510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K182922

B. Purpose for Submission:

To obtain a substantial equivalence determination for Omadacycline (OMC) at concentrations of 0.002-32 µg/mL for susceptibility testing of non-fastidious Gram-negative and non-fastidious Gram-positive organisms

C. Measurand:

Omadacycline 0.002-32 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test growth-based detection

E. Applicant:

Liofilchem s.r.l.

F. Proprietary and Established Names:

MTS Omadacycline 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 Susceptibility Test Systems

4. Panel:

   83 – Microbiology

H. Intended Use:

1. Intended use(s):

   The Liofilchem MTS (MIC Test Strip) Omadacycline 0.002-32 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 Omadacycline at concentrations of 0.002-32 µg/mL should be interpreted at 16-20 hours of incubation.

   MTS Omadacycline can be used to determine the MIC of omadacycline against the following bacteria. Omadacycline has been shown to be active both clinically and in vitro against these bacterial species according to the FDA drug approved label:

   Gram-Positive bacteria
   Staphylococcus aureus
   Staphylococcus lugdunensis
   Enterococcus faecalis

   Gram-Negative bacteria
   Enterobacter cloacae
   Klebsiella pneumoniae

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

   Gram-Positive bacteria
   Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

   Gram-Negative bacteria
   Escherichia coli
   Citrobacter freundii
   Citrobacter koseri
   Klebsiella aerogenes
   Klebsiella oxytoca

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

- *For prescription use*

- *Resistance mechanism characterization was not available for all organisms at the time of comparative testing, and therefore the performance of the MTS Omadacycline for non-fastidious gram-negative bacilli and gram-positive cocci is unknown for the following: Enterobacteriaceae [tet(B)]; Enterococcus species [tet(K), tet(L)]; S. aureus [tet(L)]*

- *The ability of the MTS 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.*
  Omadacycline: Citrobacter koseri

- *Liofilchem MIC Test Strip (MTS) Omadacycline MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. lugdunensis compared to the CLSI reference broth microdilution.*

- *The safety and efficacy of omadacycline in treating Acute Bacterial Skin and Skin Structure Infections (ABSSSI) infections due to Gram-negative organisms other than K. pneumoniae and E. cloacae and Gram-positive organisms other than S. aureus (MRSA and MSSA), S. lugdunensis, and E. faecalis may or may not have been established in adequate and well-controlled clinical trials. The clinical significance of susceptibility information in such instances is unknown.*

- *The safety and efficacy of omadacycline in treating Community-Acquired Bacterial Pneumonia (CABP) infections due to Gram-negative organisms other than K. pneumoniae and Gram-positive organisms other than S. aureus (MSSA only) may or may not have been established in adequate and well-controlled clinical trials. The clinical significance of susceptibility information in such instances is unknown.*

- *Omadacycline is not active in vitro against Morganella spp., Proteus spp., and Providencia spp.*

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Omadacycline MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of omadacycline across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the Omadacycline code (OMC) and the MIC reading scale in µg/mL. 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 MIC Test Strip. Since MTS strip generates MIC values which fall between two-fold dilutions for interpretation, the MIC value read is recorded to the next two-fold dilution value.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Liofilchem MTS, vancomycin

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

   K153687

3. Comparison with predicate:

Table 1: Comparison with the Predicate Device

Similarities		
Item	**Device Liofilchem MTS, Omadacycline (K182922)**	**Predicate Liofilchem MTS, vancomycin (K153687)**
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
Result	MIC	Same

Differences		
Item	**Device Liofilchem MTS, Omadacycline (K182922)**	**Predicate Liofilchem MTS, vancomycin (K153687)**
Intended Use	Quantitative susceptibility to antimicrobial agents against Gram-negative and Gram-positive organisms	Quantitative susceptibility to antimicrobial agents to Gram-positive organisms
Antibiotic	Omadacycline code (OMC)	Vancomycin code (VA)
Reading	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip; interpret the MIC as 80% inhibition when trailing is seen	Manual; the point where the edge of inhibition ellipse intersects the MIC Test Strip; interpret the MIC at 100% inhibition
Incubation	35 ± 2°C for 16 – 20 hours	35 ± 2°C for 24 hours

K. Standard/Guidance Document 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-S26 "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement, January 2016".

