# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209776Orig1s000

# SUMMARY REVIEW

# Combined Cross-Discipline Team Leader, Division Director, and Office Director Summary Review

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|---|---|
| **Date** | Electronic stamp |
| **From** | Dmitri Iarikov, MD, PhD, Sumathi Nambiar MD MPH, Edward Cox, MD MPH |
| **Subject** | Combined Cross-Discipline Team Leader, Division Director, and Office Director Summary Review |
| **NDA #** | 209776 |
| **Applicant** | Rempex Pharmaceuticals, Inc. |
| **Date of Submission** | December 29, 2016 |
| **PDUFA Goal Date** | August 29, 2017 |
| **Proprietary Name / Non-Proprietary Name** | Vabomere / meropenem and vaborbactam |
| **Dosage form(s) / Strength(s)** | Powder for Intravenous Injection / 2 g (1 g of meropenem and 1 g of vaborbactam) in a single vial |
| **Applicant Proposed Indication(s)/Population(s)** | Complicated urinary tract infections (cUTI), including pyelonephritis |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** | Complicated urinary tract infections (cUTI), including pyelonephritis in adults |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Rama Kapoor MD |
| Statistical Review | Daniel Rubin PhD |
| Pharmacology Toxicology Review | James Wild PhD |
| OPQ ATL | Dorota Matecka, PhD |
| Microbiology Review | Kerian Grande Roche PhD |
| Clinical Pharmacology Review | Xiaohui Wei PhD |
| OPDP | Puja Shah PharmD RAC |
| OSI | John Lee, MD |
| OSE/DMEPA | Deborah Myers, RPh, MBA |
| OSE/DRISK | Till Olickal PhD PharmD |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
ATL= Application Technical Lead
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management



Reference ID: 4146227

# 1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Vabomere (meropenem-vaborbactam) for injection is a combination of meropenem, a carbapenem antibacterial drug, and vaborbactam, a beta-lactamase inhibitor (BLI). Vaborbactam alone does not have antibacterial activity; it prevents degradation of meropenem by some carbapenemases, primarily by *Klebsiella pneumoniae* carbapenemases (KPC), thus preserving the activity of meropenem against bacteria producing these enzymes. Meropenem is marketed in the US whereas vaborbactam is a new molecular entity that has not been marketed in any country, either alone or in combination. Meropenem was approved in the US in 1996. It is approved in the US for treatment of complicated intra-abdominal infections (cIAI), complicated skin and skin structure infections, and treatment of meningitis in pediatric patients. Meropenem is not approved for treatment of cUTI.

The NDA was submitted under Section 505(b)(2) of the Food Drug and Cosmetic Act and relies in part on the Agency's prior findings of safety and effectiveness of meropenem. The Applicant is seeking an indication for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis in patients 18 years and older. The Applicant conducted a single double-blind noninferiority (NI) Phase 3 trial in cUTI and acute pyelonephritis where meropenem-vaborbactam was compared to piperacillin-tazobactam with an option to switch to oral therapy after at least 15 doses of intravenous (IV) treatment. One adequate and well-controlled trial was considered adequate to demonstrate the efficacy of meropenem-vaborbactam for the treatment of cUTI, including pyelonephritis for the following reasons: the robust finding of efficacy in Study 505, established efficacy of meropenem in the treatment of cIAI (an infection typically caused by Gram-negative bacteria similar to those that cause cUTI), the dosing regimen of meropenem-vaborbactam that utilizes a higher dose of meropenem (2 grams every 8 hours) than that approved for treatment of cIAI (1 gram every 8 hours), pharmacokinetic properties of meropenem and vaborbactam resulting in high concentrations of both drugs in urine, and data from in vitro studies and animal models of infection demonstrating the activity of meropenem-vaborbactam against bacteria relevant to cUTI.

The primary efficacy endpoint in the trial as defined in the protocol was overall success which included both clinical and microbiologic success at the end of intravenous therapy (EOIVT) visit. An important secondary endpoint was overall success at the test of cure (TOC) visit 15-19 days after randomization, following completion of IV and oral therapy. For antibacterial drugs with an intravenous formulation alone, clinical and microbiological success at the EOIV and TOC visits is recommended as a co-primary endpoint in the current FDA guidance on developing antibacterial drugs for the treatment of cUTI.[1] At the time this trial was designed, the draft guidance was under development and the endpoints selected reflect the Agency's thinking at the time.

[1] Complicated Urinary Tract Infections: Developing Drugs for Treatment, Guidance for Industry, February 2005 https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf



Reference ID: 4146227

At the EOIVT visit, clinical and microbiologic success rates were higher in the meropenem-vaborbactam (98.4%) group compared to the piperacillin-tazobactam (94.3%) group, treatment difference 4.1%, 95% confidence interval (CI), 0.3% to 8.8%. Data from two clinical study sites were excluded from the FDA analyses as there were issues with data quality at both sites. The rates of clinical cure and microbiologic eradication at the TOC visit at Day 15-19 were 76.5% in the meropenem-vaborbactam group and 73.2% in the piperacillin-tazobactam group, treatment difference, 3.3%, 95% CI, -6.2% to 13.0%.

From a safety standpoint, no significant safety concerns emerged in the clinical development program. The safety database of 407 meropenem-vaborbactam-exposed subjects (varying doses and durations) included 272 subjects in the Phase 3 trial. The common adverse reactions reported in the clinical trial included headache (8.8% and 4.4%), diarrhea (3.3% and 4.4%), infusion site reactions (2.2% and 0.7%), nausea (1.8% and 1.5%), and alanine aminotransferase increased (1.8% and 0.4%) in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively. No new safety concerns were seen with the combination compared to the known safety profile of meropenem. The rates of deaths, serious adverse events, and treatment emergent adverse events were balanced between treatment groups.

