



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

**I Background Information:**

**A 510(k) Number**

K243202

**B Applicant**

Liofilchem s. r. l.

**C Proprietary and Established Names**

MTS Ceftobiprole 0.002-32 µg/mL

**D Regulatory Information**

| Product Code(s) | Classification | Regulation Section   | Panel             |
|-----------------|----------------|--|-------------------|
| JWY             | Class II       | 21 CFR 866.1640 -<br>Antimicrobial<br>Susceptibility Test Powder | MI - Microbiology |

**II Submission/Device Overview:**

**A Purpose for Submission:**

To obtain a substantial equivalence determination of the Liofilchem MIC Test Strip (MTS) containing ceftobiprole at concentrations of 0.002 – 32 µg/mL for susceptibility testing of gram-negative and gram-positive organisms.

**B Measurand:**

Ceftobiprole in the dilution range of 0.002 to 32 µg/mL

**C Type of Test:**

Quantitative antimicrobial susceptibility test (AST) 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) Ceftobiprole (BPR) 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. MTS Ceftobiprole at concentrations of 0.002-32 µg/mL should be interpreted at 16-20 hours of incubation.

MTS BPR can be used to determine the MIC of ceftobiprole against the following microorganisms for which ceftobiprole has been shown to be active both clinically and/or *in vitro* according to the FDA drug approved label:

*Escherichia coli*

*Klebsiella pneumoniae*

*Staphylococcus aureus* (includes methicillin resistant isolates)

## **C Special Conditions for Use Statement(s):**

Rx - For Prescription Use Only

The following limitation was applied to ceftobiprole testing in the device labeling:

The ability of the MTS to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because resistant strains were not available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

Ceftobiprole: *Staphylococcus aureus*

## **D Special Instrument Requirements:**

N/A – Manual reading only

# **IV Device/System Characteristics:**

## **A Device Description:**

MTS Ceftobiprole 0.002-32 µg/mL is made of special high-quality paper impregnated with a predefined concentration gradient of ceftobiprole, across 15 two-fold dilutions like those used by conventional MIC methods. One side of the strip is labeled with the ceftobiprole code (BPR) and the MIC reading scale in µg/mL. MIC values are determined by identifying the drug concentration at which growth of the ellipse ends. The MIC Test Strip (MTS) is single use only.

## B Principle of Operation:

MTS are made of specialized high-quality paper impregnated with a predefined concentration gradient of antibiotic, across 15 two-fold dilutions similar to dilutions used by conventional MIC methods. When the MTS is applied onto an inoculated agar surface, the preformed exponential gradient of antimicrobial agent diffuses into the agar. 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  $\mu\text{g/mL}$  at the point where the edge of the inhibition ellipse intersects the strip MTS.

Growth along the entire gradient (i.e., no inhibition ellipse) indicates that the MIC value is greater than or equal to ( $\geq$ ) 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  $\mu\text{g/mL}$  is considered to be the same as 0.12  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$

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

K153687

### C Comparison with Predicate(s):

**Table 1: Predicate Comparison**

| <b>Device &amp; Predicate Device(s):</b>          | <b><u>Device:</u><br/><u>K243202</u></b>   | <b><u>Predicate:</u><br/><u>K153687</u></b>                                |
|---|--|--|
| Device Trade Name                                 | MTS Ceftobiprole<br>0.002 - 32 $\mu\text{g/mL}$  | Liofilchem MIC Test Strip (MTS)-Vancomycin<br>0.016 - 256 $\mu\text{g/mL}$ |
| <b>General Device Characteristic Similarities</b> |  |  |
| Plate Media                                       | Mueller Hinton Agar  | 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   |