L. Test Principle:

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. Given that omadacycline is a bacteriostatic drug, the ellipse should be interpreted at 80% inhibition when trailing is observed.

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.

M. Performance Characteristics:

1. Analytical performance:

   a. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using ten Gram-negative and ten Gram-positive organisms. Each isolate was tested in triplicate over three days. 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 Gram-negative reproducibility panel included four *E. coli,* three *K. pneumoniae*, and three *E. cloacae* isolates and the Gram-positive panel included two methicillin-resistant *S. aureus*, two methicillin-susceptible *S. aureus*, two *S. lugdunensis*, two vancomycin-susceptible *E. faecalis*, and two vancomycin-resistant *E. faecalis* isolates. All MIC results were on scale. The testing resulted in overall reproducibility of greater than 95% for both Gram-negative and Gram-positive isolates.

The results were acceptable.

b. Linearity/assay reportable range:

Not applicable

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

Quality Control (QC) Testing:

The CLSI recommended QC strains, namely *E. coli* ATCC 25922 for Gram-negative organisms and *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 for Gram-positive organisms were tested a sufficient number of times (i.e., at least 20/site) at each testing site using both MTS and reference methods. The results are summarized in Table 2 below. The quality control results are acceptable.

Table 2: Omadacycline MTS QC Results

Organism	Concentration (µg/mL)	Reference	MTS
E. coli ATCC 25922 Expected Result: 0.25-2 µg/mL	0.12		
	0.25		
	0.5	58	60
	1	3	1
	2		
	4		
S. aureus ATCC 29213 Expected Result: 0.12 – 1 µg/mL	0.06		
	0.12	5	13
	0.25	52	40
	0.5	3	7
	1		
	2		
E. faecalis ATCC 29212 Expected Result: 0.06 – 0.5 µg/mL	0.03		
	0.06	7	4
	0.12	41	32
	0.25	12	21
	0.5		3
	1		

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 Omadacycline MTS.

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:

The MTS, Omadacycline was evaluated at three sites located within the United States. Each clinical isolate was tested one time by MTS, Omadacycline and the reference method using the same initial standardized suspension. A total of 389 clinical non-fastidious Gram-positive isolates of which 79.7% were tested within six months of isolation (contemporary isolates) and 496 non-fastidious Gram-negative isolates were tested of which 65.7% were tested within six months of isolation. The Gram-positive organisms included 64 methicillin-susceptible *S. aureus*, 69 methicillin-resistant *S. aureus*, 60 vancomycin-susceptible *E. faecalis*, 48 vancomycin-resistant *E. faecalis*, 42 vancomycin-susceptible *E. faecium*, 46 vancomycin-resistant *E. faecium* isolates, and 60 *S. lugdunensis* isolates. The Gram-negative organisms included 15 *C. freundii*, 15 *C. koseri*, 150 *E. cloacae*, 120 *E. coli*, 30 *K. aerogenes*, 15 *K. oxytoca*, and 151 *K. pneumoniae* isolates.

Challenge testing was performed at one internal site. A total of 77 Gram-positive and 82 Gram-negative challenge isolates were tested. The Gram-positive organisms included one methicillin-susceptible *S. aureus*, 41 methicillin-resistant *S. aureus*, 12 vancomycin-susceptible *E. faecalis*, one vancomycin-resistant *E. faecalis*, one vancomycin-susceptible *E. faecium*, 11 vancomycin-resistant *E. faecium* isolates, and 10 *S. lugdunensis* isolates. The Gram-negative organisms included two *C. freundii*,

two *C. koseri*, 20 *E. cloacae*, 20 *E. coli*, five *K. aerogenes*, five *K. oxytoca*, and 28 *K. pneumoniae* isolates.

Results obtained with the Liofilchem MIC Test Strip (MTS), Omadacycline were compared to results obtained with the CLSI broth microdilution reference panel. The reference panel contained two-fold serial dilutions of Omadacycline with a range of 0.002 – 32 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 80% 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) 466 Gram-positive and 578 Gram-negative isolates is summarized in Table 3 and 4 below.

