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

## I Background Information:

### A 510(k) Number

K243169

### B Applicant

Thermo Fisher Scientific

### C Proprietary and Established Names

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole in the dilution range of 0.008-16 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 |
| LTT | Class II | 21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder | MI - Microbiology |
| LRG | Class II | 21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder | MI - Microbiology |

## II Submission/Device Overview:

### A Purpose for Submission:

To obtain substantial equivalence determination for The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole in the dilution range of 0.008-16 µg/mL with the FDA-recognized breakpoints for *Staphylococcus aureus*.

### B Measurand:

Ceftobiprole in the dilution range 0.008 to 16 µg/mL

**C Type of Test:**

Quantitative antimicrobial susceptibility test (AST) growth-based detection

## III Intended Use/Indications for Use:

**A Intended Use(s):**

The Sensititre MIC and Breakpoint Susceptibility system is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious Gram negative isolates, comprising of Enterobacteriaceae, *Pseudomonas aeruginosa*, and other non-Enterobacteriaceae and of non fastidious Gram positive isolates, comprising of *Staphylococcus* spp., *Enterococcus* spp., and beta-haemolytic streptococci other than *S. pneumoniae*.

**B Indication(s) for Use:**

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious isolates.

This 510(k) is for ceftobiprole in the dilution range of 0.008-16 µg/mL for testing non-fastidious gram-positive isolates on The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System.

Ceftobiprole has been shown to be active both clinically and *in vitro* against the following organisms according to the FDA drug label:

*Staphylococcus aureus* (including 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:

> *Studies of the following drugs were performed with the AIM Autoinoculator and read using the ARIS HiQ/OptiRead and Vizion. The use of an alternative inoculation system or alternative read methods has not been evaluated.*

Due to the insufficient number of resistant *S. aureus* isolates evaluated, the following limitation was applied to Ceftobiprole testing in the device labeling:

> *The ability of Sensititre system to detect resistance or non-susceptibility to the following antimicrobic is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, the strain should be sent to a reference laboratory for further testing.*

**D Special Instrument Requirements:**

Sensititre AIM for device inoculation
Sensititre Vizion digital viewing device
Sensititre ARIS HiQ/OptiRead automated plate reader

## IV Device/System Characteristics:

### A Device Description:

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility Plate System is an antimicrobial susceptibility test. Each plate is dosed with antimicrobial agents at appropriate dilutions. It is a micro-version of the classic broth dilution method and can provide both qualitative and quantitative susceptibility results. After inoculation, plates are sealed with an adhesive seal, incubated at 34-36°C for 18-24 hours and examined for bacterial growth.

### B Principle of Operation:

The Sensititre 18-24 hour MIC Susceptibility plates are multi-well plastic microtiter plates that contain doubled dilutions of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read using the digital viewing device (Vizion) or by use of an automated plate reader (ARIS HiQ/OptiRead).

The Sensititre Vizion digital viewing device allows the panel image to be displayed on a touch screen directly from a video camera and allows the user to visually determine MIC results. The Sensititre OptiRead utilizes fluorescence technology to read the microbroth dilution plates after 18 to 24 hours incubation. The technology involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a fluorogenic substrate. The non-fluorescent substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The enzymatic action of the bacterial surface enzymes on the bound non-fluorescent substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to the activity of bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The non-fluorescent (fluorogenic) substrate can be added to the inoculum broth which is dispensed into the test plate at the same time as the test organism, or the plates can be prepared with the substrate already added to each micro-well.

Sensititre 18-24 hour MIC plates can either be read automatically on an ARIS HiQ/OptiRead using fluorescence or by visual reading of growth on the Vizion digital viewing device.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

The Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System with Lefamulin in the dilution range of 0.008-16 µg/mL

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

K192729

### C Comparison with Predicate(s):

| **Device & Predicate Device(s):** | Device: K243169 | Predicate: K192729 |
|---|---|---|

| | | |
|---|---|---|
| Device Trade Name | The Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System with Ceftobiprole in the dilution range of 0.008-16 µg/mL | The Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System with Lefamulin in the dilution range of 0.008−16 µg/mL |
| **General Device Characteristic Similarities** | | |
| Intended Use | The Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious bacterial isolates. | Same |
| Test Panel | Each 96 well plate is precision dosed with selected antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used to rehydrate the plate. | Same |
| Incubation | 18-24 hours | Same |
| Read Method | Results can be read using fluorescence with the ARIS HiQ/OptiRead or by visual reading of growth with the Vizion | Same |
| **General Device Characteristic Differences** | | |
| Antibiotic and Dilution Range | Ceftobiprole<br>0.008-16 µg/mL | Lefamulin<br>0.008-16 µg/mL |
| Test Organism(s) | *Staphylococcus aureus* (including methicillin-resistant isolates) | *Staphylococcus aureus* (methicillin-susceptible isolates) |

## VI Standards/Guidance Documents Referenced:

CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Eleventh Edition", (January 2018)

CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing; 33rd Edition", (March 2023)

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

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

### A Analytical Performance:

1. Precision/Reproducibility:

   A reproducibility study of The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole was performed at four sites using a panel of ten (10) isolates from indicated species, *Staphylococcus aureus* (5 *Staphylococcus aureus* (MSSA), 5 *Staphylococcus aureus* (MRSA)). All isolates were tested in triplicate over three days with each read method (i.e., automatically with the ARIS HiQ/OptiRead and visually with the Vizion). The Sensititre AIM auto-inoculator was used for Sensititre plate inoculation. The mode MIC value was determined, and the reproducibility was calculated based on MIC values falling within ±1 doubling dilution of the mode MIC value. The reproducibility studies for both the ARIS HiQ/OptiRead and Vizion read methods demonstrated acceptable performance of 100%.

