

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

A. 510(k) Number:

k101425

B. Purpose for Submission:

To add doripenem at concentrations of 0.008-32 µg/mL to the Microscan® Dried Gram-Negative MIC/Combo Panels.

C. Measurand:

Doripenem 0.008-32 µg/mL

D. Type of Test:

Quantitative growth-based detection algorithm using optics light detection

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

MicroScan® Dried Gram-Negative MIC/Combo Panels

G. Regulatory Information:

1. Regulation section:
866.1640 - Antimicrobial Susceptibility Test Powder
2. Classification:
Class II
3. Product code:
LRG- Instrument for Auto Reader & Interpretation of Overnight Antimicrobial Susceptibility Systems
JWY - Manual Antimicrobial Susceptibility Test Systems
LTT – Panels, Test, Susceptibility, Antimicrobial
4. Panel:
83 Microbiology

H. Intended Use:

1. Intended use:

For use with MicroScan® Dried Gram Negative MIC/Combo Panels and Dried Gram Negative Breakpoint Combo Panels. MicroScan® panels are designed for use in determining antimicrobial agent susceptibility and/or identification to the species level of aerobic and facultative anaerobic gram-negative bacilli.

The MicroScan® Dried Gram Negative MIC/Combo Panels is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram negative bacilli.

2. Indication(s) for use:

The MicroScan® Dried Gram Negative MIC/Combo Panels is used to determine quantitative and/or qualitative antimicrobial agent susceptibility of colonies grown on solid media of rapidly growing aerobic and facultative anaerobic gram negative bacilli. After incubation, panels are incubated for 16- 20 hours at 35°C +/- 1°C in a non-CO₂ incubator, and read either visually or with MicroScan instrumentation, according to the Package insert.

This particular submission is for the addition of Doripenem at concentrations 0.008 to 32µg/mL to the test panel.

The gram-negative organisms which may be used for Doripenem susceptibility testing in this panel are:

Acinetobacter baumannii
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

3. Special conditions for use statement(s):

- For prescription use only
- The Log and Stationary Inoculum methods should not be used with Doripenem.
- The Prompt™ method of inoculation is an alternate method of inoculation preparation that is supported in the methodology along with the turbidity method.

4. Special instrument requirements:

MicroScan® WalkAway® System and MicroScan® autoSCAN®-4 are the alternate read methods for Doripenem

I. Device Description:

The MicroScan® Dried Gram-Negative MIC/Combo Panel contains micro-dilutions of each antimicrobial agent in various concentrations with Mueller Hinton Broth and various nutrients which are dehydrated and dried in panels. Each panel contains two control wells: a no-growth control well (contains water only/no nutrients or broth), and a growth control well (contains test medium without antibiotic). The panel is rehydrated and inoculated at the same time with 0.1 ml of suspension prepared by the turbidity method (inoculum prepared in water, then 0.1 ml transferred to 25 ml of inoculum water containing pluronic-D/F-a wetting solution). The Prompt® method of inoculation is also recommended as an alternate means of preparing the inoculum. The panels are incubated at 35°C in a non-CO₂ for 16- 20 hours and read by visual observation for growth. Panels may also be read automatically with the WalkAway® and autoSCAN®-4 Systems.

J. Substantial Equivalence Information:

1. Predicate device name(s):
MicroScan Dried Gram-Negative MIC/Combo Panels- Ertapenem
2. Predicate 510(k) number(s):
k032706
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	MicroScan® panels are designed for use in determining quantitative and/or qualitative antimicrobial agent susceptibility and/or identification to the species level of colonies, grown on solid media, of rapidly growing aerobic and facultative anaerobic organisms	Same
Inoculum preparation	Inoculum prepared from isolated colonies using either the Turbidity method or Prompt® system	Same
Technology	Growth based after 16 hours	Same
Results	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Same
Instrument	autoSCAN®-4 or WalkAway®	Same
Differences		

