510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K192729

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

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

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JWY, LRG, LTT	Class II	21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Lefamulin at concentrations of 0.008 – 16 µg/mL to the Sensititre 18-24-hour MIC or Breakpoint Susceptibility System for testing Gram-positive non-fastidious isolates

B Measurand:

Lefamulin in the dilution range of 0.008 – 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-hemolytic 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 Lefamulin in the dilution range of 0.08 – 16 μg/mL for testing non-fastidious gram positive on the Sensititre 18-24 hour MIC panel.

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

Staphylococcus aureus (methicillin-susceptible isolates)

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The ability of the Sensititre system to detect *Staphylococcus aureus* (MSSA) isolates that are non-susceptible to Lefamulin is unknown because an insufficient number of isolates was available at the time of the comparative testing. Isolates yielding lefamulin MIC results other than “Susceptible” should be submitted to a reference laboratory for further testing.

Studies of Lefamulin with *Staphylococcus aureus* (MSSA) were performed using the AIM autoinoculator inoculation method and OptiRead and VIZION reading methods only. The use of alternative inoculation methods or alternative reading methods when testing Lefamulin have not been evaluated.

D Special Instrument Requirements:

Sensititre AIM for device inoculation
Sensititre VIZION or OptiRead for plate reading

IV Device/System Characteristics:

A Device Description:

Sensititre MIC Susceptibility panels are multi-well microtiter plates, dosed with dried, stabilized antimicrobials. It is a miniaturized 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.

Antimicrobial susceptibility test results can be determined by reading growth using the digital device (VIZION) or automatically on an autoreader (OptiRead) using fluorescence.

B Principle of Operation:

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System includes multi-well plastic microtiter plates that contain doubled dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read by the digital device, VIZION, or by use of an automated reader (OptiRead).

The VIZION 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 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 substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The 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.

V Substantial Equivalence Information:

A Predicate Device Name(s):
The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Delafloxacin in the dilution range of 0.0005 - 8 ug/mL

B Predicate 510(k) Number(s):
K171870

C Comparison with Predicate(s):

Device & Predicate Device(s):	K192729	K171870
Device Trade Name	Sensititre 18-24 hour Susceptibility System Lefamulin	Sensititre 18-24 hour Susceptibility System Delafloxacin
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Sensititre MIC and Breakpoint Susceptibility system is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious Gram-	Same

	negative isolates comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa* and other non-*Enterobacteriaceae* and of non-fastidious gram positive isolates, comprising of *Staphylococcus* sp., *Enterococcus* sp., and Beta hemolytic *Streptococci* other than *S. pneumoniae*.	
Test Panel	96 well plate is 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
Test Organism	Non-fastidious Gram-positive isolates	Same
Read Method	Results can be read using the following methods: 1) Automatically with the OptiRead (fluorescent substrate technology) 2) On the VIZION (digital viewing device)	Same
Incubation	18-24 hours	Same
General Device Characteristic Differences		
Antimicrobial Agent	Lefamulin	Delafloxacin
Antimicrobial Concentrations	0.008 - 16 µg/ml	0.0005 - 8 µg/mL

VI Standards/Guidance Documents Referenced:

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

CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 29th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2019.

CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. 11th ed. CLSI standard M07. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   A reproducibility study was performed at four sites using a panel comprised of 10 strains of *S. aureus* (5 MSSA + 5 MRSA). All isolates were tested in triplicate over three days with each read method (i.e., VIZION and OptiRead). The Sensititre Aim inoculator was used for plate inoculation. The mode MIC value was determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. Reproducibility was greater than 95% for both read methods with the isolates that were tested and was considered to be 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):

   Quality control strains recommended by the CLSI were tested with Lefamulin at four sites. The QC organism tested was *S. aureus* ATCC 29213. The QC strain was tested a minimum of 20 times per site and read using the VIZION and OptiRead. The results demonstrate that the Sensititre Lefamulin MIC quality control results were within the recommended range >95% of the time (Table 2).

Table 2. Quality Control Results for Sensititre 18 – 24 hour MIC or Breakpoint Susceptibility System with Lefamulin with the VIZION and OptiRead Methods.

QC Organism	Lefamulin Range (µg/mL)	Concentration (µg/mL)	Reference	Read Method	
				VIZION	OptiRead
S. aureus ATCC 29213	0.06 – 0.25	0.03	0	0	0
		0.06	17	9	15
		0.12	65	78	72
		0.25	0	0	0
		0.5	0	0	0

Inoculum Density. Inoculum density checks were performed a sufficient number of times; all organism suspensions were in the acceptable range.

Purity checks. Purity checks were performed on all isolates following plate inoculation. Only results from pure cultures were evaluated.

Growth Failures. All gram-positive isolates tested showed growth in the Sensititre panels.

