510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K210873

B Applicant

Oxoid Limited (Part of Thermo Fisher Scientific)

C Proprietary and Established Names

Thermo Scientific Oxoid Lefamulin Disc (20µg) LMU20

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JTN	Class II	21 CFR 866.1620 - Antimicrobial Susceptibility Test Disc	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain substantial equivalence determination for Lefamulin Antimicrobial Susceptibility Test Disc.

B Measurand:

Lefamulin (20 µg) LMU20.

C Type of Test:

Antimicrobial Susceptibility Test Disc.

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

Thermo Scientific Oxoid Antimicrobial Susceptibility Test Discs are used in the semi-quantitative agar diffusion test method for in vitro susceptibility testing.

The Thermo Scientific Oxoid Lefamulin Disc (20 µg) LMU20 can be used to determine susceptibility to Lefamulin against the following bacteria which Lefamulin has been shown to be active both clinically and in vitro:

Gram-positive Bacteria:

Streptococcus pneumoniae
Staphylococcus aureus (methicillin-susceptible isolates)

Gram-negative Bacteria:

Haemophilus influenzae

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

Limitations:
The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than "Susceptible" should be submitted to a reference laboratory for further testing.

Isolates of H. influenzae that provide a disc zone of inhibition ≥ 17 mm should be tested by an alternative testing method prior to reporting results.

Isolates of S. aureus (MSSA) that provide a disc zone of inhibition ≥ 23 mm should be tested by an alternative testing method prior to reporting results.

Isolates of S. pneumoniae that provide a disc zone of inhibition ≥17mm should be interpreted by an alternative testing method prior to reporting results.

D Special Instrument Requirements:

Not Applicable.

IV Device/System Characteristics:

A Device Description:

Thermo Scientific Oxoid Lefamulin Disc (20µg) comprise 6mm discs prepared by impregnating high quality absorbent paper with an accurately determined amount of lefamulin. The disc is clearly marked on both sides with the code LMU20. The code designates the agent (lefamulin) and the drug content (20 µg).

Thermo Scientific Oxoid discs are supplied in cartridges containing 50 discs each, there are 5 cartridges per pack. Each cartridge is individually sealed together with a desiccant capsule in a foil covered see-through blister pack. Thermo Scientific Oxoid discs can be dispensed using a Thermo Scientific Oxoid Disc Dispenser.

B Principle of Operation:

A suitable therapeutic agent can be determined using filter paper disks impregnated with specified concentrations of antimicrobial agents placed on the surface of a suitable test medium. The test is performed by inoculating pure cultures of clinical isolates onto the test medium and placing the AST disk on the surface of the medium. The antibiotic within the disk diffuses into the agar. After incubation, the zones of inhibition around the disks are measured and compared against recognized zone diameter ranges for the specific antimicrobial agent/organism combinations being tested.

V Substantial Equivalence Information:

A Predicate Device Name(s):

HardyDisk AST Lefamulin 20µg (LMU20)

B Predicate 510(k) Number(s):

K192326

C Comparison with Predicate(s):

Device & Predicate Device(s):	**Device:** **K210873**	**Predicate:** **K192326**
Device Trade Name	Thermo Scientific Oxoid Lefamulin Disc (20 µg) LMU20	HardyDisk AST Lefamulin 20µg (LMU20)
General Device Characteristic Similarities		
Intended Use/Indications for Use	Thermo Scientific Oxoid Antimicrobial Susceptibility Test Discs are used in the semi quantitative agar diffusion test method for in vitro susceptibility testing.	Same.

Antimicrobial Agent	Lefamulin	Same
Antimicrobial Agent Concentration	20 µg	Same
Interpretation	The user will interpret the zone diameter according to the established interpretive criteria for the drug	Same
Test Method	Semi quantitative agar diffusion test method using antimicrobial discs impregnated with an antimicrobial agent.	Same
Result Interpretation Method.	Measurement of zone size	Same
General Device Characteristic Differences		
Manufacturing Specifications	Oxoid's specifications	Hardy Diagnostics' specifications

VI Standards/Guidance Documents Referenced:

- CLSI M02-13th ed., *Performance Standards for Antimicrobial Disk Susceptibility Tests*; Approved Standard; January 2018.

- CLSI M100-29th ed., *Performance Standards for Antimicrobial Susceptibility Testing*; Twenty-ninth Informational Supplement; 2019

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility was conducted at one external site using 15 organisms, tested in triplicate with two disk lots on three separate days using one lot of appropriate media (Mueller Hinton agar (MHA media) for *S. aureus*, MHA+5% sheep blood for *streptococci* and *Haemophilus* Test Medium (HTM) for *Haemophilus* spp). Each test was visually read by three independent readers with results blinded, resulting in 270 data points for evaluation (15 organisms x 2 disk lots x 1 media lot x 3 days x 3 independent readers = 270 data point).