| <b>Device &amp; Predicate<br/>Device(s):</b>     | <b><u>Device:</u><br/>K243202</b>   | <b><u>Predicate:</u><br/>K153687</b>  |
|--|---|---|
| Reading  | Manual; Interpret the MIC as 100% inhibition  | Same  |
| Result   | MIC in µg/mL  | Same  |
| <b>General Device Characteristic Differences</b> |   |   |
| Intended Use/Indications For Use                 | Quantitative susceptibility to antimicrobial agents against specified gram-negative organisms and gram-positive organisms | Quantitative susceptibility to antimicrobial agents against specified gram-positive organisms |
| Antimicrobial Agent                              | Ceftobiprole (BPR)  | Vancomycin (VA)   |
| Incubation                                       | 35°C ± 2°C for 16-20 hours  | 35°C ± 2°C for 24 hours   |

## VI Standards/Guidance Documents Referenced:

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA, August 28, 2009

CLSI M07-Ed12 “*Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*”

CLSI M100-Ed34 “*Performance Standards for Antimicrobial Susceptibility Testing February 2024*”

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

#### 1. Precision/Reproducibility:

Reproducibility testing of the Liofilchem MIC Test Strip (MTS) Ceftobiprole was performed using 10 gram-negative isolates (5 *E. coli* and 5 *K. pneumoniae*) and 10 gram-positive isolates (5 methicillin-susceptible *S. aureus* and 5 methicillin-resistant *S. aureus*). Testing was performed in triplicate at three sites on three separate days for a total of 180 results per site (20 isolates x 3 replicates x 3 days of testing). Results were used to determine site to site and overall reproducibility.

The mode MIC value was pre-determined for each organism and the reproducibility was calculated based on the number of MIC values that fell within ± one doubling dilution of the mode. All MIC results were on scale. MTS Ceftobiprole results for all gram-positive organisms were within one doubling dilution of the mode MIC determined by the reference broth microdilution method for an overall reproducibility of 100%. For gram-negative organisms, 99.6% of results were within one doubling dilution of the mode MIC determined by the reference method. The results are 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 is prepared from an overnight agar plate into saline to achieve turbidity equivalent to a 0.5 McFarland standard. The inoculum is applied to agar with swab manually or with a rotation plate. Colony counts are 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  $1 \times 10^8$  CFU/mL. Colony counts are 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 and showed similar ranges.

#### **Purity Checks:**

Purity checks are performed on all isolates following MTS inoculation. All isolates were determined to be 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.

#### **Quality Control:**

The QC strains recommended by the CLSI for routine QC testing of ceftobiprole (i.e., *E. coli* ATCC 25922 and/or *S. aureus* ATCC 29213) were tested at four sites for a minimum of 20 times at each site by both the MTS and the reference method. The results demonstrate that MTS Ceftobiprole can produce quality control results in the recommended range  $\geq 95\%$  of the time which is acceptable (**Table 2**).

**Table 2. QC Results for Ceftobiprole with CLSI Recommended QC Strains**

| QC Organism   | Concentration (µg/mL) | Reference BMD (All Sites) | MTS (All Sites) |
|---|-----------------------|---------------------------|-----------------|
| <i>E. coli</i> ATCC 25922<br><br>Expected Results:<br>0.03-0.12 µg/mL | 0.015                 |                           |                 |
|   | 0.03                  | 7                         | 7               |
|   | 0.06                  | 63                        | 50              |
|   | 0.12                  | 14                        | 27              |

|                                   |      |           |           |
|-----------------------------------|------|-----------|-----------|
|                                   | 0.25 |           |           |
|                                   | 0.06 |           |           |
| <i>S. aureus</i> ATCC 29213       | 0.12 |           |           |
|                                   | 0.25 | <b>31</b> | <b>1</b>  |
| Expected Results:<br>0.12-1 µg/mL | 0.5  | <b>35</b> | <b>65</b> |
|                                   | 1    |           |           |
|                                   | 2    |           |           |

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

## B Comparison Studies:

1. Method Comparison with Predicate Device:

Results obtained with Liofilchem MTS with Ceftobiprole were compared to results obtained from frozen reference MIC panels. Reference MIC panels are prepared, tested, and interpreted as outlined in the CLSI document M07-Ed12.