In conclusion, the Applicant has provided substantial evidence to support the safety and efficacy of meropenem-vaborbactam for the treatment of cUTI including pyelonephritis, in adults. The safety findings for Vabomere support an acceptable benefit-risk for its use for the treatment of cUTI, including pyelonephritis. .The safety findings observed in the cUTI trial will be described in labeling. A thorough QT (TQT) study will be conducted as a postmarketing requirement (PMR). Other PMRs include required pediatric studies and a microbiology surveillance study to monitor for development of resistance to meropenem- vaborbactam.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | Complicated urinary tract infections are a clinical syndrome characterized by pyuria, documented microbial pathogen on culture of urine or blood, accompanied by fever, chills, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the patients with a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Patients with pyelonephritis are considered to be a subset of patients with cUTI, regardless of underlying abnormalities of the urinary tract.<br><br>The majority of cUTI are caused by Gram-negative bacteria of the family Enterobacteriaceae. In recent years, bacteria resistant to antibacterial drugs commonly used for the treatment of cUTI have emerged. cUTI caused by carbapenem-resistant Enterobacteriaceae (CRE) are of special concern due to the limited treatment options available and the higher mortality associated with | Complicated UTI is a serious bacterial infection most commonly caused by Gram-negative bacteria of the family Enterobacteriaceae. Complicated UTI caused by CRE are of special concern due to the limited treatment options available. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | infection due to CRE. | |
| **Current Treatment Options** | Quinolones and cephalosporins have been the most commonly used antibacterial drugs for the treatment of cUTI. The spread of extended-spectrum-beta-lactamase (ESBL)-producing bacteria, however, has limited the available treatment options. ESBLs hydrolyze most cephalosporins and ESBL-producing bacteria are commonly resistant to fluoroquinolones and could also be resistant to aminoglycosides. Carbapenems remain active against most ESBL-producing bacteria but the spread of carbapenem resistance limits the utility of this class of antibacterial drugs for cUTI due to CRE.<br><br>Currently available options for treatment of cUTI caused by CRE are mostly limited to ceftazidime-avibactam. Colistin, an antibacterial drug associated with significant nephrotoxicity is also used clinically to treat cUTI due to CRE. | Currently available options for treatment of cUTI caused by CRE are limited and represent an area of unmet medical need. Meropenem-vaborbactam may provide a needed treatment option for some of these infections. |
| **Benefit** | The efficacy of meropenem- vaborbactam in the treatment of cUTI including pyelonephritis was demonstrated in a randomized, double-blind, noninferiority Phase 3 trial comparing meropenem-vaborbactam with piperacillin-tazobactam. Subjects could be switched to oral antibacterial drugs such as levofloxacin after at least 15 doses of IV therapy.<br><br>The primary efficacy endpoint in the trial as defined in the protocol was overall success which included both clinical success and microbiologic eradication at the EOIVT visit. An important secondary endpoint was overall success at the TOC visit 15-19 days after randomization, after completion of both intravenous and oral therapy. Current FDA guidance for developing drugs for treatment of cUTI that are only available as an intravenous formulation recommends demonstration of noninferiority at approximately day 5 of IV therapy and at a fixed time point after randomization that accounts for the total duration of antibacterial therapy plus a period of observation after completion of therapy. At the time, the meropenem-vaborbactam cUTI trial was designed, the draft guidance was under development and the selection of efficacy endpoints reflects FDA's thinking at that time.<br><br>Data from two clinical study sites were excluded from the FDA analyses as there | The results of the cUTI trial provide sufficient evidence to support the efficacy of meropenem-vaborbactam in treatment of cUTI including pyelonephritis. |



Reference ID: 4146227

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | were issues with data quality at both sites. At the EOIVT visit, clinical and microbiologic success rates were higher in the meropenem-vaborbactam (98.4%) group compared to the piperacillin-tazobactam (94.3%) group, treatment difference, 4.1% (95% CI, 0.3% to 8.8%). At the TOC visit at Day 15-19, meropenem-vaborbactam was noninferior to piperacillin-tazobactam. The rates of clinical cure and microbiologic eradication at the TOC visit were 76.5% in the meropenem-vaborbactam group and 73.2% in the piperacillin-tazobactam group, treatment difference, 3.3%, 95% CI, -6.2% to 13.0%.<br><br>The contribution of vaborbactam to the combination was demonstrated in in vitro studies and animal models of infection.<br><br>The NDA also included interim results of a Phase 3, open-label study of meropenem-vaborbactam versus best available therapy (BAT) in the treatment of infections, including cUTI, caused by CRE. The interim results of this study do not provide sufficient evidence for the efficacy of meropenem- vaborbactam due to small sample sizes (23 subjects in the meropenem-vaborbactam and 16 in the BAT groups) and the descriptive nature of the study. | |
| **Risk** | In the clinical trials, no new safety concerns were seen with the combination of meropenem and vaborbactam compared to the known safety profile of meropenem. The rates of deaths, serious adverse events, and treatment emergent adverse events in the cUTI trial were balanced between the treatment groups. | Meropenem-vaborbactam demonstrated an acceptable risk-benefit profile in the treatment of cUTI. |
| **Risk Management** | No specific serious risks have been identified that necessitate specific risk management strategies at this time. | In addition to the safety information from the cUTI trial, the prescribing information will include warnings and drug-interaction information related to meropenem that are included in the meropenem label. The Applicant has agreed to conduct a TQT study to assess the risk for QT prolongation. |

# 2. Background

Meropenem-vaborbactam is a combination of meropenem, a carbapenem antibacterial drug, and vaborbactam, a non-beta lactam beta-lactamase inhibitor (BLI). Vaborbactam does not have antibacterial activity and prevents degradation of meropenem by some carbapenemases, primarily KPCs and preserves activity of meropenem against Enterobacteriaceae that express these enzymes.

Meropenem was approved in the US in 1996. It is approved for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections (cIAI) in adult and pediatric patients, and for the treatment of bacterial meningitis in pediatric patients. Meropenem is not approved for the treatment of cUTI. Vaborbactam is a new chemical entity that has not been marketed in any country, either alone or in combination.

In this NDA, submitted under Section 505(b)(2) of the Food Drug and Cosmetic Act, the Applicant is seeking the indication of cUTI including pyelonephritis. The Applicant is relying in part on the Agency's previous findings of safety and effectiveness of the listed drug, Merrem (meropenem for injection), NDA 050706.

The investigational new drug application (IND) 120040 for meropenem-vaborbactam was submitted on December 23, 2013. The meropenem-vaborbactam clinical development program includes four Phase 1 trials, a Phase 3 randomized, double-blind, noninferiority trial in cUTI and an ongoing open-label Phase 3 trial in infections caused by KPC-producing CRE, including cUTI, cIAI, hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), and bacteremia. Phase 1 trials include one trial with vaborbactam alone and three trials with combinations of meropenem and vaborbactam. One of the Phase 1 trials was conducted in subjects with varying degrees of renal impairment, including subjects on hemodialysis.

