



# VABOMERE®

meropenem and vaborbactam  
for injection (4 g)

## CODING AND BILLING REFERENCE GUIDE



2 single-dose vials = 4 g dose

### 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.

**Please see Important Safety Information on back cover and accompanying Full Prescribing Information.**

## Introduction and Legal Disclaimer

The VABOMERE® (meropenem and vaborbactam) Reimbursement Guide is designed to inform United States healthcare providers on select, basic reimbursement matters for Medicare, Medicaid, and many third-party payers for its Food and Drug Administration (FDA)-approved uses as indicated in the prescribing information.

The content of this guide is general in nature, strictly for informational purposes only, and does not cover all situations or all payers' policies and guidance. The information provided in this guide was obtained from third-party sources and is subject to change without notice as a result of changes in reimbursement laws, regulations, rules, policies, and payment amounts. This guide is not intended to provide clinical practice guidelines.

Melinta Therapeutics, LLC, cannot guarantee, and is not responsible for, the payment of any claim. The coding, coverage, and payment of VABOMERE® may vary by payer, plan, patient, and setting of care. Coding determinations and analysis should always be independently researched and assessed. For more information, please check with individual payers for specific coding, coverage, and payment requirements. It is the sole responsibility of the healthcare provider to code properly and to ensure the accuracy of all claims submitted for reimbursement. Additionally, as a prerequisite for submitting a claim, the provider is responsible for ensuring that all services are medically necessary and properly supported in the patient's medical records. Melinta Therapeutics, LLC, specifically disclaims liability or responsibility for the results or consequences of any actions taken in reliance on information in this guide.

## Coding Quick View

Coding claim forms properly may help to facilitate timely claims processing and reduce the risk of denied claims. The table below is an overview of the coding requirements, coding systems, and their application when VABOMERE® is used. More detailed descriptions are included in subsequent sections. The code list below is not exhaustive; please consult current coding manuals for complete information.

One or more of the following International Classification of Disease, version 10 (ICD-10) codes may be appropriate when submitting claims for VABOMERE® and its administration. The list of codes below is not comprehensive; additional codes may apply. Providers are responsible for selecting the most appropriate diagnosis code for a specific patient.

### Common Medicare Severity Diagnosis Related Groups (MS-DRGs)

#### Setting of Care: Hospital Inpatient

<b>MS-DRG 689</b>	KIDNEY & URINARY TRACT INFECTIONS W/MCC
<b>MS-DRG 690</b>	KIDNEY & URINARY TRACT INFECTIONS W/O MCC
<b>MS-DRG 698</b>	OTHER KIDNEY & URINARY TRACT DIAGNOSES W/MCC
<b>MS-DRG 699</b>	OTHER KIDNEY & URINARY TRACT DIAGNOSES W/CC
<b>MS-DRG 700</b>	OTHER KIDNEY & URINARY TRACT DIAGNOSES W/O CC/MCC

### Transition of Care Codes<sup>1</sup>

<b>CODE 99495</b>	Covers communication with the patient or caregiver within two business days of discharge. This can be done by phone, e-mail, or in person. It involves medical decision making of at least moderate complexity and a face-to-face visit within 14 days of discharge. The location of the visit is not specified.
<b>CODE 99496</b>	Covers communication with the patient or caregiver within two business days of discharge. This can be done by phone, e-mail, or in person. It involves medical decision making of high complexity and a face-to-face visit within seven days of discharge. The location of the visit is not specified.

# Coverage of and Payment for VABOMERE® (meropenem and vaborbactam)

## Medicare Part A Coverage

In the hospital inpatient setting, products and services furnished, including VABOMERE®, are paid through the MS-DRG reimbursement methodology. The MS-DRG system is a method of reimbursement utilized by Medicare that bundles payment for the products and services used for each patient case. This is a prospective payment system (PPS) in which all costs associated with the stay are covered, except for physician services and certain other non-acute-care services.<sup>2</sup> See the Inpatient Hospital Coding Information section of this guide below for relevant billing codes.

**Permanent J Code Reporting Guidelines: Accurate reporting of the permanent J Code (J2186) as well as the quantity of VABOMERE® administered to each patient is required for appropriate reimbursement. When completing a UB-04/CMS 1450 inpatient reimbursement form for J code (J2186) for VABOMERE®, it is important to include the information listed on pages 3 and 4 of this document.**

The following is the permanent J code for appropriate Medicare billing of VABOMERE®. Medicare, private payers, and state Medicaid programs may require the reporting of this J code to facilitate appropriate reimbursement.

HCPICS	Setting	Billing Description	Billing Unit
J2186	Home Infusion	Injection, meropenem and vaborbactam, 10mg/10mg, (20mg)	100 units per vial (each vial is 2 grams or 2000mg)

## Medicaid Coverage

Each state Medicaid program determines its own eligibility standards and determines the type, amount, duration, and scope of services covered. Medicaid coverage of products and services used in the inpatient setting, including VABOMERE® and its administration, may be based on prospective payment methodologies, similar to that of Medicare. States may also employ other reimbursement methods such as per diem, cost reimbursement, or other methods.<sup>3</sup>

**Please check specific policies and requirements of state Medicaid plans.**

## Commercial Payer Coverage

Commercial plans often restrict their patients to selected networks of providers and have contractual arrangements with these “in-network” providers. Managed indemnity, preferred provider organization (PPO), point of service (POS), health maintenance organization (HMO), and other payers determine their plan’s individual reimbursement policies for VABOMERE® and the related procedures. Specific coverage requirements and restrictions may depend on a patient’s individual benefits, type of plan, and the site of service.

## Inpatient Setting

For complicated urinary tract infections (cUTI) including pyelonephritis in the hospital inpatient setting, commercial payers may base hospital reimbursement on DRGs, per diem rates, cost-basis, or other contracted reimbursement methodologies.

## Outpatient Setting

In the hospital outpatient setting, commercial payers may “bundle” services for the treatment of cUTI including pyelonephritis into a single case rate for all outpatient services, or may separately reimburse for VABOMERE®. If VABOMERE® is separately reimbursed by a commercial payer in the outpatient setting, payment may be based on a percentage of wholesale acquisition cost (WAC), until enough data have been collected to determine an average sales price (ASP) or average wholesale price (AWP), or other pricing methodology.

**Please check specific policies and requirements of the applicable commercial payer for complete information.**

## Inpatient Hospital Coding Information

Medicare does not reimburse separately for VABOMERE® when used in the inpatient setting of care; rather, it utilizes the MS-DRG payment system. Private insurers and state Medicaid agency reimbursement policies vary, but typically they will not provide a separate reimbursement for VABOMERE® in the inpatient setting. From diagnosis to treatment of disease, to products and services utilized during the delivery of healthcare, appropriate coding is vital to the reimbursement process.

## Outpatient Hospital Coding Information

Medicare will typically reimburse the hospital separately, on an occasion that VABOMERE® would be utilized in the outpatient setting of care. Reimbursement will be processed through correct reporting of a drug specific J code using the corresponding units delineated in the instructions below. Private insurers and state Medicaid agency reimbursement policies vary; many will provide a separate reimbursement in the outpatient setting, but it is crucial to the reimbursement process that the individual provider is contacted for appropriate coding information.

**Please see accompanying Full Prescribing Information for complete details.**



## Long-Term Acute Care Hospital (LTACH) Reimbursement

### Medicare Part A Coverage

In the LTACH, products and services furnished, including VABOMERE® (meropenem and vaborbactam), are paid through the MS-DRG reimbursement methodology. The MS-DRG system is a method of reimbursement utilized by Medicare that bundles payment for the products and services used for each patient case. This is a prospective payment system (PPS) in which all costs associated with the hospital stay are covered, except for physician services and certain other non-acute-care services.<sup>4</sup>

For more information about LTACH Prospective Payment System (PPS) payment updates, refer to [Hospital Inpatient Prospective Payment System \(IPPS\)](#) and [Long-Term Acute Care Hospital \(LTACH\) Final Rule in Effect for the Current Fiscal Year](#).

## Home Infusion Reimbursement

### Healthcare Common Procedure Coding System (HCPCS) Codes for VABOMERE®

#### Medicare Coverage

Any infusion drug that is not covered under Medicare Part B is potentially a Medicare Part D drug subject to the plan's formulary and any medical necessity or prior authorization criteria. For example, Medicare Part B does not cover antibiotics for home infusion because the Centers for Medicare & Medicaid Services (CMS) has determined they do not require a durable medical equipment (DME) pump. Therefore, intravenous (IV) antibiotics may be covered under Part D. Part D provides coverage only for the drug; it does not cover the equipment, supplies, and nursing services associated with home infusions.