Table 3: Overall Performance of Gram-positive Clinical and Challenge Isolates

Omadacycline	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Breakpoints												
S. aureus (MSSA+MRSA) Clinical	133	132	99.2	133	132	99.2	132	99.2	1	1	0	0
Challenge	42	41	97.6	41	40	97.6	36	95.7	30	6	0	0
Combined	175	173	98.9	174	172	98.9	168	96.0	31	7	0	0
S. lugdunensis Clinical	60	60	100	60	60	100	51	85.0	1	9	0	0
Challenge	10	10	100	10	10	100	10	100	0	0	0	0
Combined	70	70	100	70	70	100	61	87.1	1	9	0	0
E. faecalis (VSE+VRE) Clinical	108	106	98.1	108	106	98.1	89	82.4	2	19	0	0
Challenge	13	13	100	13	13	100	13	100	9	0	0	0
Combined	121	119	98.3	121	119	98.3	102	84.3	11	19	0	0
E. faecium (VSE+VRE) Clinical	88	88	100	88	88	100	86	97.7	2	2	0	0
Challenge	12	12	100	12	12	100	12	100	11	0	0	0
Combined	100	100	100	100	100	100	98	98.0	13	2	0	0
Community Acquired Bacterial Pneumonia (CABP) Breakpoints												
S. aureus (MSSA) Clinical	64	63	98.4	64	63	98.4	62	96.9	1	2	0	0
Challenge	1	1	100	1	1	100	1	100	1	0	0	0
Combined	65	64	98.5	65	64	98.5	63	96.9	2	2	0	0
S. aureus (MRSA)* Clinical	69	69	100	69	69	100	67	97.1	2	2	0	0
Challenge	41	40	97.6	40	39	97.5	39	95.1	30	2	0	0
Combined	110	109	99.1	109	108	99.1	106	96.4	32	4	0	0
S. aureus (MSSA+MRSA) Clinical	133	132	99.2	133	132	99.2	129	97.0	3	4	0	0
Challenge	42	41	97.6	41	40	97.6	40	95.2	31	2	0	0
Combined	175	173	98.9	174	172	98.9	169	96.9	34	6	0	0

*Methicillin-resistant *S. aureus* isolates were included in the study to further assess the Omadacycline MTS.

Table 4: Overall Performance of Gram-negative Clinical and Challenge Isolates

Omadacycline	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
ABSSSI and CABP Breakpoints												
Enterobacteriaceae (all) Clinical	496	494	99.6	488	486	99.6	478	96.4	16	18	0	0
Challenge	82	82	100	41	41	100	71	86.6	49	11	0	0
Combined	578	576	99.7	529	527	99.6	549	95.0	65	29	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 (MST) results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the Liofilchem MIC Test Strip (MST) result interpretation agrees exactly with the reference broth microdilution result interpretation.

The overall performance of *S. aureus* (both MRSA and MSSA) isolates when evaluated with ABSSSI breakpoints is acceptable with 98.9% EA and 96.0% CA. The overall performance of *S. aureus* (MSSA only) isolates when assessed with CAPB breakpoints is acceptable with 98.5% EA and 96.9% CA. According to the drug label for Omadacycline, only MSSA isolates are indicated for CAPB; however, MRSA were included in the study to further assess the performance of the Omadacycline MTS. The inclusion of MRSA isolates in the study demonstrated equivalent performance (i.e., 98.9% EA and 96.6% CA). There were no major or very major errors.

The evaluation of *S. lugdunensis* isolates yielded a performance of 100% EA and 87.1% CA (12.9% minor error rate). Given that all results were within EA and that there were no major or very major errors, the overall performance was deemed acceptable.

The evaluation of *E. faecalis* (VSE and VRE) isolates yielded a performance of 98.3% EA and 84.3% CA (15.7% minor error rate). Given that all results were within EA and that there were no major or very major errors, the overall performance was deemed acceptable. In addition, there was no significant difference noted in the performance between vancomycin-susceptible *E. faecalis* and vancomycin-resistant *E. faecalis* isolates.

The overall performance of *E. faecium* (VSE and VRE) isolates is acceptable with 100% EA and 98.0% CA. There were no major or very major errors and no difference noted in the performance between vancomycin-susceptible *E. faecium* and vancomycin-resistant *E. faecium* isolates.

The overall performance of all *Enterobacteriaceae* isolates is acceptable with 99.7% EA and 95.0% CA. In addition, the performance for each Gram-negative organism was evaluated separately and results for each demonstrated >90% EA and >90% CA with no major or very major errors and was, therefore, deemed acceptable.

