510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

I Background Information:

A 510(k) Number

K200180

B Applicant

Liofilchem s. r. l.

C Proprietary and Established Names

MTS Omadacycline 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 add susceptibility testing of fastidious Gram-negative and Gram-positive organisms to the list of non-fastidious organisms previously cleared (k182922) for Omadacycline at concentrations of 0.002-32 µg/mL on the Liofilchem MIC Test Strip (MTS).

B Measurand:

MTS Omadacycline in the dilution range of µg/mL 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):

See Indications for Use below.

B Indication(s) for Use:

The MTS (MIC Test Strip) Omadacycline 0.002-32 ug/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 Omadcycline at concentrations of 0.002-32 ug/mL should be interpreted at 16-20 hours (non-fastidious organisms) and 20-24 hours (fastidious organisms) of incubation.

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 feacalis
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus anginosus group (*S. anginosus* and *S. constellatus*)

Gram-negative bacteria
Enterobacter cloacae
Klebsiella pneumoniae
Haemophilus influenzae
Haemophilus parainfluenzae

Omadacycline has been shown to be active in vitro only against the bacterial species 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

C Special Conditions for Use Statement(s):

Rx-Prescription Use Only

Limitations:
The following Limitations are included in the labeling:

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: H. influenzae, H. parainfluenzae, S. anginosus, S. constellatus and S. pyogenes.

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.

Resistance mechanism characterization was not available for all organisms at the time of comparative testing, and therefore the performance of the MTS Omadacycline for fastidious Gram-negative bacilli and Gram-positive cocci is unknown for the following: S. pneumoniae [tet(K), tet (L), tet (M)]; S. pyogenes [tet(K), tet(L), tet(M)]; S. anginosus [tet(K), tet(L), tet(M)]; S. constellatus [tet(K), tet(L), tet(M)]; H. influenzae[tet(B)]; H. parainfluenzae [tet(B)].

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 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 is 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 diffuses into the agar for over an hour. After appropriate 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 µg/mL

B Predicate 510(k) Number(s):
K153687

C Comparison with Predicate(s):

Table 1. Comparison with the Predicate

Device & Predicate Device(s):	**Device: K200180**	**Predicate: K153687**
Device Trade Name	MTS Omadacyline 0.002-32 µg/mL	Liofilchem MTS Vancomycin 0.016-256 µg/mL
General Device Characteristic Similarities		
Intended Use/Indications for Use	Quantitative susceptibility to antimicrobial agents	Same
MTS Strip Material	High quality paper impregnated with a predefined concentration of gradient antimicrobial agent	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	Same
Result	MIC in µg/mL	Same
General Device Characteristic Differences		
Indicated Organisms	Fastidious Gram-negative and Gram-positive organisms.	Non-fastidious Gram-positive organisms
Antimicrobial Agent	Omadacycline (OMC)	Vancomycin (VA)
Drug Concentration Range	0.002-32 µg/mL	0.016-256 µg/mL
Plate Media	Mueller Hinton agar + 5% sheep blood (fastidious organisms)	Mueller Hinton agar (non-fastidious organisms)

Incubation	35°C ± 2°C in 5% CO_2 for 20-24 hours (fastidious organisms)	35°C ± 2°C in ambient air for 16-20 hours (non-fastidious organisms)
Reading	Manual; interpret the MIC as 100% inhibition for fastidious organisms	Manual; interpret the MIC as 80% inhibition when trailing is seen (non-fastidious organisms)

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-A11 "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"; Approved Standard, Eleventh Edition, January 2018
- CLSI M100-29th ed "Performance Standards for Antimicrobial Susceptibility Testing"; Approved Standard, Twenty-Ninth Edition, January 2019

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing was conducted at three sites using ten Gram-negative and Gram-positive fastidious bacteria. Each isolate was tested in triplicates over three days. The reproducibility panel included: two isolates of *H. influenzae*, one isolate of *H. parainfluenzae*, three isolates of *S. pneumoniae*, two isolates of *S. pyogenes*, two isolates of *S. anginosus*, and one isolate of *S. constellatus*. The mode of the MIC value was pre-determined for each organism, 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. MTS Omadaycline results for fastidious Gram-negative and Gram-positive results were within a doubling dilution of the reference broth microdilution results.