For more information on home infusion reimbursement, refer to CMS MedPac, Report to the Congress: Medicare and the Health Care Delivery System, June 2012, Chapter 6, Medicare Coverage of and Payment for Home Infusion Therapy, page 177, Medicare Part D Drug Coverage.

#### Medicaid Coverage

Each state Medicaid program determines its own eligibility standards and determines the type, amount, duration, and scope of services covered. Medicaid coverage of products and services used in the home infusion setting, including VABOMERE® and its administration, may be similar to that of Medicare. States may also employ other coding and/or reimbursement methods.

**It is vital to check specific policies and requirements of state Medicaid plans.**

#### Commercial Payer Coverage

Commercial plans often restrict their patients to selected networks of providers and have contractual arrangements with these "in-network" providers; this includes home infusion. Managed indemnity, preferred provider organization (PPO), point of service (POS), health maintenance organization (HMO), and other payers determine their plan's individual reimbursement policies for VABOMERE® and the related procedures. Specific coverage requirements, coding, reimbursement, and restrictions may depend on a patient's individual benefits, type of plan, and the site of service.

**It is vital to check the specific plan as well as the plan's requirements to determine proper coding for reimbursement.**

The following is the permanent J code for appropriate billing of VABOMERE® in the home infusion setting. Medicare, commercial payers, and state Medicaid programs, as described above, may require the reporting of the following J code to facilitate appropriate reimbursement.

HCPCS	Setting	Billing Description	Billing Unit
J2186	Home Infusion	Injection, meropenem and vaborbactam, 10mg/10mg, (20mg)	100 units per vial (each vial is 2 grams or 2000mg)

### Related billing codes for Anti-Infectives:

Billing Code	Time
S9497	Q3 hours
S9504	Q4 hours
S9503	Q6 hours
S9502	Q8 hours
S9501	Q12 hours
S9500	Q24 hours
S9494	Unspecified

## Home Infusion Reimbursement (cont'd)

**Permanent J Code Reporting Guidelines:** Accurate reporting of the permanent J code as well as the quantity of VABOMERE® (meropenem and vaborbactam) administered to each patient is required for appropriate reimbursement. When completing a UB-04/CMS 1500 form (e.g., for home infusion) for VABOMERE®, it is important to include the following information:

- Drug name: VABOMERE® (meropenem and vaborbactam) for injection, for intravenous use
- Dose of product: VABOMERE® 4 grams (meropenem 2 grams and vaborbactam 2 grams) every 8 hours in patients ≥18 years with an estimated glomerular filtration rate (eGFR) ≥ 50mL/min/1.73m<sup>2</sup>\*
- Route of administration: by intravenous infusion for up to 14 days

\*Dosage adjustment is recommended in patients with renal impairment who have an eGFR <50mL/min/1.73m<sup>2</sup>.

### Dosing in Patients With Renal Impairment

eGFR <sup>a</sup> (mL/min/1.73m <sup>2</sup> )	Recommended Dosage Regimen for VABOMERE® (meropenem and vaborbactam) <sup>b,c,d</sup>	Dosing Interval
30 to 49	VABOMERE® 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 8 hours
15 to 29	VABOMERE® 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 12 hours
Less than 15	VABOMERE® 1 gram (meropenem 0.5 grams and vaborbactam 0.5 grams)	Every 12 hours

<sup>a</sup>As calculated using the Modification of Diet in Renal Disease (MDRD) formula as follows: eGFR (mL/min/1.73m<sup>2</sup>) = 175 x (serum creatinine)<sup>-1.54</sup> x (age)<sup>-0.203</sup> x (0.742 if female) x (1.212 if African American).

<sup>b</sup>All doses of VABOMERE® are administered intravenously over 3 hours.

<sup>c</sup>Doses adjusted for renal impairment should be administered after a hemodialysis session.

<sup>d</sup>The total duration of treatment is for up to 14 days.

**NDC – 70842-0120-01:** VABOMERE® 2 grams (meropenem and vaborbactam) for injection is supplied as a white to light yellow sterile powder for constitution in single-dose, clear glass vials sealed with a rubber stopper (not made with natural rubber latex) and an aluminum overseal. Each vial contains 1 gram of meropenem (equivalent to 1.14 grams of meropenem trihydrate), 1 gram of vaborbactam, and 0.575 gram of sodium carbonate.

**NDC – 70842-0120-06:** Packaging; each vial is supplied in cartons of 6 vials.

**Storage:** Store VABOMERE® vials at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [See USP, Controlled Room Temperature (CRT)].

**Some payers may also require VABOMERE® (meropenem and vaborbactam) prescribing information, FDA-approval letter, support of medical necessity, and a drug purchase invoice.**

For additional information, including Indication and Important Safety Information, please see back cover and the accompanying Full Prescribing Information.

 **VABOMERE®**  
meropenem and vaborbactam  
for injection (4 g)

# Sample CMS 1450 Billing Form<sup>2</sup>

For service performed in the hospital

This document is provided for informational purposes only

**Fields 42-43:** Enter the appropriate revenue code and description corresponding to the HCPCS code in field 44, e.g.:

- 0636 for VABOMERE<sup>®</sup>
- 0510 for IV infusion administration in the clinic

*Note: Other revenue codes may apply.*

**Field 44:** Enter the appropriate CPT/HCPCS codes and modifiers, e.g.:

- J2186 is the designated HCPCS code for patients in the hospital outpatient setting
- 96365 for first hour of IV infusion
- 96366 for each additional hour of IV infusion

**Field 46:** Report the appropriate unit of service. VABOMERE<sup>®</sup> is typically billed in the hospital outpatient setting on a "per unit basis"; a typical dose is 4 grams or 2 vials. However, some payers may provide alternate guidance.

Example: A vial of VABOMERE<sup>®</sup> is 2g powder = 100 billing units.

A typical full course of VABOMERE<sup>®</sup> per day is equal to 600 units of J2186 (6 vials/day).

**Field 66:** Identify the type of ICD diagnosis code used, e.g., enter "0" for ICD-10-CM.

**Field 74:** Enter ICD-10-CM procedure code for injection of antibiotic.

*Note: Other ICD-10 codes used may apply.*

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39		40		41		42	
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# Sample CMS 1500 Billing Form<sup>2</sup>

For service performed in the hospital

This document is provided for informational purposes only

### Box 19: Additional Information

Enter the appropriate drug identifying information as required by payer, e.g., "brand and generic drug name, NDC code in 11 digit format, dosage, method of administration, etc."

VABOMERE® is sold 6 vials per box.

Note: Additional information may also be sent via attachment electronically or other format as allowed by payer.

### Box 21: Diagnosis


Enter the appropriate ICD-10-CM diagnosis code; e.g., cUTI including pyelonephritis.

Final code depends on medical record documentation.

Note: Other diagnosis codes may apply.

