WHITE PAPER

Use of MicroScan Dried Gram-Negative Panels for Antimicrobial Susceptibility Testing of Meropenem/vaborbactam with *Enterobacteriaceae* Isolates

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BACKGROUND INFORMATION

Carbapenem-resistant *Enterobacteriaceae* (CRE) is a worldwide public health threat. Infections caused by CRE are generally found in patients with underlying health problems, rather than healthy people. Due to the widespread use of carbapenems as empirical therapy, the frequency of CRE infections is increasing. The U.S. population CRE infection rate has been reported at ≤3 cases per 100,000 people, with higher rates in long-term healthcare facilities. However, outside the United States, an increased mortality rate has been reported to be up to 50% in carbapenem-resistant *K. pneumoniae* infections.[1]

Carbapenem resistance is caused by a variety of mechanisms, including β-lactamases. The most common cause of CRE infections in the United States is attributed to the β-lactamase KPC. Patients with KPC producing CRE having been reported in every U.S. state as of December 2017.[2] Due to its frequency and mortality, the Centers for Disease Control and Prevention has declared CRE infection an urgent threat. Isolates that are resistant to carbapenems are typically resistant to other antimicrobial classes as well, adding difficulty in selecting effective treatment. New therapeutic options combined with antibiotic stewardship are necessary to combat the spread of infection.

The U. S. Food and Drug Administration (FDA) recognized this need with the GAIN (Generating Antibiotic Incentives Now) Act to stimulate and expedite antibiotic development and offer sponsors fast-track designation for priority review.

MEROPENEM/VABORBACTAM OVERVIEW

Meropenem/vaborbactam (Vabomere™; Melinta Therapeutics, Inc.) is a recently FDA-approved antimicrobial agent, new to the market as of 2017. Meropenem is combined with a fixed concentration of vaborbactam, designed to target *Enterobacteriaceae* with β-lactamases, including KPC. This agent has demonstrated *in vitro* activity against KPC, SME, TEM, SHV, CTX-M, CMY and ACT. Some *Enterobacteriaceae* isolates demonstrated susceptibility that produced one or more beta-lactamases (e.g., OXA, KPC) to meropenem/vaborbactam; therefore, antimicrobial susceptibility testing is recommended. However, it is not active against metallo-β lactamases (class B) or oxacillinases with carbapenemase activity.[3]

Meropenem/vaborbactam has demonstrated activity against most isolates of *Escherichia coli, Klebsiella pneumoniae* and *Enterobacter cloacae* complex in *in vitro* studies as well as clinical infections. *In vitro* studies performed by Hackel et al.have shown that the MIC_{90} for *Enterobacteriaceae* results in a decrease from >32 µg/mL with meropenem alone to 1 µg/mL with the addition of vaborbactam.[4]

ABBREVIATION	DESCRIPTION	CRE CLASS
KPC	Klebsiella pneumoniae carbapenemase	A
SME	Serratia marcescens enzymes	A
TEM	Derived from patient in Temoniera	A
SHV	Sulfhydryl reagent variable	A
CTX-M	Active on cefotaxime, first isolated in Munich	A
CMY	Plasmid mediated AmpC	C
ACT	Plasmid mediated AmpC	C

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MEROPENEM/VABORBACTAM PERFORMANCE DATA

A multicenter study was performed to evaluate the accuracy of meropenem/vaborbactam on a Beckman Coulter MicroScan Dried Gram-Negative MIC Panel when compared to a frozen CLSI broth microdilution reference panel. Quality control testing of the recommended routine ATCC isolates 27853 and BAA-1705 was performed daily. The quality control met acceptance criteria of ≥95% for all read and inoculation methods tested. A total of five hundred and sixty (560) clinical isolates were tested at three sites during the clinical trial. The species selected for testing were in accordance with the FDA Antibacterial Susceptibility Test Interpretive Criteria (STIC).[5]

The minimum inhibitory concentration (MIC) of the dried test panel was either in exact agreement or within one dilution of the reference MIC result (defined as essential agreement) and met the acceptance criteria of ≥90% (Table 1).

The dried test panel and frozen reference panel agreed 100% for all inoculation and read methods when using FDA breakpoints of *Enterobacteriaceae* (Table 1). It was determined that zero minor, major and very major errors occurred.

This multicenter study showed that meropenem/vaborbactam MIC results for *Enterobacteriaceae* obtained with the MicroScan panel correlate well with MICs obtained using frozen reference panels and FDA interpretive criteria. Beckman Coulter MicroScan received FDA clearance (K183127) for MicroScan Dried Gram-Negative MIC/Combo Panels with meropenem/vaborbactam for dilutions of 0.03/8–64/8 µg/mL.

Table 1: P (Prompt) and T (turbidity) Inoculum Method

READ METHOD	ESSENTIAL AGREEMENT %		CATEGORICAL AGREEMENT %		VERY MAJOR ERRORS %		MAJOR ERRORS %		MINOR ERRORS %	
	P	T	P	T	P	T	P	T	P	T
MicroScan WalkAway *plus*	98.8 (553/560)	99.1 (555/560)	100 (560/560)	100 (560/560)	0.0 (0/1)	0.0 (0/1)	0.0 (0/559)	0.0 (0/559)	0.0 (0/560)	0.0 (0/560)
autoSCAN-4	98.0 (549/560)	98.9 (554/560)	100 (560/560)	100 (560/560)	0.0 (0/1)	0.0 (0/1)	0.0 (0/559)	0.0 (0/559)	0.0 (0/560)	0.0 (0/560)
Manual	98.8 (553/560)	98.8 (553/560)	100 (560/560)	100 (560/560)	0.0 (0/1)	0.0 (0/1)	0.0 (0/559)	0.0 (0/559)	0.0 (0/560)	0.0 (0/560)

Limitations

1. Performance of meropenem/vaborbactam when testing *Morganella morganii* using the Prompt Inoculation system with the autoSCAN-4 or manual read methods were outside of essential agreement compared to the reference method and should be tested using the turbidity inoculation method.
2. The ability of the MicroScan Dried Gram-Negative Panels to detect resistance to meropenem/vaborbactam is unknown with *C. koseri, E. aerogenes, K. oxytoca, M. morganii, P. mirabilis, Providencia* species and *S. marcescens* because resistant strains were not available at the time of comparative testing. If such isolates are observed, they should be tested on an alternate method and/or submitted to a reference lab.

References

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5. U.S. Food & Drug Administration. Antibacterial Susceptibility Test Interpretive Criteria, June 17, 2019. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria. Accessed 14 June 2019.

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