   The reproducibility study included 5 *Staphylococcus aureus,* 5 *Haemophilus influenzae* and 5 *Streptococcus pneumoniae* isolates.

Reproducibility was calculated as the percent of results which were within ±3 mm difference in zone diameter compared to the modal zone diameter value. Summary results between disk lots and across readers are shown in **Table 1** below.

Table 1: Reproducibility Summary

Between Disk Lots			Across Readers			
Lot #1	**Lot #2**	**All Lots**	**Reader# 1**	**Reader#2**	**Reader#3**	**All Readers**
100% (135/135)	100% (135/135)	100% (270/270)	100% (90/90)	100% (90/90)	100% (90/90)	100% (270/270)

The reproducibility between disk lots and across readers is >95% and meets the acceptance criteria.

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 (QC) Testing:
The CLSI-recommended quality control (QC) isolates, *Staphylococcus aureus* ATCC 25923 *Haemophilus influenzae ATCC 49247* and *Streptococcus pneumoniae ATCC 49619* were tested s (i.e., a minimum of 20 quality control test results per lot per reader and per site) on appropriate media. One predicate disk lot and two Oxoid disk lots were used. Each test was visually read by three or four independent readers. The performance is shown in **Table2**.

Table 2: Quality Control Performance

	Zone Diameter in millimeter (mm)			
QC Organism	**Range**	**Comparator Disc[1]**	**Oxoid Lot A[2]**	**Oxoid Lot B[2]**
Staphylococcus aureus ATCC 25923 Expected Range: 26-32 mm	21			
	22			
	23			
	24			
	25		1	
	26	7	1	1
	27	9	5	7
	28	14	9	9
	29	19	16	18
	30	6	16	14
	31	7	12	12

QC Organism	Zone Diameter in millimeter (mm)			
	Range	Comparator Disc[1]	Oxoid Lot A[2]	Oxoid Lot B[2]
	32		2	1
	>33			
Haemophilus influenzae ATCC 49247 Expected Range: *22-28 mm*	21			
	22			
	23			
	24	3		
	25	20		
	26	24	12	9
	27	13	28	31
	28	1	21	21
	29			
	30			
	31			
Streptococcus pneumoniae ATCC 49619 Expected Range: 19-27 mm	19			
	21			1
	22	3		
	23	13	1	
	24	25	7	5
	25	16	24	23
	26	3	23	24
	27		5	7
	28			
	29			
	30			
	31			

ATCC=American Type Culture Collection
[1]One comparator disk lot
[2]Two Oxoid disk lots were tested (lot A and lot B)

The Oxoid disk QC performance is > 95% and is acceptable.

Inoculum Density Check:
Colony counts were conducted for all QC and reproducibility isolates, as well as 10% of clinical isolates. All were within the expected range.

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

The Oxoid Lefamulin disc 20 µg (LMU20) was compared with an FDA cleared disc of the same antimicrobial, mass/concentration, and content. The study was conducted at one testing site. Three independent operators participated in reading of test results with isolates evenly distributed to mimic testing at multiple sites. Testing was performed with one lot of disk of each test manufacturer (Oxoid and comparator FDA-cleared disk) utilizing the appropriate media (MHA media for *S. aureus (MSSA)*, MHA+5% sheep blood for streptococci and HTM for *Haemophilus* spp). following the CLSI M02 13th edition method.

Clinical:
Clinical testing was performed at one U.S. site with both Thermo Scientific Oxoid Lefamulin Disc and the comparator FDA cleared disk using a total of 300 clinical isolates including 100 clinical isolates of each of the indicated species.

Challenge:
Challenge testing was performed at one U.S site. A total of 75 challenge isolates were tested which included 25 isolates of each of the three indicated species (*Staphylococcus aureus* MSSA, *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Results for the total 375 clinical and challenge isolates are shown in **Table 3.**

Table 3: Performance of Oxoid Lefamulin Disc vs. Comparator Disc.

	Total	CA#	CA%	S (#)	NS (#)	VMJ	MAJ	MIN
Staphylococcus aureus (MSSA) ≥23 (S), -, -								
Clinical	100	100	100.0	100	0	0	0	NA
Challenge	25	25	100.0	13	12	0	0	NA
Combined	125	125	**100.0**	113	12	0	0	NA
Haemophilus influenzae ≥17 (S), -, -								
Clinical	100	99	99.0	99	1	1	0	NA
Challenge	25	23	92.0	20	5	2	0	NA
Combined	125	122	**97.6**	119	6	3	0	NA
Streptococcus pneumoniae ≥17 (S), -, -								
Clinical	100	100	100.0	100	0	0	0	NA
Challenge	25	25	100.0	25	0	0	0	NA
Combined	125	125	**100.0**	125	0	0	0	NA

NA: Not Applicable.