### Box 21: ICD Indicator

Identify the type of ICD diagnosis code used; e.g., enter "0" for ICD-10-CM



## HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

<input type="checkbox"/> PICA <span style="float: right;"><input type="checkbox"/> PICA</span>											
1. MEDICARE <input type="checkbox"/> MEDICAID <input type="checkbox"/> TRICARE <input type="checkbox"/> CHAMPVA <input type="checkbox"/> GROUP HEALTH PLAN <input type="checkbox"/> FECA BILLING <input type="checkbox"/> OTHER <input type="checkbox"/> <small>(Medicare#) (Medicaid#) (TRICARE#) (Member ID#) (ID#) (ID#) (ID#)</small>										1a. INSURED'S I.D. NUMBER (For Program in Item 1)	
2. PATIENT'S NAME (Last Name, First Name, Middle Initial)						3. PATIENT'S BIRTH DATE MM DD YY		SEX M <input type="checkbox"/> F <input type="checkbox"/>		4. INSURED'S NAME (Last Name, First Name, Middle Initial)	
5. PATIENT'S ADDRESS (No., Street) CITY STATE ZIP CODE TELEPHONE (Include Area Code)						6. PATIENT RELATIONSHIP TO INSURED Self <input type="checkbox"/> Spouse <input type="checkbox"/> Child <input type="checkbox"/> Other <input type="checkbox"/>		7. INSURED'S ADDRESS (No., Street) CITY STATE ZIP CODE TELEPHONE (Include Area Code)			
9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)						10. IS PATIENT'S CONDITION RELATED TO: a. OTHER INSURED'S POLICY OR GROUP NUMBER b. RESERVED FOR NUCC USE c. RESERVED FOR NUCC USE		11. INSURED'S POLICY GROUP OR FECA NUMBER a. INSURED'S DATE OF BIRTH MM DD YY SEX M <input type="checkbox"/> F <input type="checkbox"/> b. OTHER CLAIM ID (Designated by NUCC) c. INSURANCE PLAN NAME OR PROGRAM NAME			
12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below. SIGNED _____ DATE _____						10d. CLAIM CODES (Designated by NUCC)		13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below. SIGNED _____ DATE _____			
14. DATE OF CURRENT ILLNESS, INJURY, OR PREGNANCY (LMP) MM DD YY QUAL _____						15. OTHER DATE MM DD YY QUAL _____		16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION FROM MM DD YY TO MM DD YY			
17. NAME OF REFERRING PROVIDER OR OTHER SOURCE 17a. _____ 17b. NPI _____						18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES FROM MM DD YY TO MM DD YY		20. OUTSIDE LAB? \$ CHARGES <input type="checkbox"/> YES <input type="checkbox"/> NO			
19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC) Meropenem and vaborbactam... MM/DD/YY						21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind. 0		22. RESUBMISSION CODE ORIGINAL REF. NO.			
24. A. DATE(S) OF SERVICE From MM DD YY To MM DD YY B. PLACE OF SERVICE C. EMG D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS MODIFIER E. DIAGNOSIS POINTER F. \$ CHARGES G. DRUG OR UNITS H. REPORT Family Per I. ID. QUAL. J. RENDERING PROVIDER ID. #											
1 XX XX XX XX XX XX J2186 xxx xx 100 NPI											
2 XX XX XX XX XX XX 96365 xxx xx 1 NPI											
3 XX XX XX XX XX XX 96366 xxx xx xx NPI											
4											
5											
6											
25. FEDERAL TAX I.D. NUMBER SSN EIN						26. PATIENT'S ACCOUNT NO.		27. ACCEPT ASSIGNMENT? <input type="checkbox"/> YES <input type="checkbox"/> NO		28. TOTAL CHARGE \$	
29. AMOUNT PAID \$						30. Rcvd for NUCC Use					
31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)						32. SERVICE FACILITY LOCATION INFORMATION		33. BILLING PROVIDER INFO & PH # ( )			
SIGNED _____ DATE _____						a. NPI b. _____		a. NPI b. _____			

NUCC Instruction Manual available at: [www.nucc.org](http://www.nucc.org) PLEASE PRINT OR TYPE APPROVED OMB-0938-1197 FORM 1500 (02-12)

### Box 24: Procedures, services, or suppliers

Enter the appropriate CPT/HCPCS codes and modifiers, e.g.:

- Drug J2186 for VABOMERE®
- 96365 First hour IV infusion
- 96366 Each additional hour IV infusion

### Box 24 G: Units

Enter the appropriate number of units of service. VABOMERE® is typically billed in the outpatient setting on a "per unit basis."  
Example: A vial of VABOMERE® is 2g powder = 100 billing units.

A typical full course of VABOMERE® per day is equal to 600 units of J2186 (6 vials/day).

Note: Some payers may provide alternate guidance.

For additional information, including Indication and Important Safety Information, please see back cover and the accompanying Full Prescribing Information.

**VABOMERE®**  
meropenem and vaborbactam  
for injection (4g)



# Indication and Important Safety Information

## 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.

## 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.

### 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.
- 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.
- *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.
- 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.
- 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.
- 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.

### 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 accompanying Full Prescribing Information for complete details.**

**References:** **1.** *New CPT Codes for Transitional Care Management Services*. pp. 1-2. [www.optum360coding.com/CodingCentralArticles/?id=976](http://www.optum360coding.com/CodingCentralArticles/?id=976). Accessed August 23, 2017. **2.** *Medicare Claims Processing Manual*. Chapter 3, section 20. Centers for Medicare & Medicaid Services. CMS publication 100-04. [www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html](http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html). Accessed October 4, 2017. **3.** *Medicare A Primer*. Congressional Research Service. Published July 18, 2012. <https://fas.org/sgp/crs/misc/RL33202.pdf>. Accessed October 20, 2017. **4.** *Fiscal Year (FY) 2018 Medicare Hospital Inpatient Prospective Payment (IPPS) and Long Term Acute Care Hospital (LTCH) Prospective Payment Final Rule*. Centers for Medicare & Medicaid Services. CMS publication 1677-F. Published August 2, 2017. Accessed October 4, 2017.



## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VABOMERE safely and effectively. See full prescribing information for VABOMERE.

VABOMERE® (meropenem and vaborbactam) for injection, for intravenous use

Initial U.S. Approval: 2017

### INDICATIONS AND USAGE

VABOMERE (meropenem and vaborbactam) is a combination of meropenem, a penem antibacterial, and vaborbactam, a beta-lactamase inhibitor, indicated for the treatment of patients 18 years and older with complicated urinary tract infections (cUTI) including pyelonephritis caused by designated susceptible bacteria. (1.1)

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. (1.2)

### DOSAGE AND ADMINISTRATION

- Administer VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) every 8 hours by intravenous infusion over 3 hours for up to 14 days, in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR)  $\geq 50$  mL/min/1.73m<sup>2</sup>. (2.1)
- Dosage adjustment is recommended in patients with renal impairment who have an eGFR less than 50 mL/min/1.73m<sup>2</sup>. (2.2)

eGFR <sup>a</sup> (mL/min/ 1.73m <sup>2</sup> )	Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) <sup>b, c, d</sup>	Dosing Interval
30 to 49	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 8 hours
15 to 29	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 12 hours
Less than 15	VABOMERE 1 gram (meropenem 0.5 grams and vaborbactam 0.5 grams)	Every 12 hours

<sup>a</sup> As calculated using the Modification of Diet in Renal Disease (MDRD) formula; <sup>b</sup> All doses of VABOMERE are administered intravenously over 3 hours; <sup>c</sup> Doses adjusted for renal impairment should be administered after a hemodialysis session; <sup>d</sup> The total duration of treatment is for up to 14 days.

- See Full Prescribing Information for instructions for constituting supplied dry powder and subsequent required dilution. (2.3)
- See Full Prescribing Information for drug compatibilities. (2.4)

### DOSAGE FORMS AND STRENGTHS

VABOMERE 2 grams (meropenem and vaborbactam) for injection, is supplied as a sterile powder for constitution in single-dose vials containing meropenem 1 gram (equivalent to 1.14 grams of meropenem trihydrate) and vaborbactam 1 gram. (3)

### CONTRAINDICATIONS

Known hypersensitivity to the components of VABOMERE (meropenem and vaborbactam) or anaphylactic reactions to beta-lactams. (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions were reported with the use of VABOMERE. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs. Discontinue infusion if signs of acute hypersensitivity occur. (5.1)
- Seizures and other adverse Central Nervous System experiences have been reported during treatment with meropenem, a component of VABOMERE. (5.2)
- Clostridioides difficile*-associated diarrhea has been reported with nearly all systemic antibacterial agents, including VABOMERE. Evaluate patients if diarrhea occurs. (5.3)
- Co-administration of meropenem with valproic acid or divalproex sodium reduces the serum concentration of valproic acid potentially increasing the risk of breakthrough seizures. (5.4, 7.1)

### ADVERSE REACTIONS

The most frequently reported adverse reactions occurring in  $\geq 3\%$  of patients treated with VABOMERE were headache, phlebitis/infusion site reactions, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Melinta Therapeutics at 1-844-633-6568 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2021

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1. Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

VABOMERE® 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.

#### 1.2. Usage

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. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

The recommended dosage of VABOMERE is 4 grams (meropenem 2 grams and vaborbactam 2 grams) administered every 8 hours by intravenous (IV) infusion over 3 hours in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) greater than or equal to 50 mL/min/1.73m<sup>2</sup>. The duration of treatment is for up to 14 days.