   The testing resulted in overall reproducibility of 99.3%. The results were 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:
The inoculum was prepared in saline (0.85% NaCl) to achieve turbidity equivalent to a 0.5 McFarland standard. Colony counts were performed periodically at each site for all QC replicates. Inoculum density checks were performed, and the colony counts obtained for each QC strain were within the recommended range of approximately 1 x 10^8 CFU/mL. Colony counts was also determined from 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.

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 Rate:
All clinical and challenge isolates grew in both the reference broth microdilution panels and the MTS agar plates, with the exception of four *S. constellatus* clinical isolates that did not grow in the broth microdilution panel and were excluded from analysis.

Quality Control:
The QC strains recommended for routine testing by the CLSI for testing Omadacycline, namely, *H. influenzae* ATCC 49247, and *S. pneumoniae* ATCC 49619 were tested at three sites for a minimum of 20 times at each testing site. Omadacycline MIC results for these QC strains are summarized in Table 2.

Table 2. QC Results for Omadacycline with the CLSI Recommended QC Strains

Organism	Concentration (µg/mL)	Reference BMD (All Sites)	MTS (All Sites)
S. pneumoniae ATCC 49619 Expected Results: 0.016-0.12 µg/mL	0.008	0	0
	0.016	17	0
	0.03	42	0
	0.06	7	37
	0.12	0	32
	0.25	0	0
H. influenzae ATCC 49247 Expected Results: 0.5-2 µg/mL	0.25	0	0
	0.5	3	1
	1	18	8
	2	39	52
	4	0	1[a]

[a] One (1) replicate *of H. influenzae* ATCC 49247 QC was out of range for the MTS (MIC = 4) on the day of testing, however, the *S. pneumoniae* ATCC 49619 QC strain was in range. There were no *Haemophilus* spp. clinical isolates tested on the day the QC was out of range. Three replicates of *H. influenzae* ATCC 49247 tested the next day were all within the QC range.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Results obtained with Liofilchem MIC Test Strip (MTS) with Omadacycline were compared to results obtained from frozen reference MIC panels for susceptibility testing of fastidious Gram-negative and Gram-positive organisms. Reference panels were prepared with Muller Hinton broth (cation-adjusted) plus 5% lysed horse blood and tested as outlined in CLSI recommendations in M7-A11.

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 plus 5% sheep blood plates in an inverted position at 35°C ±2°C for 20-24 hours in 5% CO_2. At the end of incubation, the MIC value where the edge of the inhibition ellipse intersects the strip was compared to MIC results obtained with the CLSI reference broth microdilution method.

Clinical:
Clinical testing was performed at three U.S. sites with both MTS Omadacycline and the reference method using a total of 336 fastidious Gram-positive and Gram-negative clinical isolates including 120 *Haemophilus* spp. (96 *H. influenzae* and 24 *H. parainfluenzae*), 36 *Streptococcus anginosus* group species (25 *S. anginosus* and 11 *S. constellatus*), 150 *Streptococcus pneumoniae*, and 30 *Streptococcus pyogenes*. There were 211 (64.4%) isolates which were tested within 6 months of isolation (contemporary isolates).

Challenge:
Challenge testing was performed at one internal site. A total of 67 challenge isolates were tested which included 5 isolates of *S. pyogenes*, 31 isolates of *S. pneumoniae*, 9 isolates of *S. anginosus* group species (2 *S. anginosus*, 7 *S. constellatus*,) and 22 isolates of *Haemophilus* spp. (16 *H. influenzae*, and 6 *H. parainfluenzae*) isolates.

Results for clinical and challenge isolates with representative species from each organism group are shown in Table 3 below based on the breakpoint/disease indication (CABP or ABSSSI) for each organism or organism group.

