Kathy

62 yo; history of hospitalizations for cUTI and multiple comorbidities, including renal impairment; admitted to the ICU for suspected cUTI

Physical findings and vital signs:

- Temperature: 101.8 °F
- Heart rate: 113 BPM
- Respiratory rate: 25 breaths/min
- Blood pressure: 105/58
- Suprapubic pain rated 9/10 by patient
- Dysuria

Medical history/concomitant conditions:

- Chronic kidney disease (eGFR: 29 mL/min/1.73 m^2)
- Type 2 diabetes
- Hypertension
- History of cUTI

Initial assessment:

- Urinary retention: 201 mL
- Medical background consistent with high risk of CRE infection
- Symptoms suggestive of cUTI

Cultures:

- Presence of KPC-producing *K pneumoniae* >100,000 CFUs/mL from urine and blood culture

Performing AST as soon as possible can lead to improved clinical outcomes by ensuring patients with CRE receive early treatment with an appropriate antimicrobial therapy.[1,2]

This hypothetical case study is meant to be illustrative. It is not intended to offer medical advice. Determination of appropriate treatment is at the discretion of the physician.

Treatment results may vary by patient.

AST=antimicrobial susceptibility testing; CFU=colony-forming unit; CRE=carbapenem-resistant Enterobacterales; cUTI=complicated urinary infections; eGFR=estimated glomerular filtration rate; ICU=intensive care unit; KPC=*Klebsiella pneumoniae* carbapenemase.

START STRONG

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

Early treatment with VABOMERE® (meropenem and vaborbactam) can benefit critically ill patients with cUTI caused by resistant, gram-negative pathogens[2]

Automated susceptibility testing finding:
Klebsiella pneumoniae (99% probability)

Susceptibility information[3]

Antimicrobial	MIC (µg/mL)	Interpretation
Meropenem	≥4	Resistant
VABOMERE	≤4/8	Susceptible

Course of action:

- First-line treatment with VABOMERE
  - Dose adjusted for renal impairment (2 g q12h)
- Routine monitoring
- Improvement of symptoms after 3 days
- Discharge to home on day 6 to complete therapy

This hypothetical case study is meant to be illustrative. It is not intended to offer medical advice. Determination of appropriate treatment is at the discretion of the physician.

Treatment results may vary by patient.

MIC=minimum inhibitory concentration; q12h=every 12 hours.

INDICATIONS AND USAGE

VABOMERE® (meropenem and vaborbactam) is indicated for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by the following susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae species* complex.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of VABOMERE® and other antibacterial drugs, VABOMERE® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DON'T WAIT TO TEST

Test for susceptibility to VABOMERE to provide early and effective treatment to your patients with cUTI caused by CRE.[1,2,4]

IMPORTANT SAFETY INFORMATION

Contraindications

VABOMERE® is contraindicated in patients with known hypersensitivity to any components of VABOMERE® (meropenem and vaborbactam), or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactam antibacterial drugs.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

CRE risk and the benefits of early treatment

In the treatment of cUTI

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

CRE presents a serious threat for critically ill patients

Infections are significantly more likely in patients with the following risk factors:

- Chronic moderate-to-severe renal insufficiency[2,5,6]
- ≥3 comorbidities[5,6]
- Prior CRE infection[2,5]
- Immune compromise[5,7]
- Prolonged hospitalization or antibiotic therapy[2,5,7,8]
- Indwelling catheters[5-7]
- Long-term care in a nursing facility[2,7]

Benefits of early, appropriate therapy[9]

In an analysis of patients with CRE infections, those treated with an appropriate antibiotic within 48 hours of positive cultures (N=229) experienced improved clinical and economic outcomes compared with those who received delayed appropriate therapy (N=285).

3.5 fewer days of antibiotic therapy
(5.4 vs 8.9)

3.7 fewer days in the hospital
(5.1 vs 8.8)

14K
in-hospital savings
(11,539 vs 25,506)

100%
increase in likelihood of discharge home
(0.4 vs 0.2)

48%
decrease in likelihood of in-hospital death
(1.9 vs 3.7)

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Hypersensitivity reactions were reported in patients treated with VABOMERE® in the clinical trials. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving therapy with beta-lactam antibacterial drugs. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam antibacterial drug. If an allergic reaction to VABOMERE® occurs, discontinue the drug immediately.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

VABOMERE was designed for CRE[4,10]

In the treatment of cUTI

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

VABOMERE addresses the challenge of CRE by combining a trusted carbapenem with a unique β-lactamase inhibitor[4,10]

Meropenem
Trusted carbapenem

- Proven to work against a broad spectrum of gram-negative pathogens[11,12]
- Well-established efficacy and safety profile[11,12]