#### 2.2 Dosage Adjustments in Patients with Renal Impairment

Dosage adjustment is recommended in patients with renal impairment who have an eGFR less than 50 mL/min/1.73m<sup>2</sup>. The recommended dosage of VABOMERE in patients with varying degrees of renal function is presented in [Table 1](#). For patients with changing renal function, monitor serum creatinine concentrations and eGFR at least daily and adjust the dosage of VABOMERE accordingly [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Meropenem and vaborbactam are removed by hemodialysis [*see Clinical Pharmacology (12.3)*]. For patients maintained on hemodialysis, administer VABOMERE after a hemodialysis session.

**Table 1: Dosage of VABOMERE in Patients with Renal Impairment**

eGFR <sup>a</sup> (mL/min/ 1.73m <sup>2</sup> )	Recommended Dosage Regimen for VABOMERE (meropenem and vaborbactam) <sup>b, c, d</sup>	Dosing Interval
30 to 49	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 8 hours
15 to 29	VABOMERE 2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 12 hours
Less than 15	VABOMERE 1 gram (meropenem 0.5 grams and vaborbactam 0.5 grams)	Every 12 hours

<sup>a</sup> As calculated using the Modification of Diet in Renal Disease (MDRD) formula as follows: eGFR (mL/min/1.73m<sup>2</sup>) = 175 x (serum creatinine)<sup>-1.154</sup> x (age)<sup>0.203</sup> x (0.742 if female) x (1.212 if African American)

<sup>b</sup> All doses of VABOMERE are administered intravenously over 3 hours.

<sup>c</sup> Doses adjusted for renal impairment should be administered after a hemodialysis session.

<sup>d</sup> The total duration of treatment is for up to 14 days.

### **2.3 Preparation and Administration of VABOMERE for Intravenous Infusion**

#### Preparation

VABOMERE is supplied as a dry powder in a single-dose vial that must be constituted and further diluted prior to intravenous infusion as outlined below. VABOMERE does not contain preservatives. Aseptic technique must be used for constitution and dilution.

1. To prepare the required dose for intravenous infusion, constitute the appropriate number of vials, as determined from [Table 2](#) below. Withdraw 20 mL of 0.9% Sodium Chloride Injection, USP, from an infusion bag and constitute each vial of VABOMERE.
2. Mix gently to dissolve. The constituted VABOMERE solution will have an approximate meropenem concentration of 0.05 gram/mL and an approximate vaborbactam concentration of 0.05 gram/mL. The final volume is approximately 21.3 mL. The constituted solution is not for direct injection.
3. The constituted solution must be diluted further, immediately, in a 0.9% Sodium Chloride Injection, USP infusion bag before intravenous infusion. The intravenous infusion of the diluted solution **must be completed** within 4 hours if stored at room temperature or 22 hours if stored refrigerated at 2°C to 8°C (36°F to 46°F).
4. To dilute the constituted solution, withdraw the full or partial constituted vial contents from each vial and add it back into the infusion bag in accordance with [Table 2](#) below.

**Table 2: Preparation of VABOMERE Doses**

<b>VABOMERE Dose (meropenem and vaborbactam)</b>	<b>Number of Vials to Constitute for Further Dilution</b>	<b>Volume to Withdraw from Each Constituted Vial for Further Dilution</b>	<b>Volume of Infusion Bag</b>	<b>Final Infusion Concentration of VABOMERE</b>
4 grams (2 grams-2 grams)	2 vials	Entire contents (approximately 21 mL)	250 mL	16 mg/mL
			500 mL	8 mg/mL
			1,000 mL	4 mg/mL
2 grams (1 gram-1 gram)	1 vial	Entire contents (approximately 21 mL)	125 mL	16 mg/mL
			250 mL	8 mg/mL
			500 mL	4 mg/mL
1 gram (0.5 gram-0.5 gram)	1 vial	10.5 mL (discard unused portion)	70 mL	14.3 mg/mL
			125 mL	8 mg/mL
			250 mL	4 mg/mL

5. Visually inspect the diluted VABOMERE solution for particulate matter and discoloration prior to administration (the color of the VABOMERE infusion solution for administration ranges from colorless to light yellow). Discard unused portion after use.

## **2.4 Drug Compatibility**

VABOMERE solution for administration by 3-hour infusion is only compatible with 0.9% Sodium Chloride Injection, USP.

Compatibility of VABOMERE solution for administration with other drugs has not been established.

### **3            DOSAGE FORMS AND STRENGTHS**

VABOMERE 2 grams (meropenem and vaborbactam) for injection, is supplied as a white to light yellow sterile powder for constitution in single-dose, clear glass vials containing meropenem 1 gram (equivalent to 1.14 grams meropenem trihydrate) and vaborbactam 1 gram.

### **4            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 [*see Warnings and Precautions (5.1)*].

### **5            WARNINGS AND PRECAUTIONS**

#### **5.1        Hypersensitivity Reactions**

Hypersensitivity reactions were reported in patients treated with VABOMERE in the clinical trials [*see Adverse Reactions (6.1)*]. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving therapy with beta-lactam antibacterial drugs. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. 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. Before initiating therapy with VABOMERE, it is important to inquire about previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactam antibacterial drugs, and other allergens. If an allergic reaction to VABOMERE occurs, discontinue the drug immediately.

#### **5.2        Seizure Potential**

Seizures and other adverse Central Nervous System (CNS) experiences have been reported during treatment with meropenem, which is a component of VABOMERE. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function [*see Adverse Reactions (6.1) and Drug Interactions (7.1)*].

Close adherence to the recommended dosage regimens is urged, especially in patients with known factors that predispose to convulsive activity. Continue anti-convulsant therapy in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, evaluate neurologically, place on anti-convulsant therapy if not already instituted, and reexamine the dosage of VABOMERE to determine whether it should be decreased or discontinued.

#### **5.3        *Clostridioides difficile*-associated Diarrhea**

*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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. 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. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### **5.4 Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid**

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. Increasing the dose of valproic acid or divalproex sodium may not be sufficient to overcome this interaction. Consider administration of antibacterial drugs other than carbapenems to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium. If administration of VABOMERE is necessary, consider supplemental anticonvulsant therapy [see *Drug Interactions (7.1)*].

#### **5.5 Thrombocytopenia**

In patients with renal impairment, thrombocytopenia has been observed in patients treated with meropenem, but no clinical bleeding has been reported [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, *Use in Specific Populations (8.5)* and *(8.6)*, and *Clinical Pharmacology (12.3)*].

#### **5.6 Potential for Neuromotor Impairment**

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. Until it is reasonably well established that VABOMERE is well tolerated, advise patients not to operate machinery or motorized vehicles [see *Adverse Reactions (6.1)*].

#### **5.7 Development of Drug-Resistant Bacteria**

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 [see *Indications and Usage (1.2)*].



## 5.8 Overgrowth of Nonsusceptible Organisms

As with other antibacterial drugs, prolonged use of VABOMERE may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the Warnings and Precautions section:

- Hypersensitivity Reactions [*see Warnings and Precautions (5.1)*]
- Seizure Potential [*see Warnings and Precautions (5.2)*]
- *Clostridioides difficile*-associated Diarrhea [*see Warnings and Precautions (5.3)*]
- Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid [*see Warnings and Precautions (5.4)*]
- Thrombocytopenia [*see Warnings and Precautions (5.5)*]
- Potential for Neuromotor Impairment [*see Warnings and Precautions (5.6)*]
- Development of Drug-Resistant Bacteria [*see Warnings and Precautions (5.7)*]
- Overgrowth of Nonsusceptible Organisms [*see Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VABOMERE was evaluated in a Phase 3 comparator-controlled clinical trial in cUTI, including pyelonephritis, which included 272 patients treated with VABOMERE and 273 patients treated with the comparator piperacillin/tazobactam 4.5 grams (piperacillin 4 g/tazobactam 0.5 g) every 8 hours. After a minimum of 15 doses of IV therapy, patients could be switched to oral levofloxacin (500 mg daily every 24 hours) to complete the treatment course. Mean duration of IV therapy was 8 days in both treatment groups. Mean duration of IV and oral therapy was 10 days; patients with baseline bacteremia could receive up to 14 days of treatment.

The mean age of patients treated with VABOMERE was 53 years (range 18 to 92 years), and 32% of patients were 65 years of age or older. Patients were predominantly female (66.5%) and White (93.4%). Most patients were enrolled in Europe (89.7%).

#### Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Treatment was discontinued due to adverse reactions in 2.9% (8/272) of patients receiving VABOMERE and in 5.1% (14/273) of patients receiving piperacillin/tazobactam. Most common adverse reactions resulting in discontinuation of VABOMERE included hypersensitivity, 1.1% (3/272) and infusion-related reactions, 0.7% (2/272). Death occurred in 2 (0.7%) patients who received VABOMERE and in 2 (0.7%) patients who received piperacillin/tazobactam.

### Common Adverse Reactions

The most frequently reported adverse reactions (3% or greater) in patients receiving VABOMERE in the Phase 3 cUTI trial were headache, phlebitis/infusion site reactions, and diarrhea. Table 3 provides adverse reactions occurring in 1% or greater of patients receiving VABOMERE in the Phase 3 cUTI trial.

**Table 3: Adverse Reactions Occurring in 1% or Greater of Patients Receiving VABOMERE in the Phase 3 Clinical Trial in cUTI**

<b>Adverse Reactions</b>	<b>VABOMERE (N=272) %</b>	<b>Piperacillin/Tazobactam<sup>a</sup> (N=273) %</b>
Headache	8.8	4.4
Phlebitis/Infusion site reactions <sup>b</sup>	4.4	0.7
Diarrhea	3.3	4.4
Hypersensitivity <sup>c</sup>	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

<sup>a</sup> Piperacillin/tazobactam 4.5 grams (piperacillin 4 g/tazobactam 0.5 g) IV infused over 30 minutes every 8 hours.

<sup>b</sup> Infusion site reactions include infusion/injection site phlebitis, infusion site thrombosis, and infusion site erythema.

<sup>c</sup> Hypersensitivity includes hypersensitivity, drug hypersensitivity, anaphylactic reaction, rash urticaria, and bronchospasm.

### Adverse Reactions Occurring in Less Than 1% of Patients Receiving VABOMERE in the Phase 3 cUTI trial:

*Blood and lymphatic system disorders:* leukopenia

*General disorders and administration site conditions:* chest discomfort

*Infections and infestations:* pharyngitis, vulvovaginal candidiasis, oral candidiasis

*Investigations:* creatinine phosphokinase increase

*Metabolism and nutrition disorders:* decreased appetite, hyperkalemia, hyperglycemia, hypoglycemia

*Nervous system disorders:* dizziness, tremor, paresthesia, lethargy

*Psychiatric disorders:* hallucination, insomnia

*Renal and urinary disorders:* azotemia, renal impairment

*Vascular disorders:* deep vein thrombosis, hypotension, vascular pain

## Other Adverse Reactions Associated with Meropenem

Additionally, adverse reactions reported with meropenem alone that were not reported in VABOMERE-treated patients in the Phase 3 clinical trial are listed below:

*Blood and lymphatic system disorders:* thrombocytosis, neutropenia, eosinophilia, thrombocytopenia, agranulocytosis, hemolytic anemia

*Gastrointestinal disorders:* abdominal pain

*Hepatobiliary disorders:* jaundice

*Nervous system disorders:* convulsions

*Investigations:* blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood bilirubin increased, blood creatinine increased, blood urea increased, blood thromboplastin decreased, prothrombin time decreased, Direct and Indirect Coombs test positive

*Skin and subcutaneous tissue disorders:* pruritus, toxic epidermal necrolysis, Stevens Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, erythema multiforme

*Immune system disorders:* angioedema

*General disorders and administration site conditions:* pain

## **7 DRUG INTERACTIONS**

### **7.1 Valproic Acid**

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. Although the mechanism of this interaction is unknown, data from in vitro and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. If administration of VABOMERE is necessary, then supplemental anti-convulsant therapy should be considered [*see Warnings and Precautions (5.4)*].

### **7.2 Probenecid**

Probenecid competes with meropenem for active tubular secretion, resulting in increased plasma concentrations of meropenem. Co-administration of probenecid with VABOMERE is not recommended.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Fetal malformations were observed in vaborbactam-treated rabbits, therefore advise pregnant women of the potential risks to the fetus. There are insufficient human data to establish whether there is a drug-associated risk of major birth defects or miscarriages with VABOMERE, meropenem, or vaborbactam in pregnant women.

Malformations (supernumerary lung lobes, interventricular septal defect) were observed in offspring from pregnant rabbits administered intravenous vaborbactam during the period of organogenesis at doses approximately equivalent to or above the maximum recommended human dose (MRHD) based on plasma AUC comparison. The clinical relevance of the malformations is uncertain. No similar malformations or fetal toxicity were observed in offspring from pregnant rats administered intravenous vaborbactam during organogenesis or from late pregnancy and through lactation at a dose equivalent to approximately 1.6 times the MRHD based on body surface area comparison [*see Data*].

No fetal toxicity or malformations were observed in pregnant rats and cynomolgus monkeys administered intravenous meropenem during organogenesis at doses up to 1.6 and 1.2 times the MRHD based on body surface area comparison, respectively. In rats administered intravenous meropenem in late pregnancy and during the lactation period, there were no adverse effects on offspring at doses equivalent to approximately 1.6 times the MRHD based on body surface area comparison [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### *Animal Data*

##### Meropenem

Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day and in cynomolgus monkeys at doses of up to 360 mg/kg/day (on the basis of body surface area comparisons, approximately 1.6 times and 1.2 times higher, respectively, than the MRHD of 2 grams every 8 hours). These studies revealed no evidence of harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (equivalent to approximately 0.4 times the MRHD of 2 grams every 8 hours based on body surface area comparison) and above in rats. In a published study<sup>1</sup>, meropenem administered to pregnant rats from Gestation Day 6 to Gestation Day 17, was associated with mild maternal weight loss at all doses, but did not produce malformations or fetal toxicity. The no-observed-adverse-effect-level (NOAEL) for fetal toxicity in this study was considered to be the high dose of 750 mg/kg/day (equivalent to approximately 1.2 times the MRHD based on body surface area comparison).

In a peri-postnatal study in rats described in the published literature<sup>1</sup>, intravenous meropenem was administered to dams from Gestation Day 17 until Postpartum Day 21. There were no adverse effects in the dams and no adverse effects in the first generation offspring (including developmental, behavioral, and functional assessments and reproductive parameters) except that female offspring exhibited lowered body weights which continued during gestation and nursing of the second generation offspring. Second generation offspring showed no meropenem-related effects. The NOAEL value was considered to be 1000 mg/kg/day (approximately 1.6 times the MRHD based on body surface area comparisons).

### Vaborbactam

In a rat embryo-fetal toxicology study, intravenous administration of vaborbactam during Gestation Days 6-17 showed no evidence of maternal or embryofetal toxicity at doses up to 1000 mg/kg, which is equivalent to approximately 1.6 times the MRHD based on body surface area comparisons. In the rabbit, intravenous administration of vaborbactam during Gestation Days 7–19 at doses up to 1000 mg/kg/day (approximately 5 times the MRHD based on AUC exposure comparison) was not associated with maternal toxicity or fetal weight loss. A low incidence of malformations occurred in the 300 mg/kg/day mid-dose group (two fetuses from different litters with interventricular septal defects, one fetus with a fused right lung lobe and one fetus with a supernumerary lung lobe), and in the 1000 mg/kg/day high-dose group (two fetuses from different litters with supernumerary lobes). The NOAEL was considered to be 100 mg/kg/day which is equivalent to 0.3 times the MRHD based on plasma AUC exposure comparison and 6-times the MRHD based on maximum plasma concentration ( $C_{max}$ ) comparison. The clinical relevance of the malformations is uncertain. Vaborbactam  $C_{max}$  values may have influenced malformations in the rabbit study, and the recommended 3-hour infusion time for clinical administration of vaborbactam is associated with lower plasma  $C_{max}$  values than the 30-minute infusions in rabbits.

In a peri-postnatal study in rats, vaborbactam administered intravenously to pregnant dams from Gestation Day 6 to Lactation Day 20 caused no adverse effects on the dams, or in first and second generation offspring. The NOAEL was considered to be 1000 mg/kg/day (equivalent to approximately 1.6 times the MRHD based on body surface area comparison).

## **8.2 Lactation**

Meropenem has been reported to be excreted in human milk. It is unknown whether vaborbactam is excreted in human milk. No information is available on the effects of meropenem and vaborbactam on the breast-fed child or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABOMERE and any potential adverse effects on the breast-fed child from VABOMERE or from the underlying maternal condition.