A single successful adequate and well-controlled clinical trial in cUTI was considered to be acceptable to support the cUTI indication. Supportive evidence for a single trial was provided by the Agency's previous findings of safety and effectiveness of meropenem in the treatment of cIAI (an infection primarily caused by Gram-negative bacteria similar to those that cause UTI), pharmacokinetic properties of meropenem and vaborbactam that result in high concentrations of meropenem and vaborbactam in urine, the dosing regimen of meropenem-vaborbactam, that utilizes a higher dose of meropenem (2 grams every 8 hours) than that approved for treatment of cIAI (1 gram every 8 hours), and data demonstrating activity of meropenem-vaborbactam from in vitro studies and animal models of infection. The agreed to noninferiority (NI) margin was 15%, which is larger than the NI margin of 10% recommended for cUTI trials. The larger margin was considered appropriate for a limited use indication as the drug had the potential to address an unmet medical need based on its spectrum of activity that included KPCs. The treatment effect (M1) for cUTI is 20% for an assessment at the end of intravenous therapy.[4] As there is greater uncertainty with respect to efficacy and safety in a trial with a larger NI margin, a limited use statement indicating that meropenem-vaborbactam



Reference ID: 4146227

should be reserved for patients who have limited or no alternative treatment options was considered to be included in the label.

The primary efficacy endpoint as defined in the protocol was overall success which included both clinical success and microbiological eradication at the end of intravenous therapy (EOIVT) visit. An important secondary endpoint was overall success at the test of cure (TOC) visit 15-19 days after randomization and occurred after completion of both intravenous and oral therapy. The FDA guidance for developing drugs for treatment of cUTI recommends that for products available only as an intravenous formulation, NI should be demonstrated at approximately day 5 of IV therapy and at a fixed time point after randomization that accounts for the total duration of antibacterial therapy plus a period of observation after completion of therapy.[2] When the meropenem-vaborbactam cUTI trial was designed, the draft guidance was under development and the selection of efficacy endpoints reflects FDA's thinking at that time.

Piperacillin-tazobactam was considered an appropriate comparator due to its activity against pathogens that typically cause cUTI and a dosing frequency similar to that of meropenem-vaborbactam. While piperacillin-tazobactam is not approved for the treatment of cUTI, as piperacillin is approved for the treatment of urinary tract infections, it was considered an acceptable comparator for an NI trial.

Meropenem-vaborbactam is a combination product and the contribution of the components was required to be assessed per 21 CFR 300.50. As the components of the combination cannot be studied as monotherapy in the clinical condition of interest, contribution of the components was assessed in in vitro and in animal models of infection as outlined in the guidance on co-development of two or more investigational drugs for use in combination.[3] The evaluation of the contribution of vaborbactam to the combination relies on in vitro microbiology, animal models of infection and hollow-fiber model.

The proposed dosing regimen of meropenem in the meropenem-vaborbactam combination differs from that approved for meropenem. In the combination, 2 g meropenem /2 g vaborbactam is administered as a 3-hour infusion every 8 hours. The approved adult dose of meropenem is up to 1 g given as an intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 mL - 20 mL) over approximately 3-5 minutes every 8 hours.

Meropenem-vaborbactam was granted a qualified infectious disease product (QIDP) designation in December 2013 and fast track designation in March 2016 and this NDA was granted a priority review.

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[2] Complicated Urinary Tract Infections: Developing Drugs for Treatment, Guidance for Industry, February 2005 https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf
[3] Co-development of Two or More New Investigational Drugs for Use in Combination; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm236669.pdf;



Reference ID: 4146227

# 3. Product Quality

The Office of Product Quality (OPQ) review team for this NDA included Gene Holbert, PhD for drug substance, George Lunn, PhD for drug product, Christine Falabella, PhD for manufacturing process, Denise Miller, PhD for product quality microbiology, and Daniel DeCiero, PhD for facilities.

The proposed drug product contains two drug substances, meropenem and vaborbactam, and an excipient, sodium carbonate. [redacted] (b) (4)

Meropenem trihydrate (b) (4) drug substance is prepared by [redacted] (b) (4) described in Drug Master File Type II (b) (4) held by (b) (4). DMF (b) (4) includes a reference to DMF Type II (b) (4) for the actual synthesis of meropenem drug substance.

The chemistry manufacturing and controls (CMC) information for vaborbactam drug substance has been provided in the NDA. Vaborbactam (b) (4) drug substance is manufactured from the starting materials [redacted] (b) (4) compounds are consistent with the recommendations for designation of starting materials as set forth in ICH Q11. Analytical data as well as the method of synthesis were found to support the proposed structure.

(b) (4) sodium carbonate is manufactured by (b) (4) under DMF (b) (4) and conforms to the National Formulary (NF) specification.

The drug product consists of 1 gram of meropenem (equivalent to 1.14 gram of meropenem trihydrate), 1 gram of vaborbactam, and 575 mg sodium carbonate. The product is supplied as a sterile powder (b) (4) in a 50 mL Type I clear glass vial that is sealed with a (b) (4) rubber stopper and an aluminum flip off seal.

[redacted] (b) (4), the drug product is supplied as a sterile powder for reconstitution. The formulation uses [redacted] (b) (4) that is filled into vials. A (b) (4)% overfill is used. The content of the vial is reconstituted with 20 mL saline and further diluted for infusion. Studies showed that (b) (4)% of the vial volume could be withdrawn and this supports the label claim of 1000 mg of each active ingredient being dispensed.

The drug product is toxicologically qualified and the unspecified impurity limit of (b) (4)% conforms to ICH Q3B. Satisfactory batch analyses are provided for three registration batches. The individual degradants from meropenem and vaborbactam that are controlled in the drug substances are also controlled in the drug product specification. Two new degradants, [redacted] (b) (4), have been identified in the drug product (b) (4) [redacted]. [redacted] (b) (4) It is tightly controlled at low levels.



Reference ID: 4146227

The Applicant has not conducted extractable/leachable studies on the container-closure system. Although the stopper undergoes minimal contact with the reconstituted solution, there is a concern that undesirable compounds may leach out from the stopper during prolonged storage of vials and may become adsorbed on the powder contents. The Applicant has agreed to conduct these studies as a Postmarketing Commitment (PMC).

The long-term and accelerated stability data indicate that the proposed drug product is stable under the storage conditions recommended in the labeling. There are no out of specification results for vials stored at 25°C/60% relative humidity (RH) for up to 12 months, 40°C/75% RH for 6 months, and in the light cabinet. The proposed expiration dating period of 24 months is acceptable.

The product quality microbiology information for sterilization validation of the drug substances and drug product, container closure integrity, and bacterial endotoxin method validation was found acceptable.