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):

   The CLSI-recommended quality control (QC) strains, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212 were tested at four sites. The QC strains were tested a minimum of 20 times per site and read automatically with the ARIS HiQ/OptiRead and visually with the Vizion. The QC strain was also tested with the reference method. The results demonstrate that The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole produced quality control results within the recommended range >95% of the time (**Table 1**).

**Table 1.** Quality Control Results for *S. aureus* and *E. faecalis* with Ceftobiprole with the Reference Method, ARIS HiQ/OptiRead, and Vizion

| QC Organism | Expected Range (µg/mL) | Concentration (µg/mL) | Reference | ARIS HiQ/OptiRead | Vizion |
|---|---|---|---|---|---|
| *S. aureus* | | ≤0.06 | | 1 | |

| | | | | | |
|---|---|---|---|---|---|
| ATCC 29213 | 0.12-1 µg/mL | 0.12 | 1 | 1 | 1 |
| | | 0.25 | 77 | 8 | 24 |
| | | 0.5 | 3 | 78 | 64 |
| | | 1 | | | |
| | | ≥2 | | | |
| *E. faecalis* ATCC 29212 | 0.06-0.5 µg/mL | ≤0.03 | | 1 | |
| | | 0.06 | 1 | 1 | 1 |
| | | 0.12 | 73 | 75 | 81 |
| | | 0.25 | 4 | 8 | 7 |
| | | 0.5 | | 1 | |
| | | ≥1 | | | |

**Inoculum Density:** Inoculum density checks were performed for all QC, reproducibility, challenge, and clinical isolates tested.

**Purity Checks:** Purity checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from pure cultures were reported.

**Growth Failure:** There were no growth failures for *S. aureus*.

**ARIS HiQ/OptiRead Invalid (No fluorescence):** There were no invalid results for *S. aureus*.

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

## B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of the Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole was performed at one internal and three external sites. Results were compared those obtained with the CLSI broth microdilution reference method. Sensititre panels were inoculated using only the AIM Autoinoculator and results were read automatically by the ARIS HiQ/OptiRead and visually by the Vizion. Reference panels were inoculated according to recommendations in the CLSI M07 document and results were read manually using a mirrored reader.

No inoculation system other than the AIM Autoinoculator and no read method other than ARIS HiQ/OptiRead and Vizion was used in the comparative study. To address the inoculation method and read method limitation, the following limitation was applied to ceftobiprole testing in the device labeling:

*Studies of the following drugs were performed with the AIM Autoinoculator and read using the ARIS HiQ/OptiRead and Vizion. The use of an alternative inoculation system or alternative read methods has not been evaluated.*

The testing conditions for the reference method consisted of the following:

- Media: per CLSI M07 guidelines for *Staphylococcus* spp.
- Inoculum: Inoculated per CLSI M07 guidelines
- Incubation: 34-36°C in a non-$CO_2$ incubator for 18 to 24 hours

Inoculation and incubation procedure for *Staphylococcus* spp.

- Media: cation-adjusted Mueller-Hinton broth with TES buffer (CAMHBT)
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared in 5 mL sterile water. Ten (10) µL of the standardized suspension was transferred to 11 mL CAMHBT. Susceptibility plates were inoculated with 50 µL of the final organism suspension using the Sensititre AIM Autoinoculator.
- Incubation: 34-36ºC in a non-$CO_2$ incubator for 18 to 24 hours

A total of 397 clinical isolates comprised of 196 methicillin-resistant *S. aureus* (MRSA) isolates and 201 methicillin-susceptible *S. aureus* (MSSA) isolates as well as 100 challenge isolates comprised of 50 MRSA isolates and 50 MSSA isolates were evaluated, and the results are provided in **Table 2**. For *S. aureus* read using the ARIS HiQ/OptiRead, the combined clinical and challenge results (497 isolates) were acceptable at 98.6% and 99.8% for EA and CA, respectively. There was 1 minor, 0 major, and 0 very major errors.

