510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K181708

B. Purpose for Submission:

To obtain a substantial equivalence determination for Plazomicin (PLZ) at concentrations of 0.016-256 µg/mL for susceptibility testing of non-fastidious Gram-negative organisms

C. Measurand:

Plazomicin 0.016-256 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 Plazomicin 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 Susceptibility Test Systems

4. Panel:

   83 – Microbiology

H. Intended Use:

1. Intended use(s):

   The Liofilchem MTS (MIC Test Strip) 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 Plazomicin at concentrations of 0.016-256 µg/mL should be interpreted at 16-20 hours of incubation.

   MTS PLZ can be used to determine the MIC of plazomicin against the microorganisms listed in the table below:

Plazomicin Activity According to the FDA Label	
Clinical and *in vitro*	***in vitro* only**
Escherichia coli *Klebsiella pneumoniae* *Enterobacter cloacae* *Proteus mirabilis*	*Citrobacter freundii* *Citrobacter koseri* *Klebsiella (Enterobacter) aerogenes* *Klebsiella oxytoca* *Morganella morganii* *Proteus vulgaris* *Providentia stuartii* *Serratia marcescens*

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   - For prescription use

   - 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.
     Plazomicin: *Citrobacter freundii, Citrobacter koseri, Klebsiella (Enterobacter) aerogenes, Klebsiella oxytoca, Providencia stuartii, Proteus vulgaris, Serratia marcescens*

   - Characterization of 16S rRNA methyltransferases, aminoglycoside modifying enzymes (AMEs), altered efflux and loss of outer membrane porins was not

available for organisms at the time of comparative testing, and therefore the performance of MTS Plazomicin for non-fastidious Gram-negative bacilli with these resistance mechanisms is unknown for the following:
Enterobacteriaceae

- The safety and efficacy of plazomicin in treating clinical infections due to Gram-negative organisms other than *E. coli, K. pneumoniae, E. cloacae* and *P. mirabilis* may not have been established in adequate and well-controlled clinical trials. The clinical significance of susceptibility information in such instances is unknown.

4. Special instrument requirements:

   Manual reading only

I. Device Description:

The Plazomicin MIC Test Strip (MTS) consists of specialized paper impregnated with a predefined concentration gradient of Plazomicin across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. One side of the strip is labelled with the Plazomicin code (PLZ) 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, Plazomicin (K181708)	Predicate Liofilchem MTS, vancomycin (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	Same

Differences		
Item	Device Liofilchem MTS, Plazomicin (K181708)	Predicate Liofilchem MTS, vancomycin (K153687)
Antibiotic	Plazomicin code (PLZ)	Vancomycin code (VA)
Incubation	35 ± 2°C for 16 - 20hrs	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 0.125µg/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-negative organisms. Each isolate was tested in triplicate over three days. The reproducibility panel included three *E. coli,* three *K. pneumoniae*, two *E. cloacae*, one *P. mirabilis*, and one *P. vulgaris* isolate. The mode MIC values were pre-determined and the reproducibility was calculated based on the number of MIC values that fell within ±1 doubling dilution of the mode MIC values. 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 CLSI recommended QC strains, namely *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 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: Plazomicin MTS QC Results

Organism	Concentration (µg/mL)	Reference	MTS
E. coli ATCC 25922 Expected Result: 0.25-2 µg/mL	0.12		
	0.25		29
	0.5	40	30
	1	20	2
	2	1	
	4		
P. aeruginosa ATCC 27853 Expected Result: 1-4 µg/mL	0.5		
	1	8	1
	2	50	47
	4	3	13
	8		

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 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.

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 Plazomicin were compared to results obtained from frozen reference MIC panels. Reference panels were prepared and interpreted as outlined in the recommendations in CLSI document 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 an inverted position at 35°C ± 2° for 16-20 hours. At the end of incubation, the MIC value at which the edge of the inhibition ellipse intersected the strip was compared to MIC results obtained with the reference method.

Growth Rate:
The growth rate for the Liofilchem MIC Test Strip (MTS) with Plazomicin was 100%.

Clinical:
Clinical testing was performed at three U.S. sites. A total of 452 clinical *Enterobacteriaceae* isolates were tested which included 15 *C. freundii,* 15 *C. koseri,* 30 *K. aerogenes*, 45 *E. cloacae*, 120 *E. coli*, 15 *K. oxytoca*, 111 *K. pneumoniae*, 15 *M. morganii,* 35 *P. mirabilis*, 15 *P. stuartii,* 21 *P. vulgaris,* and 15 *S. marcescens* isolates. Of the clinical isolates, 61.7% were tested within 6 months of isolation.

Challenge:
Challenge testing was performed at one internal site. A total of 86 challenge *Enterobacteriaceae* isolates were tested which included 2 *C. freundii,* 2 *C. koseri,* 5 *K. aerogenes*, 10 *E. cloacae*, 16 *E. coli*, 10 *K. oxytoca*, 12 *K. pneumoniae*, 4 *M. morganii,* 17 *P. mirabilis*, 2 *P. stuartii,* 5 *P. vulgaris,* and 1 *S. marcescens* isolate.

The performance for the total 538 clinical and challenge isolates is summarized in Table 3 below.