Of note, all clinical trials were conducted with a two-vial presentation with meropenem in one vial and vaborbactam in the other. Upon reconstitution, meropenem and vaborbactam were mixed in a single 250 mL IV bag. However, for convenience and to avoid medication errors, a single vial presentation is proposed for commercial use. The biopharmaceutics review evaluated in vitro data supporting the bridge between the drug product used in the clinical studies and the commercial drug product. The comparative physiochemical characteristics of the infusion solutions (i.e., pH and osmolality), drug product composition, doses, reconstitution, and dilution volumes were found to support the bridge between the proposed single-vial and the multi-vial drug products.

The product quality review team concluded that sufficient information was provided to assure the identity, strength, purity, and quality of the proposed drug product, meropenem and vaborbactam for injection. The manufacturing and testing facilities were considered acceptable and an overall “Approve” recommendation was made by the Office of Process and Facilities. The OPQ review team recommends approval of the NDA.

A postmarketing commitment (PMC) to perform extractable/leachable studies on the commercial container-closure system was agreed to by the Applicant.

# 4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is James Wild, PhD.

The main finding in Dr. Wild’s review is fetal malformations associated with vaborbactam administration in pregnant rabbits. Malformations included interventricular septal defects and supernumerary lung lobes. The No Observed Adverse Effect Level (NOAEL) for fetal malformations was equivalent to approximately 0.3 times the maximum recommended human dose (MRHD) based on AUC exposure. No similar malformations were observed in offspring from pregnant rats administered intravenous vaborbactam during organogenesis or from late



Reference ID: 4146227

pregnancy and through lactation at a dose equivalent to approximately 1.6 times the MRHD. Vaborbactam was not associated with maternal toxicity either in rabbits or rats.

Dr. Wild indicates that the clinical relevance of these findings is unknown, but fetal malformations associated with vaborbactam use should be described in the Pregnancy subsection of the product label to advise pregnant women of potential risks to a fetus.

In general toxicology studies, vaborbactam was not associated with significant toxicities in 28-day repeat-dose toxicology studies in rats and dogs at daily doses up to 3 times the MRHD dose in patients based on plasma AUC exposure when administered alone or in combination with meropenem. A similar lack of toxicity occurred in a 28-day toxicology study in juvenile rats.

Vaborbactam was not associated with genotoxicity in a full battery of testing including an in vitro Ames test, chromosome aberration test in human lymphocytes and in vivo micronucleus test in mice. In developmental and reproductive toxicity studies other than the embryo-fetal studies, vaborbactam did not negatively affect male or female fertility, and had no effects on first or second generation offspring in rats in a pre-postnatal study.

With regard to meropenem, no harm to the fetus or impairment of fertility was seen in rats and cynomolgus monkeys. Meropenem was not genotoxic in a full battery of in vitro (Ames test, Chinese hamster ovary HGPRT assay, human lymphocyte cytogenic assay) and in vivo (mouse micronucleus assay) assays.

In 1-month combination toxicology studies in rats and dogs, systemic AUC exposures for vaborbactam and meropenem were not substantially altered when administered concomitantly, and neither agent as well as the hydrolyzed metabolite of meropenem was observed to accumulate with repeated dosing.

Dr. Wild concludes that nonclinical pharmacokinetic and toxicity data for vaborbactam and meropenem do not indicate a potential for general toxicity above what is expected for treatment with meropenem alone.

Dr. Wild recommends approval of this NDA and recommends that the product label should describe the risk of fetal-malformations and instruct physicians to describe the risk to pregnant women. We agree with his recommendations.

# 5. Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Xiaohui (Tracey) Wei, PhD.

No drug-drug interaction between meropenem and vaborbactam was identified. Both meropenem and vaborbactam are primarily excreted via the kidneys. Approximately 40–60% of a meropenem dose is excreted unchanged within 24 to 48 hours, with ~22% excreted in urine as a microbiologically inactive metabolite after undergoing hydrolysis of the meropenem beta-lactam ring. Fecal elimination accounts for about 2% of a meropenem dose. For



Reference ID: 4146227

vaborbactam, 75 to 95% of the dose is excreted unchanged in the urine over 24 to 48 hours. Vaborbactam does not undergo metabolism.

The clearance of meropenem in healthy subjects following multiple doses is 15.1 L/h and for vaborbactam is 10.9 L/h. The $t_{1/2}$ is 1.22 hours and 1.68 hours for meropenem and vaborbactam, respectively.

There is a low potential for drug interactions with vaborbactam. Vaborbactam at clinically relevant concentrations does not inhibit or induce cytochrome CYP450 enzymes. Similarly, carbapenems as a class have not shown a potential for inhibition or induction of CYP450 enzymes and clinical experience suggests that such effects are unlikely.

The proposed dosing regimen of meropenem-vaborbactam in patients 18 years of age and older is meropenem 2 g and vaborbactam 2 g administered every 8 hours by IV infusion over 3 hours. The clinical pharmacology reviewer indicates that the proposed dosing regimen is supported by the efficacy, safety and PK data from the clinical trials submitted in the NDA.

The dose needs to be adjusted in patients with renal impairment. (b) (4) The FDA clinical pharmacology review team recommended dose adjustment based on eGFR calculated using the modification of diet in renal disease (MDRD) study equation. The agreed upon dose adjustment schedule is presented in Table 1**.**



Reference ID: 4146227

**Table 1: Meropenem-vaborbactam Dosing For Patients With Reduced Renal Function**

| eGFR (mL/min/1.73m$^2$)[a] | Recommended Dosage Regimen[b] |
|---|---|
| ≥50 | Meropenem 2 g and vaborbactam 2 g q8h |
| ≥30-49 | Meropenem 1 g and vaborbactam 1 g q8h |
| ≥15-29 | Meropenem 1 g and vaborbactam 1 g q12h |
| <15 | Meropenem 0.5 g and vaborbactam 0.5 g q12h[c] |

eGFR – estimated glomerular filtration rate
[a] Calculated using the MDRD equation
[b] All doses are administered intravenously over 3 hours.
[c] Both meropenem and vaborbactam can be removed by hemodialysis. For patients maintained on hemodialysis, administer meropenem-vaborbactam after hemodialysis.

Source: Modified from FDA Clinical Pharmacology Review, Table 2.2.2-1

The FDA clinical pharmacology reviewer discusses meropenem-vaborbactam susceptibility test interpretive criteria. This discussion is provided in Section 6 of this review, Clinical Microbiology.

Dr. Wei recommends approval of this NDA and we agree with her recommendations.

# 6. Clinical Microbiology

The clinical microbiology reviewer for this application is Kerian Grande Roche, Ph.D.