Vaborbactam
Unique BLI

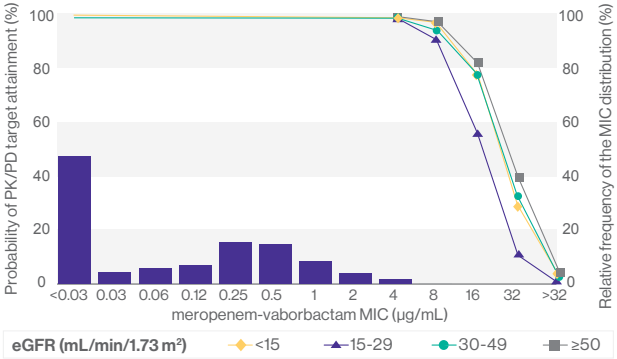
- First in a new class of cyclic boronic acid BLIs[12]
- Protects meropenem from degradation by overcoming β-lactamase resistance mechanisms[4]

VABOMERE is specifically designed to restore the power of meropenem against KPC-producing Enterobacterales.[4]

BLI=β-lactamase inhibitor.

Effective treatment for renally impaired patients[14-17]

Target attainment, regardless of renal function*



*Based upon meropenem-vaborbactam MIC distribution for 1,331 KPC-producing Enterobacteriaceae isolates. In vitro activity does not necessarily correlate with clinical efficacy.

- The similar PK profiles of meropenem and vaborbactam allow for a 1:1 fixed dose that is distinct from the 4:1 dose of ceftazidime-avibactam
  - This contributes to increased stability against enzymatic degradation even in renally impaired patients[18]

PD=pharmacodynamic; PK=pharmacokinetic.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- Seizures and other adverse Central Nervous System (CNS) experiences have been reported during treatment with meropenem, which is a component of VABOMERE®. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- Rhabdomyolysis has been reported with the use of meropenem, a component of VABOMERE®. If signs or symptoms of rhabdomyolysis such as muscle pain, tenderness or weakness, dark urine, or elevated creatine phosphokinase are observed, discontinue VABOMERE and initiate appropriate therapy.

VABOMERE efficacy and safety[4]

In the treatment of cUTI

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

Efficacy evaluated against a widely used cUTI treatment[4]

Clinical and m-MITT[4]

	VABOMERE n/N (%)	PIPERACILLIN/ TAZOBACTAM n/N (%)	DIFFERENCE (95% CI)
Overall success* (EOIVT)	98.4% (183/186)	94.3% (165/175)	4.1%† (0.3%, 8.8%)
Clinical cure plus eradication‡ (TOC)	76.5% (124/162)	73.2% (112/153)	3.3%§ (-6.2%,13.0)

*EOIVT includes patients with organisms resistant to piperacillin/tazobactam at baseline.[4]
†Primary endpoint: 4.1% treatment difference (95% CI, 0.3%, 8.8%) exceeded the lower limit for noninferiority and also superiority.[4,19]
‡TOC visit excludes patients with organisms resistant to piperacillin/tazobactam at baseline in both arms.[4]
§3.3% treatment difference (95% CI, -6.2%, 13%).[4]

Study description: A double-blind, double-dummy, randomized, multicenter noninferiority clinical trial evaluated 545 adult patients with cUTI, including acute pyelonephritis. Patients were treated with VABOMERE (meropenem 2 g and vaborbactam 2 g) or piperacillin/tazobactam (piperacillin 4 g/tazobactam 0.5 g) every 8 hours. After a minimum of 15 doses of IV therapy, patients who met prespecified criteria of improvement could be switched to oral levofloxacin.[4,6]

CI=confidence interval; EOIVT=end of intravenous treatment; IV=intravenous; m-MITT=microbiologically modified intention-to-treat; TOC=test of cure.

Proven safety and tolerability comparable to meropenem[1]

Adverse reactions occurring in 1% or greater of patients receiving VABOMERE in the phase 3 clinical trial in cUTI

ADVERSE REACTIONS	VABOMERE (N=272) %	PIPERACILLIN/ TAZOBACTAM* (N=273) %
Headache	8.8	4.4
Phlebitis/Infusion site reactions†	4.4	0.7
Diarrhea	3.3	4.4
Hypersensitivity‡	1.8	1.8
Nausea	1.8	1.5
Alanine aminotransferase increased	1.8	0.4
Aspartate aminotransferase increased	1.5	0.7
Pyrexia	1.5	0.7
Hypokalemia	1.1	1.5

*Piperacillin/tazobactam 4.5 g (piperacillin 4 g/tazobactam 0.5 g) IV infused over 30 minutes every 8 hours. VABOMERE 4 g (meropenem 2 g/vaborbactam 2 g) IV infused over 3 hours every 8 hours.
†Infusion site reactions include infusion/injection site phlebitis, infusion site thrombosis, and infusion site erythema.
‡Hypersensitivity includes hypersensitivity, drug hypersensitivity, anaphylactic reaction, rash urticaria, and bronchospasm.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including VABOMERE®, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- The concomitant use of VABOMERE® and valproic acid or divalproex sodium is generally not recommended. Case reports in the literature have shown that co-administration of carbapenems, including meropenem, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. If administration of VABOMERE® is necessary, consider supplemental anticonvulsant therapy.

IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[20]

In the treatment of cUTI

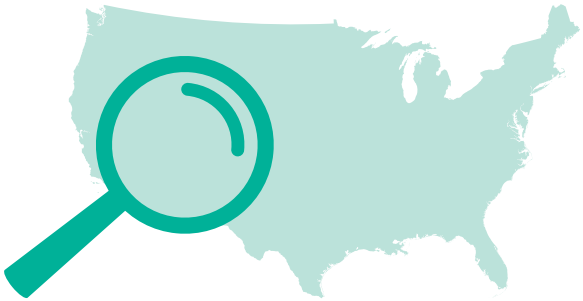
VABOMERE®
meropenem and vaborbactam
for injection (4 g)

IDSA provides guidance on the treatment of antimicrobial-resistant infections. This 2024 update replaces previous versions of the guidance document.

See the full 2024 IDSA Guidance

Carbapenemase testing and KPC prevalence

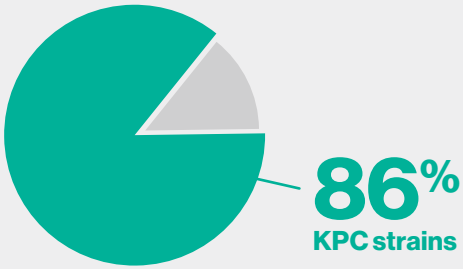
IDSA strongly encourages all laboratories in the US to pursue carbapenemase testing to inform optimal treatment decisions.



Each year in the US, CRE account for:

>13,000 infections*

>1,000 deaths



86% of carbapenemase-producing CRE in the US are KPC strains, **making KPC the most clinically relevant carbapenemase**.

*In hospitalized patients.
IDSA=Infectious Diseases Society of America.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- In patients with renal impairment, thrombocytopenia has been observed in patients treated with meropenem, but no clinical bleeding has been reported.
- Alert patients receiving VABOMERE® on an outpatient basis regarding adverse reactions such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- Prescribing VABOMERE® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of drug-resistant bacteria.
- As with other antibacterial drugs, prolonged use of VABOMERE® may result in overgrowth of nonsusceptible organisms.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

IDSA 2024 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[20]

In the treatment of cUTI

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

Emergence of resistance to novel β-lactam antibiotics

While the emergence of resistance is a concern with all of the novel β-lactams used to treat CRE infections, IDSA notes that the frequency may be highest for ceftazidime-avibactam.

Estimated emergence of resistance after clinical exposure:

<5%
with VABOMERE

~10-20%
with ceftazidime-avibactam

IDSA recommends always repeating susceptibility testing for patients previously infected with CRE who present with symptoms suggestive of a new or relapsed infection.

Patients recently treated with ceftazidime-avibactam may be treated with a different novel β-lactam agent such as VABOMERE at least until culture and susceptibility data are available.

Development of clinical resistance in real-world use

In support of its findings, the IDSA discusses a single observational study comparing the clinical outcomes of 26 patients who received VABOMERE and 105 patients who received ceftazidime-avibactam for at least 72 hours for the treatment of CRE infections.

Percentage of patients with recurrent CRE infections who developed resistance to initial therapy:

0%
with VABOMERE (n=0/3)

20%
with ceftazidime-avibactam (n=3/15)

Observational studies contain material limitations, and their results should be considered in light of the entire body of available evidence, including clinical trial data.

The statements on these pages are not intended to imply comparable safety or effectiveness between VABOMERE® (meropenem and vaborbactam) and ceftazidime-avibactam. Consult the respective products' Prescribing Information for further details, including complete indication and Important Safety Information.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

- The most frequently reported adverse reactions occurring in ≥3% of patients treated with VABOMERE® were headache, phlebitis/infusion site reactions, and diarrhea.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION

Contraindications

- VABOMERE® is contraindicated in patients with known hypersensitivity to any components of VABOMERE® (meropenem and vaborbactam), or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to beta-lactam antibacterial drugs.

