510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K163517

B. Purpose for Submission:

To obtain a substantial equivalence determination for the Liofilchem MIC Test Strip (MTS) containing Telavancin in concentrations of 0.016 – 256 µg/mL for susceptibility testing of *Staphylococcus aureus* (including methicillin-resistant isolates) and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

C. Measurand:

Telavancin 0.016 – 256 µg/mL

D. Type of Test:

Quantitative AST growth based detection

E. Applicant:

Liofilchem® s.r.l.

F. Proprietary and Established Names:

Liofilchem MIC Test Strip (MTS), Telavancin 0.016 – 256 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   II

3. Product code:

   JWY – Manual Antimicrobial Test Systems

4. Panel:

   83 – Microbiology

H. Intended Use:

1. Intended use(s):

   The Liofilchem MIC Test Strip (MTS) is a quantitative method intended for the *in vitro* determination of antimicrobial susceptibility of non-fastidious Gram negative and Gram positive aerobic bacteria (for example, *Enterobacteriaceae*, *Pseudomonas*, *Enterococcus* and *Staphylococcus* species) and fastidious bacteria (for example, anaerobes, *Haemophilus* and *Streptococcus* species and *N. gonorrhoeae*). 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.

2. Indication(s) for use:

   The Liofilchem MIC Test Strip (MTS) is a quantitative method intended for the *in vitro* determination of antimicrobial susceptibility of non-fastidious Gram negative and Gram positive aerobic bacteria (for example, *Enterobacteriaceae*, *Pseudomonas*, *Enterococcus* and *Staphylococcus* species) and fastidious bacteria (for example, anaerobes, *Haemophilus* and *Streptococcus* species and *N. gonorrhoeae*). 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 Telavancin MTS at concentrations of 0.016- 256 µg/mL should be interpreted at 16-20 hours of incubation.

   The non-fastidious bacteria that have been shown to be active both clinically and *in vitro* against Telavancin according to the FDA label:

   Staphylococcus aureus (including methicillin-resistant isolates)
   Enterococcus faecalis (vancomycin-susceptible isolates only)

3. Special conditions for use statement(s):

   Prescription use only

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Telavancin MIC Test Strip (MTS) is made of special high quality paper impregnated with a predefined concentration of gradient Telavancin, across 15 two-fold dilutions like those of a conventional MIC method. One side of the strip is labelled with the Telavancin code (TLV) 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 diffuses into the agar for over an hour. After 16-20 hours incubation, a symmetrical inhibition ellipse centered along the strip is formed. The MIC is read directly form the scale in terms of µg/mL at the point where the edge of the inhibition ellipse intersects the MIC Test Strip.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Liofilchem MIC Test Strip (MTS) – Vancomycin 0.016 – 256 µg/mL

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

   K153687

3. Comparison with predicate:

Table 1: Comparison with the Predicate Device

Similarities		
Item	Device	Predicate K153687
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
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	Same
Result	MIC (µg/mL)	Same

Differences		
Item	Device	Predicate
Antibiotic	Telavancin	Vancomycin
Incubation	35 ± 2°C for 16-20 hours	35 ± 2°C for 24 hours

K. Standard/Guidance Documents Referenced (if applicable):

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

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 like those of a conventional MIC method. 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 0.125μg/mL is considered to be the same as 0.12μg/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.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Reproducibility testing was performed using three methicillin-sensitive *Staphylococcus aureus* isolates (MSSA), two methicillin-resistant *Staphylococcus aureus* isolate (MRSA), one vancomycin-resistant *Staphylococcus aureus* isolate (VRSA), one vancomycin-intermediate *Staphylococcus aureus* isolate (VISA), and three *Enterococcus faecalis* (vancomycin-sensitive) isolates. These ten organisms were tested at three sites in triplicates on three days. The mode of MIC value was determined and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode. The testing resulted in overall reproducibility of greater than 95%. The results were acceptable.

b. *Linearity/assay reportable range:*

Not applicable

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

The recommended QC isolates were tested a sufficient number of times at all three sites with acceptable results in comparison to the reference method. All results were within the expected range greater than 95% of the time. The results are summarized in Table 2 below.

Table 2: Quality Control Test Results for Telavancin

Organism	Expected Result	Concentration (µg/mL)	Reference	MTS
S. aureus ATCC 29213	0.03 – 0.12 µg/mL	0.016		
		0.03	22	2
		0.06	32	52
		0.12	7	7
		0.25		
E. faecalis ATCC 29212	0.03 – 0.12 µg/mL	0.016		
		0.03		11
		0.06	40	46
		0.12	21	4
		0.25		

The inoculum was prepared to achieve a 0.5 McFarland standard turbidity. Colony counts were performed periodically at each site. Inoculum density checks were performed and the average colony counts of each QC strain were within the recommended range of approximately 1 x 10^8 CFU/mL.