Table 3. Overall Performance of MTS Omadacycline with Fastidious[a] Clinical and Challenge Isolates, CABP and ABSSSI

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. R	No. S	min	maj	vmj
Streptococcus pneumoniae **with Community Acquired Bacterial Pneumonia (CABP breakpoints) (≤0.12, 0.25, ≥0.5 µg/mL)**													
Clinical	150	137	91.3	150	137	91.3	147	98.0	1	149	3	0	0
Challenge	31	29	93.5	31	29	93.5	28	90.3	3	26	3	0	0
Total	181	166	**91.7**	181	166	**91.7**	175	**96.7**	4	175	6	0	0
Streptococcus pyogenes **with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) breakpoints (≤0.12, 0.25, ≥0.5 µg/mL)**													
Clinical	30	30	100	30	30	100	29	96.7	0	30	1	0	0
Challenge	5	5	100	5	5	100	3	60.0	1	4	2	0	0
Total	35	35	**100**	35	35	**100**	32	**91.4**	1	34	3	0	0
Streptococcus anginosus **group[b] with ABSSSI breakpoints (≤0.12, 0.25, ≥0.5 µg/mL)**													
Clinical	36	36	100	36	36	100	30	83.3	1	33	6	0	0
Challenge	9	9	100	9	9	100	5	55.5	0	6	4	0	0
Total	45	45	**100**	45	45	**100**	35	**77.8**	1	39	10	0	0
Haemophilus spp[c] **with CABP breakpoints (≤2, 4, ≥8 µg/mL)**													
Clinical	120	118	98.3	120	118	98.3	117	97.5	0	118	3	0	0
Challenge	22	22	100	22	22	100	20	90.9	2	16	2	0	0
Total	142	140	**98.6**	142	140	**98.6**	137	**96.5**	2	134	5	0	0

[a] Non-fastidious organisms were previously cleared (k182922) for Omadacycline at concentrations of 0.002-32 µg/mL on the Liofilchem MIC Test Strip (MTS).
[b] *S. anginosus* group (includes 27 *S. anginosus* and 18 *S. constellatus*)
[c] *Haemophilus* spp (includes 112 *H. influenzae* and 30 *H. parainfluenzae*).

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
S – Susceptible
R – Resistant

min – minor discrepancies
maj – major discrepancies
vmj – very major discrepancies

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 *Haemophilus spp.* isolates (Table 3) is acceptable with 98.6% EA and 96.5% CA. There were no major or very major discrepancies.

The overall performance of *S. pneumoniae* (Table 3) is acceptable with 91.7% EA and 96.7% CA. There were no major or very major discrepancies.

The overall performance of *S. pyogenes* (Table 3) is acceptable with 100% EA and 91.4% CA. There were no major or very major discrepancies.

The overall performance of *S. anginosus* group isolates (Table 3) is acceptable with 100% EA. The % CA of <90% is considered acceptable because the % EA of evaluable results is 100% and all discrepancies are minor.

Testing of isolates belonging to the *S. anginosus* group included 27 isolates of *S. anginosus* and 18 isolates of *S. constellatus*. *S. intermedius* isolates were not tested in the clinical and challenge studies. This was addressed by the addition of the following footnote under the performance characteristics for fastidious organisms in the labeling:

> *Omadacyline should be tested with Streptocococcus anginosus and Streptococcus constellatus isolates only. The performance of Streptococcus intermedius has not been established during the clinical study.*

Testing/Reporting MIC for 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 statements are added in the package insert:

> *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.*

Number of Resistant Isolates Tested:
A total of 8 resistant isolates were tested in the combined challenge and clinical study with Omadacycline out of 403 fastidious organisms tested (~2%). To address the insufficient number of resistant strains encountered during the clinical evaluation, the sponsor added the following limitation in the labeling:

> *The ability of the MTS to detect resistant isolates with the following drug/bacterial species combination is unknown because resistant isolates were either not available or an insufficient number was encountered at the time of comparative testing. Omadacyline: H. influenzae, H. parainfluenza, S. anginosus, S. constellatus and S. pyogenes.*