Meropenem is a carbapenem antibacterial drug that inhibits bacterial cell wall synthesis by targeting penicillin-binding proteins (PBPs), bacterial enzymes involved in the last steps of biosynthesis and cross-linking of peptidoglycan. As compared to other beta-lactams, carbapenems are more stable to degradation by serine beta-lactamases, such as class A extended spectrum beta-lactamases (ESBLs) and class C cephalosporinases but can be degraded by carbapenemases. Currently, KPCs, a type of class A serine carbapenemases, are the most prevalent enzymes responsible for carbapenem resistance in the US.

Vaborbactam is a cyclic boronate that forms a covalent adduct between the boronate moiety and the catalytic serine residue and reversibly inhibits some carbapenemases. It inhibits some class A and C serine carbapenemases, with the most potent inhibition of KPCs. It does not inhibit class D carbapenemases such as OXA-48, and class B beta-lactamases, i.e., metallo beta-lactamases (MBL).

Meropenem MICs against *P. aeruginosa* are not affected by vaborbactam as the major carbapenem resistance mechanisms in *P. aeruginosa* are the loss of specific carbapenem porins and expression of efflux pumps.



Reference ID: 4146227

The antibacterial activity of meropenem in combination with vaborbactam was compared with that of meropenem alone in mouse infection models using carbapenem-resistant, class A serine carbapenemase producing strains of *K. pneumoniae*, *E. coli*, and *E. cloacae*. The meropenem MICs for these organisms ranged from 8-512 mcg/mL. For most strains, the MICs for meropenem-vaborbactam were at least 4-fold lower than that for meropenem alone. The activity was greater with a vaborbactam concentration of 8 mcg/mL.

Based on evaluation of 1,900 isolates including 619 isolates from US surveillance studies and 22 isolates from Studies 505 and 506, vaborbactam generally enhanced the activity of meropenem against KPC-producing Enterobacteriaceae. The MIC90 of meropenem and vaborbactam in these studies ranged from 0.5 to 2 mcg/mL compared to an MIC90 of >32 mcg/mL for meropenem alone.

In development of resistance studies, meropenem and vaborbactam at a concentration of 8 mcg/mL of each component was associated with suppression of the emergence of mutants to a frequency below $10^{-9}$. The same concentrations also prevented regrowth of resistant subpopulations in time-kill studies.

There were 24 CRE isolates in Studies 505 and 506, including 22 KPCs. Most of the CRE isolates were from Study 506 (n=21); 13 in the meropenem-vaborbactam and 8 in the comparator group. There were three CRE isolates in Study 505, one in the meropenem-vaborbactam and two in the piperacillin-tazobactam groups. The MICs of meropenem-vaborbactam for CREs in the Phase 3 trials were similar to those in the recent surveillance isolates with MIC90=1 mcg/mL.

In Study 505, there were 3 subjects in the meropenem-vaborbactam group and 4 subjects in the piperacillin-tazobactam group whose baseline isolates demonstrated a ≥4-fold increase in MIC post-baseline. The isolates included *K. pneumoniae* (n=3) in the meropenem-vaborbactam group and *P. aeruginosa* (n=3) and *P. mirabilis* (n=1) in the piperacillin-tazobactam group. In the meropenem-vaborbactam group, the increased MICs remained in the susceptible range for meropenem with the highest MIC of 0.5 mcg/mL.

The activity of meropenem with vaborbactam was comparable in urine and in cation-adjusted Mueller-Hinton broth (CAMHB) against KPC-producing Enterobacteriaceae.

**Susceptibility Test Interpretive Criteria**

The PK/PD parameter of meropenem that best correlates with activity of meropenem in animal and in vitro models of infection is the percentage of time of a dosing interval during which the unbound plasma concentration of meropenem exceeds the meropenem minimum inhibitory concentration (MIC) in the presence of vaborbactam (% $T_{Cf>MIC}/\tau$) against the infecting organism. The Applicant had proposed [redacted] (b) (4) The FDA clinical pharmacology team recommends using 24h fAUC/MIC of 38 as the vaborbactam PK/PD target since this value was determined from studies in the neutropenic mouse thigh infection



Reference ID: 4146227

model and was associated with restoring the activity of meropenem in the tested KPC-producing strains.

In neutropenic murine infection models, the magnitude of meropenem $\%T_{Cf>MIC}/\tau$ associated with net bacterial stasis, a 1-, and 2- $\log_{10}$ reduction in CFU of Gram-negative bacilli from baseline was 30%, 35%, and 45%, respectively.

The FDA clinical pharmacology reviewer assessed the probability of target attainment at the FDA's recommended dose regimens, using the Applicant's population PK model. A Monte Carlo simulation of meropenem plasma concentrations in 4,000 patients distributed among different renal function groups. Results of probabilities of target attainment for a 45% $T_{Cf>MIC}/\tau$ PK/PD target are presented in Table 2.

**Table 2:Probability of PK/PD Target Attainment**

| MIC (mcg/mL) | eGFR ≥ 50 | eGFR 40-50 | eGFR 30-40 | eGFR 20-30 | eGFR 10-20 | eGFR <10 |
|---|---|---|---|---|---|---|
| 0.12 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.25 | 1 | 1 | 1 | 1 | 1 | 1 |
| 0.5 | 1 | 1 | 1 | 1 | 1 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| 4 | 1 | 1 | 1 | 1 | 1 | 1 |
| 8 | 1 | 0.99 | 0.99 | 0.99 | 0.97 | 0.97 |
| 16 | 0.94 | 0.75 | 0.81 | 0.81 | 0.75 | 0.79 |
| 32 | 0.39 | 0.18 | 0.24 | 0.27 | 0.27 | 0.28 |
| 64 | 0.03 | 0.01 | 0.02 | 0.03 | 0.03 | 0.02 |

eGFR (mL/min/1.73m$^2$ )– estimated glomerular filtration rate calculated by MDRD equation
Uses FDA-recommended dosing regimen
Source: FDA Clinical Pharmacology Review, Table 3.3.3-2

At the FDA's recommended dose adjustment, percent probabilities of PK/PD target attainment based on the above-described PK/PD target are >97% across simulated patients in each renal function group at a meropenem-vaborbactam MIC of 8 mcg/mL.

Recent surveillance studies (2014-2015) of clinical isolates of Enterobacteriaceae showed that for all Enterobacteriaceae and for KPC-producing Enterobacteriaceae, ~95% and ~50% of isolates were inhibited at meropenem-vaborbactam ≤ 0.06 mcg/mL, respectively. In recent surveillance studies, the distribution of meropenem-vaborbactam MICs for KPC-producing strains ranged from < 0.03 to >32 mcg/mL; 99% of KPC-producing Enterobacteriaceae had meropenem-vaborbactam MIC of ≤ 4 mcg/mL.