Item	Device	Predicate
Antibiotic	Doripenem at 0.008- 32 µg/mL	Ertapenem at 0.002- 32 µg/mL
Test organisms	<i>Acinetobacter baumannii</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i> <i>Pseudomonas aeruginosa</i>	<i>Enterobacteriaceae</i>

K. Standard/Guidance Document Referenced (if applicable):

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA”; Clinical and Laboratory Standards Institute (CLSI) M07-A8 “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard”; M100-S19 “Performance Standards for Antimicrobial Susceptibility Testing”

L. Test Principle:

After incubation in non-CO₂ incubator for 16- 20 hours, the MIC for the test organisms are read by determining the lowest antimicrobial concentration showing inhibition of growth. The panels are read either visually or automatically with the WalkAway® and autoSCAN®-4, which uses an optics system with growth algorithms to directly measure organism growth.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Reproducibility was demonstrated using 10 isolates tested at three sites on three separate days in triplicate. The study included the testing of the following inoculum and reading variables; turbidity inoculum method and Prompt method of inoculation with reading performed manually, by WalkAway instrument and autoSCAN-4 instrument. All results were >95% reproducible.

Difference in the number of dilutions between the mode of the MicroScan® result and the actual result with each inoculation method for between site reproducibility							
Inoculation Method	Read Method	≥Minus 2 dilutions	Minus 1 dilution	Exact	Plus 1 Dilution	≥Plus 2 dilutions	% Reproducible
Prompt	Manual	5	29	212	22	2	97.4
Prompt	WalkAway	8	18	222	22		97.0
Prompt	autoScan4		4	229	35	2	99.3
Turbidity	Manual	3	26	225	14	2	98.1
Turbidity	WalkAway		7	235	24	4	98.5
Turbidity	autoScan4		6	238	22	4	98.5

There were more results in the minus category (one dilution lower) when reading manually with the Prompt or the turbidity inoculation methods; however, there were more results in the plus category when using the auto reader (WalkAway or autoScan). The same trend was also observed in the challenge study.

b. Linearity/assay reportable range:

Not Applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

The recommended QC isolates, *E.coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times with acceptable results most of the time with the reference method. Quality control results demonstrated the ability of the different reading parameters (manual, WalkAway, and autoScan) by Turbidity or Prompt inoculation methods to produce acceptable results.

The following table provides the frequency of the results in each concentration with the expected range stated.

Organism	µg/mL	ref	Results					
			Turbidity			Prompt		
Doripenem			Manual	Walk Away	Auto Scan	Manual	Walk Away	Auto Scan
<i>E. coli</i> ATCC 25922	<=0.008							
	0.015		29	3	12	6	1	2
Expected range	0.03	115	89	76	70	69	70	73
0.015- 0.06 µg/mL	0.06	3	1		1	5	7	5
	0.12							
	0.25							
	0.5							
	1							
	2							
	4							
	8						1	
<i>P. aeruginosa</i> ATCC 27853	0.12		21	47	1	2		1
	0.25	83	77	29	59	69	59	68
Expected range	0.5	32	19	1	22	12	21	15
0.12- 0.5 µg/mL	1	3	1		1		2	1
	2							
	4							
	8						1	

Inoculum density control: A turbidity meter was used for the turbidity inoculation method. Colony counts were performed weekly on *E. coli* ATCC 25922 for the Prompt inoculation method.

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:*

Clinical efficacy testing was conducted at three external sites using fresh isolates supplemented with stock isolates. The study included a total of 573 Gram-negative isolates, of which 535 were Intended for Testing (IFT) organisms. There were 538 fresh and 36 stock isolates. Of the 573 isolates

tested, there were 74 *Acinetobacter baumannii*, 330 *Enterobacteriaceae*, 131 *Pseudomonas aeruginosa*. There were 75 challenge isolates tested and compared to the reference broth dilution result mode that was determined by previous testing of each isolate multiple times in the recommended reference panel. All isolates grew in the MicroScan panels.