## **8.4 Pediatric Use**

The safety and effectiveness of VABOMERE in pediatric patients (younger than 18 years of age) has not been established. Studies of VABOMERE have not been conducted in patients younger than 18 years of age.

## 8.5 Geriatric Use

Of the 272 patients treated with VABOMERE in the Phase 3 cUTI trial, 48 (18%) patients were 65 years of age and older, while 39 (14%) patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Meropenem, a component of VABOMERE, is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Population pharmacokinetic (PK) analysis found no clinically relevant change in pharmacokinetic parameters in elderly patients. No dosage adjustment based on age is required. Dosage adjustment for elderly patients should be based on renal function [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

## 8.6 Renal Impairment

Pharmacokinetic studies conducted with meropenem and vaborbactam in subjects with renal impairment have shown that the plasma exposures of both meropenem and vaborbactam increased with decreasing renal function [see *Clinical Pharmacology (12.3)*]. Dosage adjustment for VABOMERE is recommended in patients with renal impairment (eGFR less than 50 mL/min/1.73m<sup>2</sup>) [see *Dosage and Administration (2.2)*].

For patients with changing renal function, monitor serum creatinine concentrations and eGFR at least daily and adjust the dosage of VABOMERE accordingly. Meropenem and vaborbactam are removed by hemodialysis. Following a single dose of VABOMERE, vaborbactam exposure was substantially greater when VABOMERE was administered after hemodialysis than before hemodialysis [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

In the event of overdose, discontinue VABOMERE and institute general supportive treatment.

Meropenem and vaborbactam can be removed by hemodialysis. In subjects with end-stage renal disease (ESRD) administered meropenem 1 gram and vaborbactam 1 gram, the mean total recovery in dialysate following a hemodialysis session was 38% and 53% of the administered dose of meropenem and vaborbactam, respectively.

No clinical information is available on the use of hemodialysis to treat VABOMERE overdose.

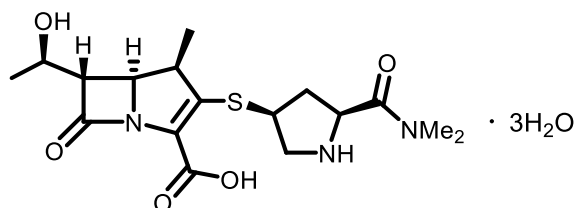


## 11 DESCRIPTION

VABOMERE (meropenem and vaborbactam) for injection is a combination product that contains meropenem, a synthetic penem antibacterial drug and vaborbactam, a cyclic boronic acid beta-lactamase inhibitor, for intravenous administration.

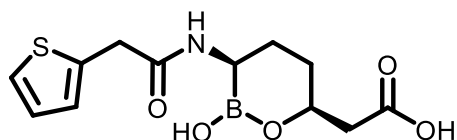
Meropenem, present as a trihydrate, is a white to light yellow crystalline powder, with a molecular weight of 437.52. The chemical name for meropenem trihydrate is (4*R*,5*S*,6*S*)-3-[[*(3S,5S)*-5-(dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, trihydrate. The empirical formula of meropenem trihydrate is C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>S · 3H<sub>2</sub>O and its chemical structure is:

**Figure 1: Structure of Meropenem Trihydrate**



Vaborbactam is a white to off-white powder, with a molecular weight of 297.14. The chemical name for vaborbactam is (3*R*,6*S*)-2-hydroxy-3-[[2-(2-thienyl)acetyl]amino]-1,2-oxaborinane-6-acetic acid. Its empirical formula is C<sub>12</sub>H<sub>16</sub>BN<sub>2</sub>O<sub>5</sub>S and its chemical structure is:

**Figure 2: Structure of Vaborbactam**



VABOMERE is supplied as a white to light yellow sterile powder for constitution that contains meropenem trihydrate, vaborbactam, and sodium carbonate. Each 50 mL glass vial contains 1 gram of meropenem (equivalent to 1.14 grams of meropenem trihydrate), 1 gram of vaborbactam, and 0.575 gram of sodium carbonate. The total sodium content of the mixture is approximately 0.25 grams (10.9 mEq)/vial.

Each vial is constituted and further diluted with 0.9% Sodium Chloride Injection, USP. Both the constituted solution and the diluted solution for intravenous infusion should be a colorless to light yellow solution [see *Dosage and Administration* (2.3)].

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

VABOMERE is an antibacterial drug [see *Microbiology* (12.4)].

## 12.2 Pharmacodynamics

Similar to other beta-lactam antibacterial drugs, the percentage of time of a dosing interval that unbound plasma concentration of meropenem exceeds the meropenem-vaborbactam minimum inhibitory concentration (MIC) against the infecting organism has been shown to best correlate with efficacy in animal and in vitro models of infection. The ratio of the 24-hour unbound plasma vaborbactam AUC to meropenem-vaborbactam MIC is the index that best predicts efficacy of vaborbactam in combination with meropenem in animal and in vitro models of infection.

### Cardiac Electrophysiology

At a dose of 1 and 3 times the maximum approved recommended dose, Vabomere (meropenem and vaborbactam) does not prolong the QT interval to any clinically relevant extent.

## 12.3 Pharmacokinetics

### Pharmacokinetic (PK) Parameters

The mean PK parameters of meropenem and vaborbactam in healthy adults with normal renal function after single and multiple 3-hour infusions of VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) administered every 8 hours are summarized in [Table 4](#).

The PK parameters of meropenem and vaborbactam were similar for single and multiple dose administration of VABOMERE.

**Table 4: Pharmacokinetic Parameters (Mean [SD]) of Meropenem and Vaborbactam Following Administration of VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) by 3-hour Infusion in Healthy Adult Subjects**

Parameter	Meropenem		Vaborbactam	
	Single VABOMERE 4 gram <sup>a</sup> Dose (N=8)	Multiple VABOMERE 4 gram <sup>a</sup> Doses Administered Every 8 hours for 7 Days (N=8)	Single VABOMERE 4 gram <sup>a</sup> Dose (N=8)	Multiple VABOMERE 4 gram <sup>a</sup> Doses Administered Every 8 hours for 7 Days (N=8)
C <sub>max</sub> (mg/L)	46.0 (5.7)	43.4 (8.8)	50.7 (8.4)	55.6 (11.0)
CL (L/h)	14.6 (2.7)	15.1 (2.8)	12.3 (2.2)	10.9 (1.8)
AUC (mg•h/L) <sup>b</sup>	142.0 (28.0)	138.0 (27.7)	168.0 (32.2)	196.0 (36.7)
T <sub>1/2</sub> (h)	1.50 (1.0)	1.22 (0.3)	1.99 (0.8)	1.68 (0.4)

C<sub>max</sub> = maximum observed concentration; CL = plasma clearance; AUC = area under the concentration time curve; T<sub>1/2</sub> = half-life.

<sup>a</sup> Meropenem 2 grams and vaborbactam 2 grams administered as a 3-hour infusion

<sup>b</sup> AUC<sub>0-inf</sub> reported for single-dose administration; AUC<sub>0,8</sub> reported for multiple-dose administration; AUC<sub>0-24</sub> is 414 mg•h/L for meropenem and 588 mg•h/L for vaborbactam.

The maximum plasma concentration (C<sub>max</sub>) and area under the plasma drug concentration time curve (AUC) of meropenem and vaborbactam proportionally increased with dose across the dose range studied (1 gram to 2 grams for meropenem and 0.25 grams to 2 grams for vaborbactam)

when administered as a single 3-hour intravenous infusion. There is no accumulation of meropenem or vaborbactam following multiple intravenous infusions administered every 8 hours for 7 days in subjects with normal renal function.

The mean population PK parameters of meropenem and vaborbactam in 295 patients (including 35 patients with reduced renal function) after 3-hour infusions of VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) administered every 8 hours (or dose adjusted based on renal function) are summarized in [Table 5](#).