Analyses of clinical and microbiological responses relative to MICs of infecting pathogens as well as analyses of individual patient PK-PD indices in Study 505 did not identify an MIC cutoff value associated with efficacy. This was due to the high success rates of >90% with no obvious MIC cutoff discriminating between successes and failures.



Reference ID: 4146227

As presented in Table 3, 98% of Enterobacteriaceae isolates in Study 505 had an MIC of ≤0.06 mcg/mL. The only three microbiological and clinical failures in the meropenem-vaborbactam group had isolates with MIC ≤0.06 mcg/mL, two *E. coli* and one *K. pneumoniae*.

**Table 3: Outcomes in Enterobacteriaceae Infections at the End of IV Therapy Visit by Meropenem-vaborbactam MIC (m-MITT Population), Study 505**

| Meropenem-vaborbactam MIC (mcg/mL) | Microbiological Eradication n/N (%) | Clinical Cure n/N (%) | Overall Success n/N (%) |
|---|---|---|---|
| ≤ 0.06 | 146/149 (98%) | 146/149 (98%) | 146/149 (98%) |
| 0.125 | 11/12* (91.7%) | 12/12 (100%) | 12/12 (100%) |
| 0.25 | 2/2 (100%) | 2/2 (100%) | 2/2 (100%) |
| 0.5 | 1/1 (100%) | 1/1 (100%) | 1/1 (100%) |
| 1 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 |
| 16 | 0 | 0 | 0 |
| 32 | 1/1 (100%) | 1/1 (100%) | 1/1 (100%) |

* One outcome was indeterminate, i.e., presumed eradication
N is the number of subjects who had a baseline pathogen with the specified MIC.
m-MITT: Microbiological Modified Intent-to-Treat Population
Source: FDA Clinical Pharmacology Review; Table 3.3.5-4

The susceptibility test interpretive criteria proposed by the clinical microbiology and clinical pharmacology teams and accepted by the Applicant are presented in Table 4.

**Table 4: Susceptibility Test Interpretive Criteria for Meropenem-vaborbactam**

| Pathogen | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameters in mm) | | |
|---|---|---|---|---|---|---|
| | S | I | R | S | I | R |
| Enterobacteriaceae | ≤4/8 | 8/8 | ≥16/8 | ≥ 17 | 14-16 | ≤ 13 |

All breakpoints were tested with a fixed vaborbactam concentration of 8 mcg/mL.

While probability of target attainment analyses might support a susceptible breakpoint of up to 8 mcg/mL, there are no clinical data to support this breakpoint. The majority of isolates in Study 505 had MICs of ≤ 0.06 mcg/mL and there are very limited clinical data on the efficacy of meropenem-vaborbactam with isolates that had MICs ≥ 0.125 mcg/mL. Although the clinical data at higher MICs were limited, a susceptible breakpoint of 4 mcg/mL was considered acceptable as it covers 99% of the KPC-producing isolates in recent surveillance studies and is supported by the probability of target attainment analyses. Additionally, a susceptible breakpoint of 4 mcg/mL and an intermediate breakpoint of 8 mcg/mL provide a buffer for laboratory errors in MIC testing so that isolates resistant to meropenem-vaborbactam are not erroneously characterized as being susceptible.



Reference ID: 4146227

With regard to organisms to be included in the indication, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex will be listed. (b) (4)

Dr. Grande Roche recommends approval of this NDA and we agree with her recommendations.

# 7. Clinical/Statistical- Efficacy

Daniel Rubin, PhD is the statistical reviewer and Rama Kapoor, MD is the clinical reviewer for this application.

Efficacy analyses are based on a Phase 3 randomized, double-blind, double-dummy, NI trial (Study 505) comparing meropenem-vaborbactam with piperacillin-tazobactam in the treatment of cUTI including pyelonephritis in subjects 18 years of age and older. Subjects were randomized in a 1:1 ratio to either meropenem-vaborbactam (2 g/2 g) infused as a 250 mL infusion over 3 hours every 8 hours or piperacillin-tazobactam 4.5 g (piperacillin 4 g/tazobactam 0.5 g) infused as a 100 mL infusion over 30 minutes every 8 hours. In addition, subjects randomized to meropenem-vaborbactam received a 100 mL infusion of normal saline administered over 30 minutes and subjects randomized to piperacillin-tazobactam received a 250 mL infusion of normal saline administered over 3 hours.

Subjects with an estimated creatinine clearance (CrCL) ≥ 30-49 mL/min using the Cockcroft-Gault formula received meropenem-vaborbactam (1 g/1 g) every 8 hours. No dose adjustment was required for piperacillin-tazobactam. Subjects with CrCL < 30 mL/min were excluded.

After at least 15 doses of IV therapy, switch to oral antibacterial drugs was allowed provided the subject was afebrile for at least 24 hours, baseline cUTI symptoms and leukocytosis had improved, urine culture at 24 hours had growth at < $10^4$ CFU/mL, blood culture was negative in subjects with bacteremia, and the subject was able to tolerate oral medications. Subjects with baseline urinary pathogen(s) resistant to levofloxacin could be switched to trimethoprim/sulfamethoxazole, cefdinir, cefixime or cefpodoxime. The planned duration of therapy (IV and oral) was 10 days; subjects with concurrent bacteremia could receive 14 days of therapy.

The primary analysis population was the microbiological modified intent-to-treat (m-MITT) population of all randomized subjects who received any dose of study drug and had a baseline bacterial pathogen of ≥$10^5$ CFU/mL in a urine culture or had the same pathogen growing in blood and urine, regardless of CFU/mL. Presence of up to two bacterial species, each at ≥ $10^5$ CFU/mL was considered acceptable. If three or more bacterial species were cultured, the urine culture was considered contaminated. An organism was not considered a contaminant, however, if it grew in a concurrent blood culture.



Reference ID: 4146227

The primary efficacy endpoint as defined in the protocol was overall success at the EOIVT visit. This was a composite endpoint defined as having both a successful clinical outcome (investigator judgment of cure or improvement) and microbiological outcome (baseline pathogen(s) reduced to $<10^4$ CFU/mL on urine culture). Of note, for antibacterial drugs with an IV formulation alone, evaluation of clinical and microbiological response at the end of IV treatment and the TOC visits is recommended as a co-primary efficacy endpoint in the current FDA guidance on developing antibacterial drugs for the treatment of cUTI.

