancomycin**
General Device Characteristic Similarities		
Media	Mueller-Hinton agar	Same
Inoculation	Isolated colonies from culture in suspension equivalent to 0.5 McFarland. Inoculum is applied manually using the manual plate inoculation method or plate rotator for even distribution of inoculum	Same
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip; interpret the MIC at 100% inhibition	Same
Result	MIC	Same
General Device Characteristic Differences		
Intended Use/Indications For Use	Quantitative susceptibility to antimicrobial agents against non-fastidious Gram-negative organisms	Quantitative susceptibility to antimicrobial agents against Gram-positive organisms
Antimicrobial Agent	Imipenem/relebactam (I/R)	Vancomycin (VA)
Drug Concentration Range	0.002/4 – 32/4 µg/mL	0.016 -256 ug/mL
Incubation	35 ± 2°C for 16 – 20 hours	35 ± 2°C for 24 hours

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-A10 “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard, Tenth Edition January 2015”.
- CLSI M100-29th ed. “Performance Standards for Antimicrobial Susceptibility Testing (January 2019).

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using nine Gram-negative organisms. Each isolate was tested in triplicate over three days for a total of 243 data points. The mode of 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. The Gram-negative reproducibility panel included two *E. coli*, two *K. pneumoniae*, one *K. oxytoca*, one *K. aerogenes*, one *E. cloacae*, and two *P. aeruginosa* isolates. In addition, the sponsor tested an additional isolate, *C. freundii*, in triplicate over three days with three different readings for an additional 27 data points. All MIC results were on scale. When combined with the other nine isolates, the testing resulted in overall reproducibility of greater than 95%.

   The results were acceptable.

2. Linearity:

   N/A

3. Analytical Specificity/Interference:

   N/A

4. Assay Reportable Range:

   N/A

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

   Inoculum Density Check:
   The inoculum was 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 and challenge strains tested. Inoculum density checks were performed, and the colony counts obtained for each isolate were within the recommended range of approximately 1x 10^8 CFU/mL.

   Purity Checks:
   Purity checks were performed on all isolates following MTS inoculation. All isolates were pure in both the broth microdilution reference panels and the MTS agar plates.

Growth Failure Rate:
None of the isolates in the study failed to grow with the Imipenem/relebactam MTS.

Quality Control (QC) Testing:
The QC strains recommended by the CLSI for testing the combination of imipenem/relebactam (i.e., *K. pneumoniae* ATCC BAA 1705 and *K. pneumoniae* ATCC BAA 2814) were tested at three sites for a minimum of 20 times at each site by both the MTS and the reference method. The results demonstrate that the imipenem/relebactam MTS can produce quality control results in the recommended range >95% of the time (Table 2).

Table 2: Quality Control Summary for Imipenem/relebactam with the CLSI-Recommended QC Strain

QC Organism	Imipenem/ Relebactam Expected Range (µg/mL)	Concentration (µg/mL)	Reference	MTS
K. pneumoniae ATCC BAA-1705	0.03/4 – 0.25/4 µg/mL	0.015		
		0.03		
		0.06		
		0.12	50	40
		0.25	12	25
		0.5		
K. pneumoniae ATCC BAA-2814	0.06/4 – 0.25/4	0.03		
		0.06		
		0.12	21	17
		0.25	41	45
		0.5		

In addition to testing *K. pneumoniae* ATCC BAA 1705 and *K. pneumoniae* ATCC BAA 2814, "Auxiliary" QC strains, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 QC, were tested at each site by both the MTS and the reference. 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 3).

Table 3: Quality Control Summary for Imipenem/relebactam with Auxiliary QC Strains

Organism	Imipenem/ Relebactam Expected Range (µg/mL)	Concentration (µg/mL)	Reference	MTS
E. coli ATCC 25922	0.06/4 -0.25/4	0.03		
		0.06	1	0
		0.12	48	33
		0.25	13	29
		0.5		
P. aeruginosa ATCC 27853	0.25/4 – 1/4	0.12		
		0.25	18	9
		0.5	44	52
		1		1
		2		

QC Strain Integrity Check: Additional QC testing was performed to confirm the integrity of the quality control strains *K. pneumoniae* ATCC 1705 by testing it with imipenem alone (Table 4). All results were acceptable.