**Table 5: Population Pharmacokinetic Parameters (Mean [SD]) of Meropenem and Vaborbactam Following Administration of VABOMERE 4 grams (meropenem 2 grams and vaborbactam 2 grams) by 3-hour Infusion in Patients<sup>a</sup>**

Parameter	Meropenem	Vaborbactam
C <sub>max</sub> (mg/L)	57.3 (23.0)	71.3 (28.6)
AUC <sub>0-24, Day 1</sub> (mg•h/L)	637 (295)	821 (369)
AUC <sub>0-24, steady-state</sub> (mg•h/L)	650 (364)	835 (508)
CL (L/h)	10.5 (6.4)	7.95 (4.3)
T <sub>1/2</sub> (h)	2.30 (2.5)	2.25 (2.1)

<sup>a</sup> Meropenem 2 grams and vaborbactam 2 grams administered as a 3-hour infusion.

### Distribution

The plasma protein binding of meropenem is approximately 2%. The plasma protein binding of vaborbactam is approximately 33%.

The steady-state volumes of distribution of meropenem and vaborbactam in patients were 20.2 L and 18.6 L, respectively.

### Elimination

The clearance of meropenem in healthy subjects following multiple doses is 15.1 L/h and for vaborbactam is 10.9 L/h. The t<sub>1/2</sub> is 1.22 hours and 1.68 hours for meropenem and vaborbactam, respectively.

### *Metabolism*

A minor pathway of meropenem elimination is hydrolysis of the beta-lactam ring (meropenem open lactam), which accounts for 22% of a dose eliminated via the urine.

Vaborbactam does not undergo metabolism.

### *Excretion*

Both meropenem and vaborbactam are primarily excreted via the kidneys.

Approximately 40–60% of a meropenem dose is excreted unchanged within 24-48 hours with a further 22% recovered as the microbiologically inactive hydrolysis product. The mean renal clearance for meropenem was 7.8 L/h. The mean non-renal clearance for meropenem was 7.3 L/h which comprises both fecal elimination (~2% of dose) and degradation due to hydrolysis.

For vaborbactam, 75 to 95% of the dose was excreted unchanged in the urine over a 24 to 48 hour period. The mean renal clearance for vaborbactam was 8.9 L/h. The mean non-renal clearance for vaborbactam was 2.0 L/h indicating nearly complete elimination of vaborbactam by the renal route.

### Specific Populations

#### *Patients with Renal Impairment*

Following a single dose of VABOMERE, pharmacokinetic studies with meropenem and vaborbactam in subjects with renal impairment have shown that meropenem AUC<sub>0-inf</sub> ratios to subjects with normal renal function are 1.28, 2.07, and 4.63 for subjects with mild (eGFR of 60 to 89 mL/min/1.73m<sup>2</sup>), moderate (eGFR of 30 to 59 mL/min/1.73m<sup>2</sup>), and severe (eGFR <30 mL/min/1.73m<sup>2</sup>) renal impairment, respectively; vaborbactam AUC<sub>0-inf</sub> ratios to subjects with normal renal function are 1.18, 2.31, and 7.8 for subjects with mild, moderate, and severe renal impairment, respectively [see *Dosing and Administration (2.2)*]. Hemodialysis removed 38% of the meropenem dose and 53% of the vaborbactam dose. Vaborbactam exposure was high in subjects with ESRD (eGFR <15 ml/min/1.73 m<sup>2</sup>). Vaborbactam exposure was higher when VABOMERE was administered after hemodialysis (AUC<sub>0-inf</sub> ratio to subjects with normal renal function of 37.5) than when VABOMERE was administered before hemodialysis (AUC<sub>0-inf</sub> ratio to subjects with normal renal function of 10.2) [see *Use in Specific Populations (8.6)* and *Dosing and Administration (2.2)*].

#### *Patients with Hepatic Impairment*

A pharmacokinetic study conducted with an intravenous formulation of meropenem in patients with hepatic impairment has shown no effects of liver disease on the pharmacokinetics of meropenem.

Vaborbactam does not undergo hepatic metabolism. Therefore, the systemic clearance of meropenem and vaborbactam is not expected to be affected by hepatic impairment.

#### *Geriatric Patients*

In elderly patients with renal impairment, plasma clearances of meropenem and vaborbactam were reduced, correlating with age-associated reduction in renal function [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.5)*].

#### *Male and Female Patients*

Meropenem and vaborbactam C<sub>max</sub> and AUC were similar between males and females using a population pharmacokinetic analysis.

#### *Racial or Ethnic Groups*

No significant difference in mean meropenem or vaborbactam clearance was observed across race groups using a population pharmacokinetic analysis.

### Drug Interactions

No drug-drug interaction was observed between meropenem and vaborbactam in clinical studies with healthy subjects.

Based upon the in vitro and in vivo data available to date, there is a low potential for clinically significant drug interactions with vaborbactam.

Vaborbactam at clinically relevant concentrations does not inhibit the cytochrome P450 isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro human liver microsomes. Vaborbactam showed no potential for in vitro induction of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. Studies evaluating the potential for meropenem to interact with CYP450 enzymes or active transport systems have not been conducted. However, carbapenems as a class have not shown the potential for inhibition or induction CYP450 enzymes and clinical experience suggests that such effects are unlikely.

Vaborbactam does not inhibit the following hepatic and renal transporters in vitro at clinically relevant concentrations: P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. Vaborbactam was not a substrate of OAT1, OAT3, OCT2, P-gp, and BCRP.

Meropenem is a substrate of OAT1 and OAT3 and as such, probenecid competes with meropenem for active tubular secretion and thus inhibits the renal excretion of meropenem. Following administration of probenecid with meropenem, the mean systemic exposure increased 56% and the mean elimination half-life increased 38% [see *Drug Interactions (7.2)*].

Concomitant administration of meropenem and valproic acid has been associated with reductions in valproic acid concentrations with subsequent loss in seizure control [see *Drug Interactions (7.1)*].

## 12.4 Microbiology

### Mechanism of Action

The meropenem component of VABOMERE is a penem antibacterial drug. The bactericidal action of meropenem results from the inhibition of cell wall synthesis. Meropenem penetrates the cell wall of most gram-positive and gram-negative bacteria to bind penicillin-binding protein (PBP) targets. Meropenem is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria, with the exception of carbapenem hydrolyzing beta-lactamases.

The vaborbactam component of VABOMERE is a non-suicidal beta-lactamase inhibitor that protects meropenem from degradation by certain serine beta-lactamases such as *Klebsiella pneumoniae* carbapenemase (KPC). Vaborbactam does not have any antibacterial activity. Vaborbactam does not decrease the activity of meropenem against meropenem-susceptible organisms.

### Resistance

Mechanisms of beta-lactam resistance may include the production of beta-lactamases, modification of PBPs by gene acquisition or target alteration, up-regulation of efflux pumps, and loss of outer membrane porin. VABOMERE may not have activity against gram-negative bacteria that have porin mutations combined with overexpression of efflux pumps.

Clinical isolates may produce multiple beta-lactamases, express varying levels of beta-lactamases, or have amino acid sequence variations, and other resistance mechanisms that have not been identified.

Culture and susceptibility information and local epidemiology should be considered in selecting or modifying antibacterial therapy.

VABOMERE demonstrated in vitro activity against Enterobacteriaceae in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBLs) of the following groups: KPC, SME, TEM, SHV, CTX-M, CMY, and ACT. VABOMERE is not active against bacteria that produce metallo-beta lactamases or oxacillinases with carbapenemase activity.

In the Phase 3 cUTI trial with VABOMERE, some isolates of *E. coli*, *K. pneumoniae*, *E. cloacae*, *C. freundii*, *P. mirabilis*, *P. stuartii* that produced beta-lactamases, were susceptible to VABOMERE (minimum inhibitory concentration  $\leq 4$  mcg /mL). These isolates produced one or more beta-lactamases of the following enzyme groups: OXA (non-carbapenemases), KPC, CTX-M, TEM, SHV, CMY, and ACT.

Some beta-lactamases were also produced by an isolate of *K. pneumoniae* that was not susceptible to VABOMERE (minimum inhibitory concentration  $\geq 32$  mcg/mL). This isolate produced beta-lactamases of the following enzyme groups: CTX-M, TEM, SHV, and OXA.

No cross-resistance with other classes of antimicrobials has been identified. Some isolates resistant to carbapenems (including meropenem) and to cephalosporins may be susceptible to VABOMERE.

#### Interaction with Other Antimicrobials

In vitro synergy studies have not demonstrated antagonism between VABOMERE and levofloxacin, tigecycline, polymyxin, amikacin, vancomycin, azithromycin, daptomycin, or linezolid.