6. Detection Limit:

   Not Applicable

7. Assay Cut-Off:

   Not Applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

   Results obtained with Sensititre Lefamulin MIC panels were compared to results obtained with the CLSI broth microdilution reference panel. Drug dilutions were prepared using fresh Mueller Hinton broth as indicated in CLSI M7, 11th ed. Clinical testing was performed at four sites, three of which were in the U.S. A total of 201 clinical methicillin-susceptible *S. aureus* (MSSA) isolates were tested. All of the clinical isolates tested were fresh isolates. In addition, a total of 50 challenge MSSA isolates were tested at a single. During the course of the clinical trial, all Sensititre dried MIC panels were inoculated using the Sensititre Autoinoculator (AIM) and the same panel was read on both the VIZION (manual read) and the OptiRead in a blinded manner. The sponsor added the following limitations to the device labeling to reflect the evaluation of these inoculation and read methods:

   Studies of Lefamulin with Staphylococcus aureus (MSSA) were performed using the AIM autoinoculator inoculation method and OptiRead and VIZION reading methods only. The use of alternative inoculation methods or alternative reading methods when testing Lefamulin have not been evaluated.

Essential Agreement (EA) is when the Sensititre results agree exactly or within one doubling dilution of the reference broth microdilution results. Category Agreement (CA) is when the Sensititre result interpretation agrees exactly with the reference broth microdilution result interpretation.

The results from clinical and challenge testing determined with the VIZION demonstrated a combined EA of 100% and CA of 100% for MSSA (Table 3). The results from clinical and challenge testing determined with the OptiRead demonstrated a combined EA of 99.6% and CA of 100% for MSSA (Table 4).

Table 3. Performance of *S. aureus* Clinical and Challenge Isolates, Read Using VIZION

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***Staphylococcus aureus* (MSSA)**													
Clinical	201	201	100.0	201	201	100.0	201	100	2	199	NA	0	0
Challenge	50	50	100.0	50	50	100.0	50	100	0	50	NA	0	0
Total	251	251	100.0	251	251	100.0	251	100	2	249	NA	0	0

Table 4. Performance of *S. aureus* Clinical and Challenge Isolates, Read Using OptiRead

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***Staphylococcus aureus* (MSSA)**													
Clinical	201	201	100.0	200	200	100.0	201	100	2	199	NA	0	0
Challenge	50	49	98.0	50	49	98.0	50	100	0	50	NA	0	0
Total	251	250	99.6	251	251	99.6	251	100	2	249	NA	0	0

EA – Essential agreement
CA – Category agreement
Eval – Evaluable isolates
NS – Non-susceptible isolates
NA – Not Applicable due to lack of intermediate category
maj – Major errors
vmj – Very major errors
min – Minor errors
S - Susceptible

Due to insufficient number of resistant isolates tested in the comparison study, the sponsor included the following to instruct users to use an alternative method of testing when non-susceptible isolates of MSSA have been isolated:

> *The ability of the Sensititre system to detect Staphylococcus aureus (MSSA) isolates that are non-susceptible to Lefamulin is unknown because an insufficient number of isolates was available at the time of the comparative testing. Isolates yielding lefamulin MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.*

To address the testing and reporting of non-indicated species the following comment was added to the Precautions section of the device 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.*

MIC Trending

An analysis of trending was calculated using the combined clinical and challenge data for each organism group. This trending calculation takes into account 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. Trending results are shown in Table 5. Results for *S. aureus* were stratified by methicillin-susceptibility to determine if particular trends were observed. The acceptable percent difference between higher and lower dilution readings is <30%. Based on the results observed, there were no trends identified.

Table 5: Lefamulin Trending Analysis for *S. aureus*, Read by VIZION and OptiRead

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
***S. aureus* (MSSA) VIZION**	**251**	**18 (7.2)**	**184 (73.3)**	**49 (19.5)**	**12.4 (6.5-18.3)**	**No**
***S. aureus* (MSSA) OptiRead**	**251**	**58 (23.1)**	**147 (58.6)**	**46 (18.3)**	**-4.8 (-11.8-2.3)**	**No**

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 lefamulin are as listed in Table 6.

Table 6: FDA-Recognized Interpretive Criteria[a] for Lefamulin (µg/mL)

	Susceptible (S)	Intermediate (I)	Resistant (R)
S. aureus (MSSA)	≤0.25	-	-

[a] 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 included a breakpoint change protocol that was reviewed and accepted by FDA. This 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/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm). The protocol outlined the specific procedures and acceptance criteria that ThermoFisher intends to use to evaluate the Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System with Lefamulin in the dilution range of 0.008-16ug/ml when revised breakpoints for lefamulin are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, ThermoFisher will update the lefamulin 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.