Efficacy testing was performed using the turbidity inoculation method and read manually after incubation for 16- 20 hours at 35°C +/- 1°C in a non-CO₂ incubator. A comparison to the reference method was provided with the following agreement.

Overall Performance Summary- Overnight Manual (Efficacy + Challenge)

Doripenem	EA Tot	EA #	EA %	Eval EA Tot	Eval EA #	Eval EA %	CA #	CA %	#NS	CA Err	
										#	%
Efficacy	535	522	97.6	510	499	97.8	522	97.6	91	13	2.4
Challenge	75	70	93.3	70	66	94.3	71	94.7	16	4	5.3
Combined	610	592	97.0	580	565	97.4	593	97.2	107	17	2.6

EA - Essential Agreement
CA - Category Agreement

NS – Not Susceptible

EA is when there is agreement between the reference method and the new method is within plus or minus one serial two-fold dilution of antibiotic. Category agreement (CA) is when the new method result interpretation agrees exactly with the reference panel result interpretation. Evaluable EA is when the MIC result is on scale for both the new method and the reference method and have on-scale EA.

There were thirteen categorical errors in the Efficacy study; eleven of which were from *P. aeruginosa*, one from *A. baumannii*, all were within EA and one dilution lower when comparing to the reference method. A limitation was included when testing *P. aeruginosa* with Doripenem.

A challenge set was tested at one site. The challenge set of organisms was tested using both Prompt and Turbidity inoculation methods and read either visually or with MicroScan instrumentation (autoSCAN-4, WalkAway). The table below demonstrated those that were in exact agreement with the reference method result and those that differed by one or more 2-fold dilutions:

Difference in the number of dilutions between the expected reference result and the MicroScan® Result						
Inoculation Method	Read Method	≥Minus 2 dilutions	Minus 1 dilution	Exact	Plus 1 Dilution	≥Plus 2 dilutions
Prompt	Manual	2	12	45	10	1
Prompt	WA	1	6	43	17	3
Prompt	AS4		7	43	17	3
Turbidity	Manual	2	13	46	7	2
Turbidity	WA		6	46	15	3
Turbidity	AS4		6	42	19	3

Overall EA in the challenge study was >90% by all reading methods with both Prompt and Turbidity inoculation methods, and they all were in similar exact agreement. However, there were more results in the plus category with the WA and AS4 reads in both inoculation methods. With the Manual reads, more results were in the minus category. The trend was consistent with the reproducibility study data.

The following table demonstrated the performance based on essential agreement (EA) and category agreement (CA) for the challenge set and the different inoculation and reading methods.

	Total	EA	CA Errors	Major Errors	Very Major Errors	CA
Prompt/Manual	75	71 (94.7%)	2 (2.7%)	N/A	N/A	73 (97.3%)
Prompt/WA	75	70 (93.3%)	2 (2.7%)	N/A	N/A	73 (97.3%)
Prompt/AS4	75	71 (94.7%)	2 (2.7%)	N/A	N/A	73 (97.3%)
Turbidity/Manual	75	70 (93.3%)	4 (5.3%)	N/A	N/A	71 (94.7%)
Turbidity/WA	75	71 (94.7%)	5 (6.7%)	N/A	N/A	70 (93.3%)
Turbidity/AS4	75	71 (94.7%)	5 (6.7%)	N/A	N/A	70 (93.3%)

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:

Enterobacteriaceae ≤0.5

Pseudomonas aeruginosa ≤2

Acinetobacter baumannii ≤1

CLSI interpretive breakpoints have not been established when the Doripenem was submitted for review.

The current absence of resistant isolates precludes defining results other than Susceptible. Isolates yielding MIC results suggestive of Non-susceptible category should be submitted to a reference laboratory for further testing.

N. Proposed Labeling:

The expected value range, interpretive criteria and QC for gram negative panels are included in the package insert. The labeling is sufficient and 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.