Table 4: Quality Control Summary for Imipenem Alone

Organism	Imipenem Expected Range (µg/mL)	Concentration (µg/mL)	Reference	MTS
K. pneumoniae ATCC BAA-1705	4 - 16	2		
		4		
		8		
		16	62	
		32		

6. Detection Limit:

   N/A

7. Assay Cut-Off:

   N/A

B Comparison Studies:

1. Method Comparison with Predicate Device:

   The MTS, Imipenem/relebactam was evaluated at three sites located within the United States. Each clinical isolate was tested one time by MTS Imipenem/relebactam and the reference

method using the same initial standardized suspension. A total of 390 non-fastidious Gram-negative isolates were tested of which 64.4% were tested within six months of isolation (contemporary isolates). The indicated Gram-negative organisms that were tested for imipenem/relebactam included 30 *C. freundii*, 9 *C. koseri*, 8 *E. asburiae*, 31 *E. cloacae*, 75 *E. coli*, 30 *K. aerogenes*, 30 *K. oxytoca*, 60 *K. pneumoniae*, and 60 *P. aeruginosa* isolates. In addition, testing included 65 non-indicated *Enterobacteriaceae* organisms distributed as follows: 12 *M. morganii*, 15 *P. mirabilis*, 15 *P. vulgaris*, and 15 *S. marcescens* isolates. Those non-indicated organisms were excluded from the performance of the MTS.
Even though the final performance was assessed by excluding non-indicated organisms, data was also analyzed with indicated and non-indicated species combined (See tables below).

Challenge testing was performed at one internal site. A total of 75 Gram-negative challenge isolates were tested. The Gram-negative organisms included 3 *C. freundii*, 12 *E. cloacae*, 11 *E. coli*, 10 *K. aerogenes*, 7 *K. oxytoca*, 11 *K. pneumoniae*, 2 *M. morganii*, 2 *P. mirabilis*, 3 *S. marcescens*, and 14 *P. aeruginosa* isolates. Eight non-indicated organisms were excluded from the performance of the MTS.

Results obtained with the MTS Imipenem/relebactam were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel contained two-fold serial dilutions of Imipenem/relebactam with a range of 0.002/4 – 32/4 μg/mL. The testing conditions for the reference method were consistent with CLSI guidelines as listed in the CLSI document M07-A10. Isolated colonies from an overnight blood agar plate were suspended in saline to achieve a 0.5 McFarland standard turbidity (approximately 10^8 CFU/mL). Testing conditions consisted of incubation of the inoculated Mueller Hinton agar plates in an inverted position at 35°C ± 2° for 16-20 hours. At the end of incubation, the MIC value determined at 100% inhibition of growth along the strip was compared to MIC results obtained with the reference method. Visual aids were provided in reading guides to each laboratory to assist in interpretation.

The performance for the total (combined clinical and challenge) 319 indicated *Enterobacteriaceae* isolates and 74 *P. aeruginosa* is summarized in Table 5 and 7 below. Performance of combined indicated and non-indicated *Enterobacteriaceae* species is summarized in Table 6. To address testing of 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 labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

Table 5: Overall Performance of *Enterobacteriaceae* Clinical and Challenge Isolates (Indicated)

Imipenem/ relebactam	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
Enterobacteriaceae Clinical	265	261	98.5	260	256	98.5	262	98.9	11	3	0	0
Challenge	54	50	92.6	41	37	90.2	50	92.6	32	4	0	0
Combined	319	311	97.5	301	293	97.3	312	97.8	43	7	0	0

Table 6: Overall Performance of *Enterobacteriaceae* Clinical and Challenge Isolates (Indicated + Non-indicated)

Imipenem/ relebactam	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
Enterobacteriaceae Clinical	330	320	97	325	315	96.9	317	96.1	15	13	0	0
Challenge	61	56	91.8	46	41	89.1	57	93.4	35	4	0	0
Combined	391	376	96.2	371	356	96	374	95.7	50	17	0	0

Table 7: Overall Performance of *P. aeruginosa* Clinical and Challenge Isolates

Imipenem/ relebactam	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
P. aeruginosa Clinical	60	60	100	57	57	100	56	93.3	3	4	0	0
Challenge	14	14	100	13	13	100	12	85.7	3	2	0	0
Combined	74	74	100	70	70	100	68	91.9	6	6	0	0

EA – Essential agreement
CA – Category agreement
Eval. – Evaluable isolates
R – Resistant isolates
maj – Major errors
vmj – Very major errors
min – Minor errors

Essential Agreement (EA) is when the Liofilchem MIC Test Strip (MTS) results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the Liofilchem MIC Test Strip (MTS) result interpretation agrees exactly with the reference broth microdilution result interpretation.