Isolated colonies from an overnight 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 plate in an inverted position at  $35^\circ\text{C} \pm 2^\circ\text{C}$  for 16-20 hours. At the end of the appropriate 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 two external U.S. sites and one external outside U.S. site with both MTS Ceftobiprole and the reference method. A total of 630 clinical isolates are evaluated including: 300 gram-negative Enterobacterales isolates (150 *E. coli* and 150 *K. pneumoniae*) and 330 gram-positive isolates of *S. aureus* (151 methicillin-susceptible and 179 methicillin-resistant). The clinical testing included 479 (76.0%) contemporary isolates (isolated no longer than 6 months prior to testing) and 151 (24.0%) stock isolates (isolated over 6 months prior to testing).

### Challenge:

Challenge testing was performed at one internal U.S. site. A total of 165 challenge isolates were evaluated, including 64 Enterobacterales isolates (35 *E. coli*, 29 *K. pneumoniae*) and 101 *S. aureus* isolates.

Results of MTS Ceftobiprole testing with clinical and challenge isolates are shown in **Table 3**.

**Table 3. Overall Performance of MTS Ceftobiprole with Clinical and Challenge Isolates**

|  | Tot | EA<br>N | EA<br>%     | Eval<br>Tot | Eval<br>EA N | Eval<br>EA % | CA<br>Tot | CA<br>%     | No.<br>R | No.<br>S | min | major | vmj |
|--|-----|---------|-------------|-------------|--------------|--------------|-----------|-------------|----------|----------|-----|-------|-----|
| <b>Enterobacterales* (Breakpoints (µg/mL): S≤0.25, I 0.5, R≥1)</b> |     |         |             |             |              |              |           |             |          |          |     |       |     |
| <b>Clinical</b>  | 300 | 296     | 98.7        | 223         | 219          | 98.2         | 296       | 98.7        | 85       | 213      | 4   | 0     | 0   |
| <b>Challenge</b>   | 64  | 63      | 98.4        | 19          | 18           | 94.7         | 64        | 100         | 53       | 10       | 0   | 0     | 0   |
| <b>Total</b>   | 364 | 359     | <b>98.6</b> | 242         | 237          | 97.9         | 360       | <b>98.9</b> | 138      | 223      | 4   | 0     | 0   |
| <b>S. aureus (Breakpoints (µg/mL): S≤2, I 4, R≥8)</b>              |     |         |             |             |              |              |           |             |          |          |     |       |     |
| <b>Clinical</b>  | 330 | 326     | 98.8        | 330         | 326          | 98.8         | 322       | 97.6        | 0        | 330      | 8   | 0     | 0   |
| <b>Challenge</b>   | 101 | 100     | 99.0        | 101         | 100          | 99.0         | 61        | 60.4        | 0        | 73       | 40  | 0     | 0   |
| <b>Total</b>   | 431 | 426     | <b>98.8</b> | 431         | 426          | 98.8         | 383       | <b>88.9</b> | 0        | 403      | 48  | 0     | 0   |

\*Includes 150 each for *E. coli* and *K. pneumoniae* clinical isolates and 35 *E. coli* and 29 *K. pneumoniae* challenge isolates.

EA – Essential Agreement

CA – Category Agreement

EVAL – Evaluable MIC results

S – Susceptible

min – minor discrepancies

maj – major discrepancies

vmj – very major discrepancies

R – resistant

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.

For Enterobacterales, the combined clinical and challenge results (364 isolates) were acceptable with an EA of 98.6% and CA of 98.9%. There were 4 minor errors and no major or very major errors. For *S. aureus*, the combined clinical and challenge results (431 isolates) were acceptable with an EA of 98.8% and CA of 88.9%. There were 48 minor errors and no major or very major errors. Although the CA is below 90%, the Evaluable EA is 98.8% which is acceptable.