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

Plazomicin	EA Tot	EA N	EA %	Eval. EA Tot	Eval. EA N	Eval. EA%	CA N	CA%	#R	min	maj	vmj
Enterobacteriaceae (all species) Clinical	452	437	96.7	449	434	96.7	434	96.0	10	18	0	0
Challenge	86	85	98.8	75	74	98.7	83	96.5	44	3	0	0
Combined	538	522	97.0	524	508	96.9	517	96.1	54	21	0	0

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable isolates
R – Resistant isolates
min – minor errors
maj – major errors
vmj – very major 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 all *Enterobacteriaceae* isolates is acceptable with 97.0% EA and 96.1% CA. There were 18 minor discrepancies (3.9%) and no major or very major errors.

When the performance was evaluated individually by species, it was noted that the CA for both *P. mirabilis* and *P. stuartii* was less than 90%. However, all categorical errors for these species were minor and within essential agreement and therefore, acceptable.

Resistance Mechanisms:

Molecular characterization for resistance to Plazomicin was not evaluated for all organisms as this information was not available of the time of testing. This was addressed by adding the following footnote in the labeling:

> *"Characterization of 16S rRNA methyltransferases, aminoglycoside modifying enzymes (AMEs), altered efflux and loss of outer membrane porins was not available for organisms at the time of comparative testing, and therefore the performance of MTS Plazomicin for non-fastidious Gram-negative bacilli with these resistance mechanisms is unknown for the following: Enterobacteriaceae"*

Trending:

Trending was observed (Table 4) for MIC values for *C. freundii, C. koseri, K. aerogenes, E. coli, M. morganii, P. stuartii, P. vulgaris* and *S. marcescens* which tended to be in exact agreement or lower when compared to the reference method. The difference between higher and lower dilutions for these organisms was ≥30%. The following footnote was included in the labeling to indicate this trending:

> *"The MTS Plazomicin MIC values tended to be in exact agreement or at least one doubling dilution lower when testing C. freundii, C. koseri, K. aerogenes, E. coli, M. morganii, P. stuartii, P. vulgaris and S. marcescens compared to the CLSI reference broth microdilution."*

Table 4. Trending for *Enterobacteriaceae* by Species

Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
***C. freundii*[a]**					
17	0	6	10	1	0
	(35.29%)		(58.82%)	(5.88%)	
***C. koseri*[b]**					
17	0	7	10	0	0
	(41.18%)		(58.82%)	(0%)	
***K. aerogenes*[c]**					
35	1	16	17	1	0
	(48.57%)		(48.57%)	(2.86%)	
***E. cloacae*[d]**					
51	0	13	36	2	0
	(25.49%)		(70.59%)	(3.92%)	
***E. coli*[e]**					
132	12	59	61	0	0
	(53.79%)		(46.21%)	(0%)	

***K. oxytoca*[f]**					
25	0	7	17	1	0
	(28%)		(68%)	(4%)	
***K. pneumoniae*[g]**					
119	0	19	86	14	0
	(15.97%)		(72.27%)	(11.76%)	
***M. morganii*[h]**					
19	0	9	10	0	0
	(47.37%)		(52.63%)	(0%)	
***P. mirabilis*[i]**					
52	0	15	37	0	0
	(28.85%)		(71.15%)	(0%)	
***P. stuartii*[j]**					
17	0	7	9	1	0
	(41.18%)		(52.94%)	(5.88%)	
***P. vulgaris*[k]**					
26	1	9	16	0	0
	(38.46%)		(61.54%)	(0%)	
***S. marcescens*[l]**					
16	0	5	11	0	0
	(31.25%)		(68.75%)	(0%)	
All *Enterobacteriaceae*[m]					
526	16	170	320	20	0
	(35.36%)		(60.84%)	(3.8%)	

[a]Difference between the higher and lower dilutions for *C. freundii* is: -29.41%; 95% C.I. (-53.31% to -1.69%)
[b]Difference between the higher and lower dilutions for *C. koseri* is: -41.18%; 95% C.I. (-63.99% to -14.30%)
[c]Difference between the higher and lower dilutions for *K. aerogenes* is: -45.71%; 95% C.I. (-61.75% to -26.25%)
[d]Difference between the higher and lower dilutions for *E. cloacae* is: -21.57%; 95% C.I. (-35.24% to -7.96%)
[e]Difference between the higher and lower dilutions for *E. coli* is: -53.79%; 95% C.I. (-62.07% to -44.84%)
[f]Difference between the higher and lower dilutions for *K. oxytoca* is: -24%; 95% C.I. (-43.85% to -3.27%)
[g]Difference between the higher and lower dilutions for *K. pneumoniae* is: -4.2%; 95% C.I. (-13.12% to 4.71%)
[h]Difference between the higher and lower dilutions for *M. morganii* is: -47.37%; 95% C.I. (-68.29% to -21.21%)
[i]Difference between the higher and lower dilutions for *P. mirabilis* is: -28.85%; 95% C.I. (-42.27% to -16.28%)
[j]Difference between the higher and lower dilutions for *P. stuartii* is: -35.29%; 95% C.I. (-58.62% to -6.52%)
[k]Difference between the higher and lower dilutions for *P. vulgaris* is: -38.46%; 95% C.I. (-57.47% to -17.90%)
[l]Difference between the higher and lower dilutions for *S. marcescens* is: -31.25%; 95% C.I. (-55.60% to -5.43%)
[m]Difference between the higher and lower dilutions for all *Enterobacteriaceae* is: -31.56%; 95% C.I. (-35.94% to -27.12%)

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 Plazomicin are as listed in Table 5.

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

Organisms	S	I	R
Enterobacteriaceae	≤2	4	≥8

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.