#### Activity against Meropenem Non-susceptible Bacteria in Animal Infection Models

Vaborbactam restored activity of meropenem in animal models of infection (e.g., mouse thigh infection, urinary tract infection and pulmonary infection) caused by some meropenem non-susceptible KPC-producing Enterobacteriaceae.

#### Antimicrobial Activity

VABOMERE has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections [see *Indications and Usage (1.1)*].

Gram-negative bacteria:

- *Enterobacter cloacae* species complex
- *Escherichia coli*
- *Klebsiella pneumoniae*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro MIC less than or equal to the susceptible breakpoint for VABOMERE against isolates of a similar genus or organism group. However, the efficacy of VABOMERE in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.



Gram-negative bacteria:

- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus mirabilis*
- *Providencia* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

#### Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see:

<https://www.fda.gov/STIC>.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Long-term carcinogenicity studies have not been performed with VABOMERE, meropenem, or vaborbactam.

#### Mutagenesis

##### *Meropenem*

Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutation potential found in any of these tests.

##### *Vaborbactam*

Genetic toxicity studies were performed with vaborbactam using the bacterial reverse mutation test, chromosomal aberration test and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

## Impairment of Fertility

### *Meropenem*

Reproductive studies were performed with meropenem in male and female rats at doses up to 1000 mg/kg/day with no evidence of impaired fertility (approximately equivalent to 1.6 times the MRHD based on body surface area comparison).

In a reproductive study in cynomolgus monkeys at doses of meropenem up to 360 mg/kg/day (on the basis of body surface area comparison, approximately equivalent to 1.2 times the MRHD) no reproductive toxicity was seen.

### *Vaborbactam*

Vaborbactam had no adverse effect on fertility in male and female rats at doses up to 1000 mg/kg/day, which is equivalent to approximately 1.6 times the MRHD based on body surface area comparison.

## **14 CLINICAL STUDIES**

### **14.1 Complicated Urinary Tract Infections (cUTI), including Pyelonephritis**

A total of 545 adults with cUTI, including pyelonephritis were randomized into a double-blind, double dummy, multi-center trial comparing VABOMERE (meropenem 2 grams and vaborbactam 2 grams) to piperacillin/tazobactam (piperacillin 4 grams/tazobactam 0.5 grams) intravenously every 8 hours. Switch to an oral antibacterial drug, such as levofloxacin was allowed after a minimum of 15 doses of IV therapy.

The microbiologically modified intent to treat population (m-MITT) included all randomized patients who received any study drug and had at least 1 baseline uropathogen. Clinical and microbiological response at the end of IV treatment (EOIVT) required both a clinical outcome of cure or improvement and a microbiologic outcome of eradication (all baseline uropathogens at  $>10^5$  CFU/mL are to be reduced to  $<10^4$  CFU/mL). Clinical and microbiological response was also assessed at the Test of Cure (TOC) visit (approximately 7 days after completion of treatment) in the m-MITT population and required both a clinical outcome of cure and a microbiological outcome of eradication.

Patient demographic and baseline characteristics were balanced between treatment groups in the m-MITT population. Approximately 93% of patients were Caucasian and 66% were females in both treatment groups. The mean age was 54 years with 32% and 42% patients greater than 65 years of age in VABOMERE and piperacillin/tazobactam treatment groups, respectively. Mean body mass index was approximately 26.5 kg/m<sup>2</sup> in both treatment groups. Concomitant bacteremia was identified in 12 (6%) and 15 (8%) patients at baseline in VABOMERE and piperacillin/tazobactam treatment groups respectively. The proportion of patients with diabetes mellitus at baseline was 17% and 19% in VABOMERE and piperacillin/tazobactam treatment groups, respectively. The majority of patients (approximately 90%) were enrolled from Europe, and approximately 2% of patients were enrolled from North America. Overall, in both treatment

groups, 59% of patients had pyelonephritis and 40% had cUTI, with 21% and 19% of patients having a non-removable and removable source of infection, respectively.

Mean duration of IV treatment in both treatment groups was 8 days and mean total treatment duration (IV and oral) was 10 days; patients with baseline bacteremia could receive up to 14 days of therapy. Approximately 10% of patients in each treatment group in the m-MITT population had a levofloxacin-resistant pathogen at baseline and received levofloxacin as the oral switch therapy. This protocol violation may have impacted the assessment of the outcomes at the TOC visit. These patients were not excluded from the analysis presented in Table 6, as the decision to switch to oral levofloxacin was based on post-randomization factors.

VABOMERE demonstrated efficacy with regard to clinical and microbiological response at the EOIVT visit and TOC visits in the m-MITT population as shown in Table 6.

**Table 6: Clinical and Microbiological Response Rates in a Phase 3 Trial of cUTI Including Pyelonephritis (m-MITT Population)**

	<b>VABOMERE n/N (%)</b>	<b>Piperacillin/ Tazobactam n/N (%)</b>	<b>Difference (95% CI)</b>
<b>Clinical cure or improvement AND microbiological eradication at the End of IV Treatment Visit*</b>	183/186 (98.4)	165/175 (94.3)	4.1% (0.3%, 8.8%)
<b>Clinical cure AND microbiological eradication at the Test of Cure visit approximately 7 days after completion of treatment**</b>	124/162 (76.5)	112/153 (73.2)	3.3% (-6.2%, 13.0%)

CI = confidence interval; EOIVT = End of Intravenous Treatment; TOC = Test of Cure

\*End of IV Treatment visit includes patients with organisms resistant to piperacillin/tazobactam at baseline

\*\*Test of Cure visit excludes patients with organisms resistant to piperacillin/tazobactam at baseline

In the m-MITT population, the rate of clinical and microbiological response in VABOMERE-treated patients with concurrent bacteremia at baseline was 10/12 (83.3%).

In a subset of the *E. coli* and *K. pneumoniae* isolates, genotypic testing identified certain ESBL groups (e.g., TEM, CTX-M, SHV and OXA) in both treatment groups of the Phase 3 cUTI trial. The rates of clinical and microbiological response were similar in the ESBL-positive and ESBL-negative subset at EOIVT; at TOC, clinical and microbiological response was lower in the ESBL-positive as compared to ESBL-negative subset in both treatment groups.

## 15 REFERENCES

1. Kawamura S, Russell AW, Freeman SJ, and Siddall, RA: Reproductive and Developmental Toxicity of Meropenem in Rats. *Chemotherapy*, 40:S238-250 (1992).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

VABOMERE 2 grams (meropenem and vaborbactam) for injection is supplied as a white to light yellow sterile powder for constitution in single-dose, clear glass vials (NDC 70842-120-01) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum overseal. Each vial is supplied in cartons of 6 vials (NDC 70842-120-06).

Each vial contains 1 gram of meropenem (equivalent to 1.14 grams of meropenem trihydrate), 1 gram of vaborbactam, and 0.575 gram of sodium carbonate.

Store VABOMERE vials at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].

## 17 PATIENT COUNSELING INFORMATION

### Serious Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask patient about any previous hypersensitivity reactions to VABOMERE (meropenem and vaborbactam), penicillins, cephalosporins, other beta-lactams, or other allergens [see *Warnings and Precautions* (5.1)].

### Seizures

Patients receiving VABOMERE on an outpatient basis must be alerted of adverse events such as seizures, delirium, headaches and/or paresthesias that could interfere with mental alertness and/or cause motor impairment. Until it is reasonably well established that VABOMERE is well tolerated, patients should not operate machinery or motorized vehicles [see *Warnings and Precautions* (5.2)].

### Potentially Serious Diarrhea

Counsel patients that diarrhea is a common problem caused by antibacterial drugs including VABOMERE, which usually ends when the antibacterial drug is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible [see *Warnings and Precautions* (5.3)].

### Interaction with Valproic Acid

Counsel patients to inform their physician if they are taking valproic acid or divalproex sodium. Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with VABOMERE. If treatment with VABOMERE is necessary and continued, alternative or supplemental anti-convulsant medication to prevent and/or treat seizures may be needed [see *Warnings and Precautions* (5.4)].

### Antibacterial Resistance

Counsel patients that antibacterial drugs, including VABOMERE, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When VABOMERE is prescribed to treat a bacterial infection, tell patients that although it is common

to feel better early in the course of therapy, take the medication exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by VABOMERE or other antibacterial drugs in the future [*see Warnings and Precautions (5.7)*].

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