For clinical and challenge isolates tested with the Liofilchem MTS Ceftobiprole, the overall % EA and % CA meet the acceptance criteria.

### Testing/Reporting 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 statement is added in the precautions section of labeling:

*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.*

### Resistant Isolates:

A total of 364 clinical and challenge isolates were tested for Enterobacterales and 138 (37.9%) resistant isolates were available for testing which is acceptable.

Due to the insufficient number of resistant *S. aureus* isolates evaluated, the following limitation is included in the device labeling:

*The ability of the MTS to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because resistant strains were not available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.*

*Ceftobiprole: Staphylococcus aureus*

#### Resistance Mechanism in Challenge Isolates:

Isolates with the following resistance mechanisms were evaluated:

aac(3)-IIId, aac(6')-aph(2''), aac(6')Ib-cr, aadA5, aadD, ac(6')-aph(2''), ACT-type, aph(3')-III, blaZ, catA1, catB3, cfr, cfr+, CMY-65, CMYII, CTX-M-1, CTX-M-15, CTX-M9, dfrA17, dfrG, erm(A), G2576T\_Lnz, IMP, KPC, KPC-3, KPC-low mic, L3\_wildtype, L4\_wildtype, mecA, mph(C), msr(A), NDM, NDM-1, NDM-5, OXA-1, OXA-10, OXA-181, OXA-30, OXA-9, SHV-1, SHV-7, spc, strA, strB, sul2, TEM, TEM-1, TEM-1B, TEM-34, TEM-OSBL(b), tet(B), tet(K), tet(M), VEB-1a, VEB-9, VIM, VIM-1.

#### 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 MIC readings was  $\geq 30\%$  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.

A trend toward higher MIC readings for *S. aureus* with MTS Ceftobiprole was observed when compared to the CLSI broth micro-dilution reference method, as summarized in **Table 4**.

**Table 4. Observed Trending of Results Obtained with MTS Ceftobiprole**

| Organism Name               | Total Evaluable for Trending | $\geq 1$ Dilution Lower No. (%) | Exact No. | $\geq 1$ Dilution Higher No. (%) | Percent Difference (95% CI) | Trending Noted |
|-----------------------------|------------------------------|---------------------------------|-----------|----------------------------------|-----------------------------|----------------|
| <i>E. coli</i>              | 136                          | 28, (20.6)                      | 72        | 36, (26.5)                       | 6% (-4%, 16%)               | No             |
| <i>K. pneumoniae</i>        | 106                          | 30, (28.3)                      | 53        | 23, (21.7)                       | -7% (-18%, 5%)              | No             |
| Enterobacterales (combined) | 242                          | 58, (24.0)                      | 125       | 59, (24.4)                       | 0% (-7%, 8%)                | No             |
| <i>S. aureus</i>            | 431                          | 18, (4.2)                       | 189       | 224, (52.0)                      | 48% (43%, 53%)              | Yes, high      |

The trending towards higher MIC values for MTS Ceftobiprole when testing was addressed in the labeling by adding the following footnote to the performance table:



*“Liofilchem MIC Test Strip (MTS) Ceftobiprole MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. aureus”*

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 Ceftobiprole are listed in **Table 5**.

**Table 5. FDA-Recognized Interpretive Criteria for Ceftobiprole**

| Organisms  | Minimum Inhibitory Concentration (µg/mL) <sup>a</sup> |                  |               |
|--|---|------------------|---------------|
|  | Susceptible (S)                                       | Intermediate (I) | Resistant (R) |
| Enterobacterales   | ≤ 0.25  | 0.5              | ≥ 1           |
| <i>Staphylococcus aureus</i><br>(includes methicillin<br>resistant isolates) | ≤ 2   | 4                | ≥ 8           |

<sup>a</sup>[FDA STIC Webpage](#)

**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.