An insufficient number of resistant strains were evaluated for C. koseri. As such, the sponsor included the following limitation in the package insert:

> *The ability of the MTS Imipenem-relebactam to detect resistant isolates with the following drug/bacterial species combinations is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing.*
>
> *Imipenem-relebactam: Citrobacter koseri*

The overall performance of indicated *Enterobacteriaceae* isolates (Table 5) is acceptable with 97.5% EA and 97.8% CA. There were no major or very major errors. When *E. asburiae* was evaluated separately, it yielded an EA of 75% (6/8) and CA of 100%,

however, because of a limited number of isolates were tested, the low EA could indicate a possible performance issue with Imipenem/relebactam MTS. Due to the lower number of isolates tested for *E. asburiae*, the following was included as a limitation in the package insert:

> *Due to a limited number of isolates for testing, performance for E. asburiae could not be adequately evaluated. Therefore, an alternative test should be performed for imipenem/relebactam when E. asburiae is isolated.*

When performance was evaluated with indicated and non-indicated species combined, it was acceptable at 96.2% EA and 95.7% CA (Table 6). However, when the non-indicated species, *P. mirabilis* was evaluated separately, it demonstrated EA and CA performance less than 90% (76.5%, 70.6% respectively). Given this low performance, the following limitation was included in the package insert instructing users to perform alternative testing when *P. mirabilis* is isolated:

> *Due to low essential and categorical agreement for P. mirabilis, an alternative test should be performed for the imipenem/relebactam when P. mirabilis is isolated.*

The overall performance of *P. aeruginosa* isolates (Table 7) is acceptable with 100% EA and 91.9% CA. There were no major or very major errors.

Enzyme Group Characterization/Resistance Markers Information:

Enterobacteriaceae and *P. aeruginosa* isolates with beta-lactamases were included in the imipenem/relebactam comparative studies which consisted of the challenge isolates that were tested. Isolates with the following beta lactamases were included: AmpC (9), KPC (8), OXA (11), CTX-M (10), TEM (8), CMY (3), DHA (2), ACT (4), NDM (21), VIM (10), IMP (4), and SHV (8). The *Enterobacteriaceae* included *C. freundii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *M. morganii*, *S. marcescens*, and *P. mirabilis*.

Trending:

Trending was assessed separately for Gram-negative organisms using data for challenge and clinical isolates (Tables 8). Trending was assessed using current trending review practices (i.e., ≥30% difference between higher and lower dilution readings). No significant trending was observed for *Enterobacteriaceae* overall; however, trending was observed for *C. freundii*, *E. cloacae*, and *E. coli* which tended to be in exact agreement or higher when compared to the reference method. Given the observed trending, the following was included in the labeling:

> *Liofilchem MIC Test Strip (MTS) Imipenem-relebactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing C. freundii, E. cloacae, and E. coli compared to the CLSI reference broth microdilution.*

Table 8: Imipenem/relebactam Trending Analysis for Gram-negative organisms

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
C. freundii	**33**	**3 (9.4)**	**11 (34.4)**	**18 (56.3)**	**46.9 (24.4-63.6)**	**Yes**
C. koseri	**9**	**0**	**7 (77.8)**	**2 (22.2)**	**22.2 (-11.7-54.7)**	**No**
E. cloacae	**40**	**7 (17.5)**	**12 (30)**	**21 (52.5)**	**35 (14.2-52)**	**Yes**
E. coli	**83**	**8 (9.6)**	**39 (47)**	**36 (43.4)**	**33.7 (20.7-45.3)**	**Yes**
K. aerogenes	**39**	**13 (33.3)**	**21 (53.9)**	**5 (12.8)**	**-20.5 (-37.8-1.7)**	**No**
K. oxytoca	**37**	**13 (35.1)**	**18 (48.7)**	**6 (16.2)**	**-18.9 (-37.2-1.1)**	**No**
K. pneumoniae	**66**	**26 (39.4)**	**25 (37.9)**	**15 (22.7)**	**-16.7 (-31.4- -0.87)**	**No**
Enterobacteriaceae	**376**	**91 (24.2)**	**171 (45.5)**	**114 (30.3)**	**6.1 (-0.3-12.4)**	**No**
P. aeruginosa	**70**	**14 (20)**	**38 (54.3)**	**18 (25.7)**	**5.7 (-8.2-19.4)**	**No**

2. Matrix Comparison:

   N/A

C Clinical Studies:

1. Clinical Sensitivity:

   N/A

2. Clinical Specificity:

   N/A

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

   N/A

D Clinical Cut-Off:

N/A

E Expected Values/Reference Range:

The FDA-identified susceptibility interpretive criteria for imipenem/relebactam are as listed in Table 9.

Table 9: FDA-Identified Interpretive Criteria[a] for Imipenem/relebactam (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (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] Clinical efficacy was shown for *Klebsiella aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Klebsiella oxytoca*.

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 Liofilchem intends to use to evaluate the Liofilchem MIC test strip (MTS) 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, Liofilchem will update the 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.