Resistance Mechanism Characterization:
Challenge isolates harboring the resistance mechanisms against which Omadacycline has been shown to be active were not tested. The sponsor added the following limitation to the device 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 fastidious Gram-negative bacilli and Gram-positive cocci is unknown for the following: S. pneumoniae [tet(K), tet (L), tet (M)]; S. pyogenes [tet(K), tet(L), tet(M)]; S. anginosus [tet(K), tet (L), tet (M)]; S. constellatus [tet(K), tet(L), tet(M)]; H. influenzae [tet(B); H. parainfluenzae [tet(B)].*

MIC Trending Analysis

Using the combined clinical and challenge data, an analysis of trending was conducted for all claimed organisms and for organism groups. Results are stratified by species 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 *Haemophilus spp (H. influenzae, H. parainfluenzae),* however, a trend toward higher MIC reading was observed for *S. pneumoniae*, *S. anginosus* group *(S. anginosus* and *S. constellatus*), and S. *pyogenes* with MTS Omadacycline when compared to the reference method (Table 4).

Table 4. Trending for MTS Omadacycline with Fastidious[1] Gram-Negative and Gram-Positive Organisms

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)[2]	Trending Noted
H. influenzae	112	20 (17.9%)	49 (43.8%)	43 (38.4%)	20.5 (8.8-31.5)	No
H. parainfluenzae	30	3 (10%)	21 (70%)	6 (20%)	10.0% (-8.8%-28.5)	No
Haemophilus spp combined	142	23 (16.2%)	70 (49.3%)	49 (34.5%)	18.3% (8.2-7.9)	No
S. anginosus	27	1 (3.7%)	6 (22.2%)	20 (74.1%)	70.4% (46.6-83.5)	Yes
S. constellatus	18	0 (0.0%)	5 (27.8%)	13 (72.2%)	72.2% (43.2-87.5)	Yes
S. anginosus group combined	45	1 (2.2%)	11 (24.4%)	33 (73.3%)	71.1% (54.0%-82.0%)	Yes
S. pyogenes	35	1 (2.9%)	10 (28.6%)	24 (68.6%)	65.7% (45.5-78.8)	Yes
S. pneumoniae	181	2 (1.1%)	27 (14.9%)	152 (84.0%)	82.9% (45.5-78.8)	Yes

[1]Non-fastidious organisms were previously cleared (k182922) for Omadacycline at concentrations of 0.002-32 µg/mL on the Liofilchem MIC Test Strip (MTS).

[2]A percent difference ≥30% is considered significant trending; a positive percentage difference value in trending analysis indicates higher MIC observed with the device and could cause potential major discrepancies. A negative percentage difference value in trending analysis indicates lower MIC observed with the device and could cause potential very major discrepancies.

To address the observed high trend, the following footnote has been added to the labeling in the performance characteristics section:

Liofilchem MIC Test Strip (MTS) Omadacycline MIC values tended to be in exact

agreement or at least one doubling dilution higher when testing S. anginosus, S. constellatus, S. pneumoniae, and S. pyogenes compared to the CLSI reference broth microdilution.

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 Omadacycline are listed in Table 5.

Table 5. FDA Identified Interpretive Criteria for Omadacycline

Organism	Infection Type	FDA-Recognized Interpretive Criteria for Omadacycline, MIC[3] (µg/mL)		
		Susceptible	Intermediate	Resistant
S. pyogenes	ABSSSI	≤0.12	0.25	≥0.5
S. anginosus group[1]		≤0.12	0.25	≥0.5
S. pneumoniae	CABP	≤0.12	0.25	≥0.5
Haemophilus spcies[2]		≤2	4	≥8

[1]*S. anginosus* group includes *S. anginosus, S. intermedius*, and *S. constellatus*.
[2]*Haemophilus* species includes *H. influenzae* and *H. parainfluenzae*
[3]FDA STIC Webpage https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

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 the 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 outlined the specific procedures and acceptance criteria that Liofilchem intends to use to evaluate the Liofilchem MIC test strip (MTS) when revised breakpoints for Omadacycline 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 Omadacycline 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.