The clinical outcome was assessed as cure, improved, failure, or indeterminate based on the following signs and symptoms: fever (oral or tympanic temperature ≥38°C or rectal/core temperature ≥38.3°C), urinary frequency, urinary urgency, dysuria, nausea, vomiting, abdominal pain, supra-pubic pain or discomfort, flank pain, and costo-vertebral angle tenderness. At the EOIVT visit, if all symptoms present at baseline were classified as mostly resolved or decreased, with no new onset of symptoms, the subject had a clinical outcome of cure. Subjects with incomplete resolution or no worsening of the baseline symptoms and needed no additional antimicrobial therapy, had a clinical outcome of improvement. The category of improvement was not used in the assessment of clinical outcome at the End of Therapy (EOT), Test of Cure (TOC), and Late Follow-up (LFU) visits where only the category of cure was used.

Secondary efficacy endpoints included overall success at both the EOIVT and TOC visits, microbiologic eradication at TOC, clinical cure at Day 3, EOIVT, EOT, and at the LFU visits.

The pre-specified NI margin was 15%. The statistical analysis plan stated that if NI was demonstrated, superiority was to be assessed. This form of sequential testing is statistically appropriate and does not lead to Type I error rate inflation.

A total of 550 subjects were randomized including 274 to meropenem-vaborbactam and 276 to piperacillin-tazobactam; 545 received at least one dose of study drug: 272 in the meropenem-vaborbactam group and 273 in the piperacillin-tazobactam group. A similar percentage of subjects with acute pyelonephritis (59.2% and 59.0%) and cUTI (40.8% and 41.0%) were enrolled in each treatment group. The m-MITT population included 192 subjects in the meropenem-vaborbactam and 182 subjects in the piperacillin-tazobactam groups.

Among subjects who received at least one dose of study drug, 91.5% in the meropenem-vaborbactam and 86.1% in the piperacillin-tazobactam groups completed study treatment (both IV and oral step-down therapy). The main reason for not completing treatment was premature discontinuation of IV therapy, 8.1% and 12.8%, in the meropenem-vaborbactam and in the piperacillin-tazobactam groups, respectively. The primary reasons for discontinuations in the meropenem-vaborbactam and piperacillin-tazobactam groups were adverse events, 2.2% and 5.1%, and physician decision, 2.9% and 4.8%, respectively.

The mean duration of IV therapy was 8 days in both groups, ranging from 1 day to 15 days in the meropenem-vaborbactam and 2 days to 15 days in the piperacillin-tazobactam group. Approximately 95% of subjects in the meropenem-vaborbactam and 94% in the piperacillin-



Reference ID: 4146227

tazobactam group received IV therapy for 5 or more days. Mean duration of IV and oral step-down therapy was approximately 10 days in both treatment groups.

About 61% of subjects in the meropenem-vaborbactam and 51% of subjects in the piperacillin-tazobactam group switched to oral therapy. Mean duration of oral therapy was similar in the meropenem-vaborbactam and piperacillin-tazobactam groups, 4.6 days and 4.5 days, respectively.

Demographic characteristics were balanced between treatment groups. The majority of subjects were enrolled in Europe (89.7% and 89%), were white (93.4% and 92.3%), female (66.5% and 65.9%), and had a mean age of 53 and 52.6 years, in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively. The course of the illness and management of subjects enrolled from sites outside US was considered to be similar to that seen in US patients and hence data from this trial, although primarily obtained from non-US sites, was considered acceptable. Most subjects had CrCL > 50 mL/min, 87.1% and 85.3%, in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively.

Most infections were mono-microbial, 93.8% and 89%, in the meropenem-vaborbactam and piperacillin-tazobactam groups respectively. The most commonly identified pathogens were *E. coli* (~65%) and *K. pneumoniae* (~15%). In the meropenem-vaborbactam group, the majority of organisms identified in urine culture were susceptible to meropenem; only one isolate of *K. pneumonia*e and two isolates of *P. aeruginosa* were resistant to meropenem. Therefore, the contribution of vaborbactam to the efficacy of meropenem-vaborbactam could not be evaluated in Study 505.

Two study sites in Study 505 were found to have significant data quality issues and were closed by the Applicant. One site enrolled 13 subjects and was closed due to protocol noncompliance. The other site enrolled 6 subjects and was closed due to inadequate source documentation and lack of investigator oversight. The FDA efficacy analyses exclude data from these two study sites.

Study 505 was designed as an NI trial and for an informative NI assessment it is important that the test drug be compared to an effective comparator. There were 49 subjects who had baseline isolates that were resistant to piperacillin-tazobactam, including 23 in the piperacillin-tazobactam group. Patients whose baseline pathogens were resistant to piperacillin-tazobactam were removed from the NI assessment at TOC. As susceptibility to piperacillin-tazobactam is a baseline characteristic, removal of these patients from the analyses preserves randomization.

For the pre-specified primary efficacy analysis of clinical and microbiological response at the EOIVT visit, meropenem-vaborbactam demonstrated superiority over the comparator. Under this circumstance the concerns regarding the efficacy of the comparator become less as efficacy of meropenem-vaborbactam was established by a finding of superiority rather than an NI assessment.

Another factor considered in the efficacy analyses was the susceptibility of baseline isolates to levofloxacin as levofloxacin was one of the commonly used oral switch therapies. Overall,



Reference ID: 4146227

there were 137 subjects in the m-MITT population with a levofloxacin-resistant baseline pathogen (37%). The majority of these patients either remained on IV therapy or were switched to an oral drug other than levofloxacin as specified in the protocol. However, in each treatment group, 20 subjects with levofloxacin-resistant pathogens received oral levofloxacin. This protocol violation may have impacted the results at the TOC visit. However, given that the decision to switch to oral levofloxacin was based on post-randomization factors, these patients were not excluded from the analysis.

For the TOC efficacy analysis, meropenem-vaborbactam was not superior to piperacillin-tazobactam. At the TOC visit, meropenem-vaborbactam was noninferior to piperacillin-tazobactam after excluding patients whose baseline pathogens were resistant to piperacillin-tazobactam. The lower bound of the 95% CI was less than the 10% NI margin recommended for standard development programs. Considering limitations of the TOC analyses discussed above, the results support the NI of meropenem-vaborbactam as compared to piperacillin-tazobactam in the treatment of cUTI and pyelonephritis. In both treatment groups, clinical and microbiologic response rate were lower at the TOC visit compared to the EOIVT visit, Table 5.