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:*

Clinical testing was conducted at three sites (two U.S. sites and one outside the U.S.). A total of 441 organisms were tested and all organisms grew in the study. There were 304 (68.9%) isolates that were tested within seven days of collection and 137 (31.1%) isolates that were tested within one year of collection. The study included 351 *S. aureus* (201 MSSA and 150 MRSA) and 90 *E. faecalis* isolates. In addition to clinical isolates, 63 *S. aureus* and 8 *E. faecalis* challenge isolates were tested for a combined total of 414 *S. aureus* and 98 *E. faecalis* isolates tested.

Results obtained with Liofilchem MIC Test Strip (MTS) with Telavancin were compared to results obtained from frozen reference MIC panels. Reference panels were prepared and interpreted as outlined in CLSI recommendations in M7-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 and inverted position at 35°C ±2 for 16-20 hours. At the end of incubation, the MIC value where the edge of the inhibition ellipse intersects the strip was compared to the reference method. The performance is listed in Table 3 below:

Table 3: Performance of *S. aureus* (201 MSSA and 150 MRSA clinical isolates) and 90 *E. faecalis* clinical isolates

	EA Tot*	EA N	EA%	Eval. EA N	Eval. EA%	CA N	CA%	#NS	min	maj	vmj
S. aureus ≤0.12 (Susceptible), -- (Intermediate), -- (Resistant)											
S. aureus (combined MSSA and MRSA)	414	404	97.6	404	97.6	411	99.3	45**	N/A	3	0
E. faecalis ≤0.25 (Susceptible), -- (Intermediate), -- (Resistant)											
E. faecalis (vancomycin sensitive)	98	94	95.9	93	95.9	98	100	8	N/A	0	0

***EA** – Essential Agreement
CA – Category Agreement
NS – Non-susceptible isolates
maj – major discrepancies
vmj – very major discrepancies
min – minor discrepancies

**The labeled breakpoint for Telavancin was altered from ≤ 1 to ≤ 0.12 for *S. aureus* on February 7, 2014. The majority of these isolates (44/45) were drawn the challenge group of MRSA isolates, and 43 of these isolates would have been identified as susceptible prior to this change in breakpoint. The MIC results for these isolates remained the same, and the change in the MIC interpretive criteria did not affect the performance calculations.

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

For clinical and challenge isolates tested with the Liofilchem MTS for Telavancin, the overall %EA and %CA met the acceptance criteria of greater than or equal to 90%

(Table 3). There were 3 major errors when testing *S. aureus* 0.7%, no major errors with *E. faecalis* and no very major errors for either isolate which met the acceptance criteria.

MIC Trends:

Using the data provided by the sponsor in the diagonal table format recommended in the AST Guidance, an analysis was conducted to check for trending in MIC values. This trending calculation takes into account MIC values that are determined to be ≤1 and ≥1 doubling dilutions compared to the reference method irrespective of whether the device MIC values are on-scale or not. A higher MIC reading trend was observed in the overall performance for *S. aureus* isolates and a lower MIC reading trend was observed in the overall performance for *E. faecalis* compared to the CLSI broth micro-dilution reference method, as summarized in Table 4.

Table 4: Trending – All Clinical and Challenge Isolates

Organism	≥ -3	≥ -2	≥ -1	Exact	≥ +1	≥ +2	≥ +3	Eval.	Non-eval.
S. aureus	0	5	42	203	159	4	1	414	0
	0	1.2%	10.1%	49%	38.4% (39.6% all dilutions higher)[a]	1.0%	0.2%		
E. faecalis	1	3	18	68	7	0	0	97	1
	1.0%	3.1%	18.6% (22.7% all dilutions lower)[b]	70%	7.2%	0	0		

a. Difference: 95% CI (-33.76% to -22.53%)
b. Difference: 95% CI (5.47% to 25.45%)

The trending towards higher MIC values and the potential for occurrence of major errors for Telavancin when testing *S. aureus* (both MSSA and MRSA) isolates was addressed in the labeling by adding the following footnote:

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

In addition, the trending towards lower MIC values and the potential for occurrence of very major error(s) when testing *E. faecalis* isolates was addressed in the labeling by adding the following footnote:

> *"The Liofilchem MIC Test Strip (MTS) telavancin values tended to be in exact agreement or at least one doubling dilution lower when testing E. faecalis compared to the CLSI reference broth microdilution."*

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:

Table 5. Interpretive Criteria for Telavancin (FDA Drug Label)

Organism	FDA Interpretive Criteria for Telavancin MIC (µg/mL)		
	S	I	R
S. aureus (including MRSA)	≤ 0.12	--	--
E. faecalis (vancomycin-susceptible isolates only)	≤ 0.25	--	--

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.