Resistance Mechanisms:

Molecular characterization of challenge isolates was provided with respect to tetracycline-specific resistance mechanisms for both MTS and reference method to include *tet*(A), *tet*(D), *tet*(G) for Gram-negative organisms and *tet*(K) and *tet*(M) for Gram-positive organisms. Specifically, six *K. pneumoniae* and three *E. cloacae* encoding *tet*(A) were evaluated in which all isolates were found to be resistant to omadacycline by

both methods. In addition, one *E. cloacae* isolate encoding *tet*(G) was found to be resistant to omadacycline. Furthermore, one *E. cloacae* isolate encoding *tet*(D) was found to be intermediate by both methods. Regarding Gram-positive isolates, one *E. faecalis* and two *S. aureus* isolates encoding *tet*(M) were tested. The *E. faecalis* isolate and one of the two *S. aureus* isolates were found to be resistant while the other was found to be susceptible by both methods. In addition, two *S. aureus* isolate encoding *tet*(k) were evaluated and found to be resistant. Given that some claimed organisms with their associated resistance mechanisms were not available [e.g., *tet*(B), *tet*(L)] during the time of testing, the following limitation was included in the labeling:

- *Resistance mechanism characterization was not available for all organisms at the time of comparative testing, and therefore the performance of the MTS Omadacycline for non-fastidious gram-negative bacilli and gram-positive cocci is unknown for the following: Enterobacteriaceae [tet(B)]; Enterococcus species [tet(K), tet(L)]; S. aureus [tet(L)]*

Trending:

Trending was assessed separately for Gram-positive and Gram-negative groups using data for challenge and clinical isolates (Tables 5 and 6). No significant trending (i.e., ≥30% difference) was observed for Gram-negative, *S. aureus*, or *E. faecalis* isolates; however, trending was observed for *S. lugdunensis* which tended to be in exact agreement or higher when compared to the reference method. The difference between higher and lower dilutions for this organism was >30%. Given the observed trending, the following was included in the labeling:

- *Liofilchem MIC Test Strip (MTS) Omadacycline MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. lugdunensis compared to the CLSI reference broth microdilution.*

Table 5. Trending for Gram-positive Organisms by Species

Total	≥1 dil. lower	Exact	≤1 dil. higher
***S. aureus* (MSSA+MRSA)[a]**			
175	45	118	12
	(25.71%)	(67.43%)	(6.86%)
***E. faecalis* (VSE+VRE)[b]**			
121	10	74	37
	(8.26%)	(61.16%)	(30.58%)
***E. faecium* (VSE+VRE)[c]**			
100	10	79	11
	(10.00%)	(79.00%)	(11.00%)
***S. lugdunensis*[d]**			
70	2	37	31
	(2.86%)	(52.86%)	(44.29%)

[a]Difference between the higher and lower dilutions for *S. aureus* is: -18.86%; 95% C.I. (-26.38% to -11.28%)

[b]Difference between the higher and lower dilutions for *E. faecalis* is: 22.31%; 95% C.I. (12.53% to 31.78%)
[c]Difference between the higher and lower dilutions for *E. faecium* is: 1.00%; 95% C.I. (-7.82% to 9.85%)
[d]Difference between the higher and lower dilutions for *S. lugdunensis* is: 41.43%; 95% C.I. (28.37% to 53.24%)

Table 6. Trending for *Enterobacteriaceae* by Species

Total	≥1 dil. lower	Exact	≤1 dil. higher
All *Enterobacteriaceae*[a]			
546	115	367	64
	(21.06%)	(67.22%)	(11.72%)

[a]Difference between the higher and lower dilutions for all *Enterobacteriaceae* is: -9.34%; 95% C.I. (-13.70% to -4.97%)

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):

Not Applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Omadacycline are as listed in **Table 7**.

Table 7: FDA Interpretive Criteria for Omadacycline (µg/mL)

Organisms	S	I	R
ABSSSI			
Enterobacteriaceae	≤4	8	≥16
S. aureus (MSSA + MRSA)	≤0.5	1	≥2
S. lugdunensis	≤0.12	0.25	≥0.5
E. faecalis	≤0.25	0.5	≥1
CABP			
Enterobacteriaceae	≤4	8	≥16
S. aureus (MSSA only)	≤0.25	0.5	≥1

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.