**Table 2.** Ceftobiprole Performance of *S. aureus* Read by ARIS HiQ/OptiRead

| | Tot | EA N | EA% | Eval Tot | Eval EA N | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***S. aureus* (including MRSA) [≤ 2 (S), 4 (I), ≥8 (R)]** | | | | | | | | | | | | | |
| **Clinical** | 397 | 390 | 98.2 | 397 | 390 | 98.2 | 397 | 100 | 0 | 397 | 0 | 0 | 0 |
| **Challenge** | 100 | 100 | 100 | 100 | 100 | 100 | 99 | 99 | 0 | 100 | 1 | 0 | 0 |
| **Combined** | 497 | 490 | 98.6 | 497 | 490 | 98.6 | 496 | 99.8 | 0 | 497 | 1 | 0 | 0 |

EA – Essential Agreement
CA – Categorical Agreement
S – Susceptible
Maj – Major Discrepancies
Eval – Evaluable MICs
R – Resistant
min – Minor Discrepancies
vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

A total of 397 clinical isolates comprised of 196 methicillin-resistant (MRSA) *S. aureus* isolates and 201 methicillin-susceptible (MSSA) *S. aureus* isolates as well as 100 challenge isolates comprised of 50 MRSA isolates and 50 MSSA isolates were evaluated, and the results are provided in **Table 3**. For *S. aureus* read using the digital viewing device (Vizion), the combined clinical and challenge results (497 isolates) were acceptable at 99.4% and 99.8% for EA and CA, respectively (**Table 3**). There was 1 minor, 0 major, and 0 very major errors.

**Table 3.** Ceftobiprole Performance of *S. aureus* Read by Vizion

| | Tot | EA N | EA% | Eval Tot | Eval EA N | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***S. aureus* (including MRSA) [≤ 2 (S), 4 (I), ≥8 (R)]** | | | | | | | | | | | | | |
| **Clinical** | 397 | 394 | 99.2 | 397 | 394 | 99.2 | 397 | 100 | 0 | 397 | 0 | 0 | 0 |
| **Challenge** | 100 | 100 | 100 | 100 | 100 | 100 | 99 | 99 | 0 | 100 | 1 | 0 | 0 |
| **Combined** | 497 | 494 | 99.4 | 497 | 494 | 99.4 | 496 | 99.8 | 0 | 497 | 1 | 0 | 0 |

EA – Essential Agreement
CA – Categorical Agreement
S – Susceptible
Maj – Major Discrepancies
Eval – Evaluable MICs
R – Resistant
min – Minor Discrepancies
vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Due to the insufficient number of resistant *S. aureus* isolates evaluated, the following limitation was applied to ceftobiprole testing in the device labeling:

> *The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.*

**MIC Trending**

A trending analysis was conducted using the combined data (clinical and challenge) obtained for both the ARIS HiQ/OptiRead and the Vizion for *S. aureus.* This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher than 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 or at least one dilution higher or in exact agreement with the CLSI reference method were 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 shows higher or lower MIC values compared to the reference is addressed in the labeling.

Evaluation of results for *S. aureus* with ceftobiprole using ARIS HiQ/OptiRead and Vizion are summarized in **Table 4**. A trend toward higher MIC values was observed for *S. aureus* using both ARIS HiQ/OptiRead and Vizion when compared to the CLSI broth microdilution reference method.

To address the MIC trending, the sponsor included the following footnotes in the performance table in the device labeling:

For ARIS HiQ/OptiRead:
*Ceftobiprole MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. aureus with the ARIS HiQ/OptiRead compared to the CLSI broth microdilution reference method.*

For Vizion:
*Ceftobiprole MIC values tended to be in exact agreement or at least one doubling dilution higher when testing S. aureus with the Vizion compared to the CLSI broth microdilution reference method.*

**Table 4.** Ceftobiprole Trending Analysis for *Staphylococcus aureus* with ARIS HiQ/OptiRead and Vizion

| Read Method | Organism | Total Evaluable for Trending | ≥ 1 Dilution lower No. (%) | Exact No. (%) | ≥ 1 Dilution Higher No. (%) | Percent Difference (95% CI) | Trending Noted |
|---|---|---|---|---|---|---|---|
| **ARIS HiQ/ OptiRead** | *Staphylococcus aureus* | 497 | 1 (0.2) | 159 | 337 (67.8) | 68% (63% to 72%) | Yes, high |
| **Vizion** | *Staphylococcus aureus* | 497 | 1 (0.2) | 204 | 292 (58.8) | 59% (54% to 63%) | Yes, high |

**Testing/Reporting MICs for Non-indicated Species.**
For this review, the interpretive 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 included in the Warnings and Precautions section of the device labeling to address testing and reporting of non-indicated species:

> *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 labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.*

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:

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

| Organism | Minimum Inhibitory Concentrations (µg/mL)[a] | | |
|---|---|---|---|
| | Susceptible | Intermediate | Resistant |
| *Staphylococcus aureus* (including methicillin resistant isolates) | ≤2 | 4 | ≥8 |

[a] According to the 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.

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission incorporated by reference a breakpoint change protocol that was reviewed and accepted by FDA in submission K231994 cleared on August 25, 2023. This referenced 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/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria). The referenced protocol outlined the specific procedures and acceptance criteria that Thermo Fisher Scientific intends to use to evaluate The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole when revised breakpoints for Ceftobiprole are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Thermo Fisher Scientific will update the Ceftobiprole device label to include (1) the new breakpoints, (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.