510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172542

B. Purpose for Submission:

To add susceptibility testing of fastidious Gram positive organisms to the list of organisms previously cleared (k170892) for Tedizolid on the Liofilchem MIC Test Strip (MTS)

C. Measurand:

Tedizolid 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:

Liofilchem MIC Test Strip (MTS), Tedizolid 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 MIC Test Strip (MTS) 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 Tedizolid MTS at concentrations of 0.002-32 µg/mL should be interpreted at 16-20 hours of incubation for non-fastidious organisms and 20-24 hours for fastidious organisms

   The Tedizolid has been shown to be active both clinically and *in vitro* against the non-fastidious bacteria listed below according to the FDA label:

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

   The Tedizolid has been shown to be active both clinically and *in vitro* against the fastidious bacteria listed below according to the FDA label:

   Streptococcus pyogenes
   Streptococcus agalactiae
   Streptococcus anginosus group (includes S. anginosus, S. constellatus, S. intermedius)

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use

   Limitation:
   "The ability of the Liofilchem MIC Test (MTS) to detect non-susceptible isolates with the following drug/bacterial species combinations is unknown because non-susceptible isolates were either not available or an insufficient number were encountered at the time of comparative testing. If a result other than susceptible is observed for the following organisms, it should be submitted to a reference laboratory for further testing:
   Tedizolid: S. pyogenes, S. agalactiae, S. anginosus group, S. anginosus, S. constellatus, S. intermedius"

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Tedizolid MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of Tedizolid across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the Tedizolid code (TDZ) 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 for non-fastidious bacteria and 20-24 hours incubation for fastidious bacteria, 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, Tedizolid (K172542)	Predicate Liofilchem MTS, vancomycin (K153687)
Intended Use	Quantitative susceptibility to antimicrobial agents against Gram positive organisms	Same
Media	Mueller Hinton agar (non-fastidious organisms),Mueller Hinton agar + 5% sheep blood (fastidious organisms)	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

Similarities		
Item	Device Liofilchem MTS, Tedizolid (K172542)	Predicate Liofilchem MTS, vancomycin (K153687)
MTS Strip Material	High quality paper impregnated with a predefined concentration of gradient Antimicrobial Agent	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 Liofilchem MTS, Tedizolid (K171906)	Predicate Liofilchem MTS, vancomycin (K153687)
Antibiotic	Tedizolid code (TDZ)	Vancomycin code (VA)
Incubation	35 ± 2°C for 16 - 20hrs (non-fastidious organisms), 20-24 hours (fastidious organisms)	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-S27 "Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Seven Informational Supplement, January 2017".

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 for non-fastidious bacteria and 20-24 hours incubation for fastidious bacteria, 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:

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility testing was conducted at three sites using ten gram positive organisms. Each isolate was tested in triplicates over three days. The reproducibility panel included four *S. pyogenes*, three *S. agalactiae,* and three *S. anginosus* group (one *S. anginosus,* one *S. constellatus* and one *S. intermedius)* isolates. The mode of MIC value was pre-determined 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. 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):

Quality Control (QC) Testing:

The QC strain recommended by both FDA and CLSI, namely *S. pneumoniae* ATCC 49619 was tested a sufficient number of times (i.e., at least 20/site) at each testing site. The Tedizolid MIC results for this QC strain are summarized in Table 2. The QC results are acceptable.

Table 2: Tedizolid MTS QC Results

Organism	Concentration (µg/mL)	Reference BMD	MTS
S. pneumoniae ATCC 49619 Expected Result: 0.12-0.5 µg/mL	0.008		
	0.015		
	0.03		
	0.06		
	0.12	18	7
	0.25	45	59
	0.5	2	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. Inoculum density checks were performed and the colony counts obtained for each QC strain were within the recommended range of approximately 1x 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.

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:

Results obtained with Liofilchem MIC Test Strip (MTS) with Tedizolid were compared to results obtained from frozen reference MIC panels. Reference panels were prepared with Muller Hinton broth (Cation-Adjusted) plus 5% lysed horse blood and tested 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 plus 5% sheep blood in and inverted position at 35°C ±2 for 20-24 hours incubation in 5% CO_2 for fastidious bacteria. At the end of incubation, the MIC value where the edge of the inhibition ellipse intersects the strip was compared to the reference method.

Growth Rate:
One isolate did not grow in the Broth microdilution MIC panel and was excluded from analysis. The growth rate with Tedizolid was 99.5% (238/239).

Clinical:
Clinical testing was performed at three US sites. A total of 240 clinical isolates were tested which include 90 *S. Pyogenes,* 75 *S. agalactiae,* and 74 *S. anginosus group (*32 *S. anginosus,* 13 *S. intermedius,* 29 *S. constellatus).* There were 94 (39.3%) fresh isolates that were tested within seven days of isolation, 95 (39.7%) recent isolates that were tested within one year of isolation and 50 (20.9%) of stock isolates that were tested within three years of isolation.

Challenge:
Challenge testing was performed at one internal site. A total of 50 challenge isolates were tested which included 20 *S. pyogenes*, 15 *S. agalactiae*, 15 *S. anginosus* group (7 *S. anginosus*, 2 *S. constellatus*, 6 S. intermedius) isolates.