References

1. Gajic IJ, Kabic J, Kekic D, et al. Antimicrobial susceptibility testing: a comprehensive review of currently used methods. *Antibiotics (Basel).* 2022;11(4):427. doi:10.3390/antibiotics11040427 **2.** Alosaimy S, Lagnf AM, Morrisette T, et al. Real-world, multicenter experience with meropenem-vaborbactam for gram-negative bacterial infections including carbapenem-resistant Enterobacterales and Pseudomonas aeruginosa. *Open Forum Infect Dis.* 2021;8(8):ofab371. doi:10.1093/ofid/ofab371 **3.** Antibacterial susceptibility test interpretive criteria. U.S. Food & Drug Administration. Updated May 25, 2023. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria **4.** VABOMERE [package insert]: Melinta Therapeutics, LLC. **5.** Alexander EL, Loutit J, Tumbarello M, et al. Carbapenem-resistant Enterobacteriaceae infections: results from a retrospective series and implications for the design of prospective clinical trials. *Open Forum Infect Dis.* 2017;4(2):ofx063. doi:10.1093/ofid/ofx063 **6.** Kaye KS, Bhowmick T, Metallidis S, et al. Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. *JAMA.* 2018;319(8):788-799. doi:10.1001/jama.2018.0438 **7.** About carbapenem-resistant Enterobacterales. Centers for Disease Control and Prevention. Updated April 11, 2024. Accessed January 6, 2025. https://www.cdc.gov/cre/about/index.html **8.** Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther.* 2018;7(4):439-455. doi:10.1007/s40121-018-0214-1 **9.** Lodise TP, Berger A, Altincatal A, et al. Antimicrobial resistance or delayed appropriate therapy-does one influence outcomes more than the other among patients with serious infections due to carbapenem-resistant versus carbapenem-susceptible enterobacteriaceae? *Open Forum Infect Dis.* 2019;6(6):ofz194. doi:10.1093/ofi d/ofz194 **10.** Wenzler E, Scoble PJ. An appraisal of the pharmacokinetic and pharmacodynamic properties of meropenem-vaborbactam. *Infect Dis Ther.* 2020;9(4):769-784. doi:10.1007/s40121-020-00344-z **11.** Merrem IV [package insert]. New York, NY: Pfizer, Inc; 2019. **12.** Baldwin CM, Lyseng-Williamson KA, Keam SJ. Meropenem: a review of its use in the treatment of serious bacterial infections. *Drugs.* 2008;68(6):803-838. doi:10.2165/00003495-200868060-00006 **13.** Hecker SJ, Reddy KR, Totrov M. Discovery of a cyclic boronic acid β-lactamase inhibitor (RPX7009) with utility vs class A serine carbapenemases. *J Med Chem.* 2015;58(9):3682-3692. doi:10.1021acs.jmedchem.5b00127 **14.** Grupper M, Kuti JL, Nicolau DP. Continuous and prolonged intravenous β-lactam dosing: implications for the clinical laboratory. *Clin Microbiol Rev.* 2016;29(4):759-772. doi:10.1128/CMR.00022-16 **15.** Kuti JL, Dandekar PK, Nightingale CH, Nicolau DP. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. *J Clin Pharmaco*l. 2003;43(10):1116-1123. doi:10.1177/0091270003257225 **16.** Lee LS, Kinzig-Schippers M, Nafziger AN, et al. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. *Diagn Microbiol Infect Dis.* 2010;68(3):251-258. doi:10.1016/j.diagmicrobio.2010.06.012 **17.** Bhavnani SM, Trang M, Griffith DC, et al. Meropenem-vaborbactam pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses as support for dose selection in patients with normal renal function and varying degrees of renal impairment. Poster presented at: IDWeek; October 4-8, 2017; San Diego, CA. Abstract 1852. **18.** Shoulders BR, Casapao AM, Venugopalan V. An update on existing and emerging data for meropenem-vaborbactam. *Clin Ther.* 2020;42(4):692-702. doi:10.1016/j.clinthera.2020.01.023 **19.** Data on file: Melinta Therapeutics, LLC. **20.** Tamma PD, Heil EL, Justo JA, et al. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clin Infect Dis.* 2024;ciae403. doi:10.1093/cid/ciae403

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Hypersensitivity reactions were reported in patients treated with VABOMERE® in the clinical trials. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving therapy with beta-lactam antibacterial drugs. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam antibacterial drug. If an allergic reaction to VABOMERE® occurs, discontinue the drug immediately.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

CRE poses an urgent threat[2,5-8]

- Critically ill patients are at greater risk of being infected and experiencing poor outcomes

Early testing and treatment are essential[1,2]

- Early treatment of CRE cUTI is associated with improved outcomes, and susceptibility testing is essential to providing effective treatment sooner

VABOMERE addresses the threat of CRE cUTI[4,10]

- VABOMERE combines meropenem, a trusted carbapenem, with vaborbactam, a unique BLI, to address the challenge of CRE

Consider early use of VABOMERE in your patients with CRE cUTI.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- Seizures and other adverse Central Nervous System (CNS) experiences have been reported during treatment with meropenem, which is a component of VABOMERE®. Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity.

Please see full Important Safety Information throughout and accompanying full Prescribing Information.

melinta therapeutics

VABOMERE®
meropenem and vaborbactam
for injection (4 g)

PP-VAB-US-0496