CA – Category Agreement
S – Susceptible isolates
NS – Non-susceptible isolates
MIN – minor errors
MAJ – major errors
VMJ – very major errors

Category Agreement (CA) is when the Thermo Scientific Oxoid disc result interpretation agrees exactly with the comparator result interpretation.

The performance of the Thermo Scientific Oxoid Lefamulin disc as compared to the FDA cleared comparator disc for *Staphylococcus aureus* (MSSA) is acceptable with 100% CA. There were no major and no very major discrepancies.

The performance of the Thermo Scientific Oxoid Lefamulin disc as compared to the FDA cleared comparator disc for *Streptococcus pneumoniae* is acceptable with 100% CA. There were no major and no very major discrepancies.

The performance of the Thermo Scientific Oxoid Lefamulin disc as compared to the FDA cleared comparator for *H. influenzae* is acceptable with 97.6% CA. However, there were 3 very major errors resulting in a very major error rate of 50% (3/6 non-susceptible isolates) which does not meet FDA acceptance criteria of ≤2% very major errors. To address the very major error rate, the following limitation was included in the device labeling:

> *Isolates of H. influenzae that provide a disc zone of inhibition ≥ 17 mm should be tested by an alternative testing method prior to reporting results.*

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included as a footnote to the performance table in the device labeling to address testing of non-indicated species:

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

Non-susceptible Isolates Tested:

Lefamulin interpretive criteria does not have intermediate or resistant breakpoints for the indicated organisms. The following limitation was included in the device labeling:

> *The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than "Susceptible" should be submitted to a reference laboratory for further testing*.

Resistance Mechanisms in Challenge Isolates:

Challenge isolates harboring the resistance mechanisms against which lefamulin has been shown to be active were not tested. The following footnote was included in the device labeling:

> *The performance of the Thermo Scientific Oxoid Lefamulin 20 µg disc was not evaluated with challenge isolates harboring resistance mechanisms listed in the FDA drug label*.

Secondary Analysis:

A secondary analysis of the total 375 combined clinical and challenge isolates was also performed (including 125 isolates of each of the indicated species). The analysis was conducted to compare qualitative categorical agreement of the Thermo Scientific Oxoid disc and the CLSI broth microdilution reference MIC values (based on historical data from testing performed at the initial recovery of isolates during the drug clinical trials).

Analysis of the Oxoid disk data for *S. aureus* (MSSA) isolates was acceptable with 98% CA. There were no major errors. However, there were two very major errors out of 14 non-susceptible isolates (14.29%) observed with the Thermo Scientific Oxoid disc compared to MIC values which does not meet the FDA acceptance criteria of ≤2% very major error rate.

Due to the occurrence of potential very major errors with the Lefamulin and the Thermo Scientific Oxoid disc with MSSA isolates, the following limitation was included in the device labeling:

Isolates of S. aureus (MSSA) that provide a disc zone of inhibition ≥ 23 mm should be tested by an alternative testing method prior to reporting results.

Analysis of the Oxoid disk data for *Streptococcus pneumoniae* isolates was acceptable with 97% CA. There were no major errors. However, there were 4 very major errors out of 4 non-susceptible isolates (100%) observed with the Thermo Scientific Oxoid disc compared to MIC values which does not meet the FDA acceptance criteria of ≤2% VMJ rate.

Due to the occurrence of potential very major errors with the lefamulin and the Thermo Scientific Oxoid disc with *Streptococcus pneumoniae isolates*, the following limitation was included in the device labeling:

Isolates of S. pneumoniae that provide a disc zone of inhition ≥ 17mm should be tested by an alternative testing method prior to reporting results.

Analysis of the Oxoid disk data for *H. influenzae* isolates was acceptable with 92.8% CA. There were no major errors. However, the were 9 very major errors out of 12 non-susceptible isolates (75%) observed with the Thermo Scientific Oxoid disc compared to MIC values. In these instances, 2 out of the 9 very major errors were 1mm close to the breakpoints. After EA adjustment, the adjusted VMJ is 7/12 non-susceptible isolates (58.3%) which still does not meet the FDA acceptance criteria of ≤2% VMJ rate. Due to the occurrence of potential very major errors with the Lefamulin and the Thermo Scientific Oxoid disc with *H. influenzae* isolates, a limitation was included in the device labeling (refer to the limitation listed in section B1 above).

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 listed in **Table 4**.

Table 4: FDA- Identified Interpretative Criteria Lefamulin[1]

Pathogen	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion (mm)		
	S	I	R	S[2]	I	R
Staphylococcus aureus (MSSA isolates)	≤0.25	-	-	≥23	-	-
Streptococcus pneumoniae	≤0.5	-	-	≥17	-	-
Haemophilus influenzae	≤2	-	-	≥17	-	-

S = Susceptible; I = Intermediate; R = Resistant

[1] According to FDA STIC Website.

[2]The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

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.