The total of 289 clinical and challenge isolates is summarized in Table 3 below.

Table 3: Overall Performance of Clinical and Challenge Isolates (Combined)

Tedizolid	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA %	#NS	maj	vmj
S. pyogenes	110	107	97.3	110	107	97.3	110	100	0	0	0
S. agalactiae	90	88	97.8	90	88	97.8	90	100	0	0	0
S. anginosus	39	36	92.3	39	36	92.3	39	100	4	0	0
S. constellatus	31	29	93.5	31	29	93.5	31	100	1	0	0
S. intermedius	19	18	94.7	19	18	94.7	19	100	0	0	0
S. anginosus group[a]	89	83	93.3	89	83	93.3	89	100	5	0	0
All Organisms	289	278	96.2	289	278	96.2	289	100	5	0	0

[a]Includes 39 *S. anginosus, 31 S. intermedius, 19 S. constellatus* which are also listed separately in the table.

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R or NS – Resistant or non-susceptible isolates
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 all organisms is acceptable with 96.2% EA and 100% CA. The FDA drug label defines only a "susceptible" interpretive category. For data analysis, potentially major and potentially very major discrepancies (errors) were calculated using the susceptible and non-susceptible isolates respectively. There were no major or very major discrepancies.

Non-Susceptible Organisms:
A total of 5 non-susceptible isolates were identified out of 289 organisms tested (1.73%) and were found to be resistant to Tedizolid by the reference method. However, the following indicated organisms had no isolates that were categorized as non-susceptible and/or had an insufficient number of non-susceptible isolates (based on the interpretive criteria for fastidious organisms see Table 5 below): *S. pyogenes, S. agalactiae, S. anginosus group, S. anginosus, S. constellatus*, and *S. intermedius*. This was addressed by adding the following limitation in the labeling:

"The ability of the Liofilchem MIC Test (MTS) to detect non-susceptible isolates with the following drug/bacterial species combinations is unknown because non-susceptible isolates were either not available or an insufficient number were encountered at the time of comparative testing. If a result other than susceptible is observed for the following organisms, it should be submitted to a reference laboratory for further testing:
Tedizolid: S. pyogenes, S. agalactiae, S. anginosus group, S. anginosus, S. constellatus, S. intermedius"

Trending

Using the combined clinical and challenge data an analysis of trending was conducted for each claimed fastidious organism. This trending calculation takes into account MIC values that are determined to be one or more doubling dilution lower or higher compared to the reference method irrespective whether the device MIC values are on-scale or not. The trending analysis is shown in Table 4 below:

Table 4. Trending in Combined Clinical and Challenge

Organism	Difference in MIC as Compared to the CLSI Reference Method					
	# Eval Isolates for Trending	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
S. pyogenes[a]	110	0	4	76 (69.09%)	27	3
		4 (3.64%)			30 (27.27%)	
S. agalactiae[b]	90	0	4	62 (68.89%)	22	2
		4 (4.44%)			24 (26.67)	
S. anginosus group[c]	89	0	1	57 (64.04%)	25	6
		1 (1.12%)			31 (34.83%)	
S. anginosus[d]	39	0	0	26 (66.67%)	10	3
		0 (0%)			13 (33.33%)	
S. constellatus[e]	31	0	0	18	11	2
		0 (0%)		18 (58.06%)	13 (41.94%)	

[a]Difference between the higher and lower dilutions for *S. pyogenes* is 23.64%, 95CI: (14.47% 32.89%)
[b]Difference between the higher and lower dilutions for S. *agalactiae* is 22.22%, 95% CI: (11.92% 32.54%)
[c]Difference between the higher and lower dilutions for *S. anginosus* group is 33.71%, 95% CI: (23.35% 44.09%)
[d]Difference between the higher and lower dilutions for *S. anginosus* is 33.33%, 95% CI: (11.79% 49.02%)
[e]Difference between the higher and lower dilutions for *S. constellatus* is 41.94%, 95% CI: (22.90% 59.23%)

Note: A positive percent difference value indicates higher MIC when compared to the reference method.

A higher MIC reading trend was observed in the overall performance of *S. pyogenes, S. agalactiae, S. anginosus group, S. anginosus, and S. constellatus* compared to the

CLSI broth microdilution reference method, which raises concerns for potential major discrepancy. This trending and the potential for occurrence of major discrepancies were addressed by a modification of the existing footnote to include the non-fastidious organisms in the Performance Characteristics section of the labeling, "Drug Specific Supplement for Tedizolid MIC Test Strip (MTS)":

"The Liofilchem MIC Test Strip (MTS) Tedizolid values tended to be in exact agreement or one doubling dilution higher when testing S. aureus, E. faecalis, S. pyogenes, S. agalactiae, S. anginosus, S. constellatus and S. intermedius compared to the CLSI reference broth microdilution".

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 Tedizolid are as listed in Table 5.

Table 5: FDA Interpretive Criteria for Tedizolid (µg/mL)

Organisms	S	I	R
S. pyogenes	≤0.5	-	-
S. agalactiae	≤0.5	-	-
S. anginosus Group*	≤0.25	-	-

*Includes *S. anginosus, S. intermedius, S. constellatus*

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.