**Table 5: Clinical and Microbiological Response Rates at the EOIVT and TOC Visits (m-MITT Population), Study 505**

| Visit | Meropenem-Vaborbactam | Piperacillin-Tazobactam | Difference | 95% CI |
|---|---|---|---|---|
| EOIVT | 183/186 (98.4) | 165/175 (94.3) | 4.1% | 0.3%, 8.8% |
| TOC | 124/162 (76.5) | 112/153 (73.2) | 3.3% | (-6.2%, 13.0%) |

EOIVT analysis includes patients with organisms resistant to piperacillin-tazobactam at baseline
TOC analysis excludes patients with organisms resistant to piperacillin-tazobactam at baseline
Source: FDA Statistical Reviewer analyses

The lower clinical and microbiological response rates at TOC as compared to EOIVT visit in both treatment groups was primarily driven by lower microbiologic eradication rates. At EOIVT, clinical response rates were 98.4% and 96% in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively, and microbiologic eradication rates were 97.8% and 93.1% in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively. At TOC, clinical response was 91.4% and 86.3% in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively, and microbiological eradication rates were 69.8% and 63.4% in the meropenem-vaborbactam and piperacillin-tazobactam groups, respectively.

Dr. Rubin notes that although Study 505 was designed as an NI trial, the finding of superiority at the EOIV visit, provides relatively strong evidence of treatment effect of meropenem-vaborbactam at the EOIVT visit. In addition, the findings of superiority make the pre-defined size of the NI margin less relevant.

The NDA also included interim results of Study 506 that was ongoing at the time of NDA submission. Study 506 is a Phase 3, randomized, open-label trial of meropenem-vaborbactam versus best available therapy (BAT) in the treatment of cUTI, cIAI, HABP/VABP, and



Reference ID: 4146227

bacteremia, suspected or known to be caused by CRE. Subjects were randomized in a 2:1 ratio to meropenem-vaborbactam or BAT to receive study treatment for up to 14 days. Study 506 was not designed for inferential testing and was analyzed descriptively.

The primary efficacy population was the microbiological carbapenem-resistant Enterobacteriaceae Modified Intent-to-Treat (mCRE-MITT) population that included all subjects who received at least one dose of study drug and had Enterobacteriaceae at baseline that were confirmed as meropenem-resistant.

Efficacy endpoints were defined based on the underlying infection type. For subjects with cUTI endpoints included proportion of subjects with clinical cure, microbiologic eradication, and overall success at the EOT (Day 7 to Day 14) visit and at the TOC (7 days ± 2 days post-EOT) visit, and all-cause mortality at Day 28.

The interim analysis included data on 39 subjects who received at least one dose of study drug including 23 subjects in the meropenem-vaborbactam and 16 in the BAT groups. These 39 subjects included 23 subjects with cUTI (15 in the meropenem-vaborbactam and 8 in the BAT groups), 11 subjects with bacteremia (6 in the meropenem-vaborbactam and 5 in the BAT groups, respectively), 4 subjects with HABP/VABP (2 in the meropenem-vaborbactam and 2 in the BAT groups, respectively); 1 subject with cIAI received BAT.

A total of 25 subjects were included in the mCRE-MITT population, 15 in the meropenem-vaborbactam and 10 in the BAT groups. For subjects with cUTI, the mCRE-MITT population included 9 subjects in the meropenem-vaborbactam and 3 subjects in the BAT groups. Overall success was 7/9 and 2/3 at the EOT visit and 2/9 and 3/3 at the TOC visit in the meropenem-vaborbactam and BAT groups, respectively. All-cause mortality at Day 28 was 22.2% (2/9) in the meropenem-vaborbactam and 0% (0/3) in the BAT groups.

Dr. Rubin noted that the interpretation of this ongoing trial is limited by small sample sizes, the descriptive nature of the study, and inconclusive results. We agree that the interim results of Study 506 are difficult to interpret and no meaningful supportive efficacy data can be garnered from this study at this point. The results of this trial will not be included in the Clinical Studies section of labeling.

Drs. Rubin and Kapoor conclude that the Applicant has provided sufficient evidence of efficacy of meropenem-vaborbactam in the treatment of cUTI, including pyelonephritis. We agree that the results of Study 505 provide sufficient evidence of efficacy of meropenem-vaborbactam in the treatment of cUTI including pyelonephritis. A single adequate and well-controlled trial was considered adequate to demonstrate the efficacy of meropenem-vaborbactam for the treatment of cUTI, including pyelonephritis for the following reasons: the robust finding of efficacy in Study 505, known efficacy of meropenem in the treatment of cIAI, an infection typically caused by Gram-negative bacteria similar to those that cause cUTI, the dosing regimen of meropenem-vaborbactam that utilizes a higher dose of meropenem (2 grams every 8 hours) than that approved for treatment of cIAI (1 gram every 8 hours), pharmacokinetic properties of meropenem-vaborbactam resulting in high concentrations of



Reference ID: 4146227

both drugs in urine, and data from in vitro studies and animal models of infection demonstrating the activity of meropenem-vaborbactam against bacteria relevant to cUTI.

# 8. Safety

The safety review was conducted by Rama Kapoor, MD. Dr. Kapoor concluded that meropenem-vaborbactam has a favorable risk-benefit profile for the treatment of cUTI including pyelonephritis.

The safety database includes 407 subjects who received meropenem-vaborbactam in two Phase 3 trials (Study 505 and 506) and three Phase 1 trials. A total of 337 subjects received the proposed dose of meropenem 2 g/vaborbactam 2 g, including 272 subjects in Study 505, 23 in Study 506, and 42 in Phase 1 trials. Seventy subjects in Phase 1 trials received a combination of meropenem and vaborbactam at the doses below the proposed dose. In addition, 70 subjects received vaborbactam alone.

The safety evaluation of meropenem-vaborbactam in this review focuses on the results of Study 505. Safety population in this trial included all randomized subjects who received at least one dose of study drug. A total of 272 subjects received meropenem-vaborbactam and 273 subjects received piperacillin-tazobactam.

There were two deaths in each treatment group. In the meropenem-vaborbactam group, one subject died from aspiration and one from sudden cardiac death.

Serious adverse events (SAEs) were reported at similar rates in the meropenem-vaborbactam and piperacillin-tazobactam groups, 4% (11/272) and 4.4% (12/273), respectively. Study treatment was discontinued due to TEAEs in 2.9% (8/272) of subjects in the meropenem-vaborbactam and in 5.1% (14/273) of subjects in the piperacillin-tazobactam groups. Most common adverse reactions resulting in discontinuation of meropenem-vaborbactam included hypersensitivity in 3 (1.1%) subjects and infusion-related reactions in 2 (0.7%) subjects.

One subject discontinued study treatment after developing atrial fibrillation with rapid ventricular response necessitating cardioversion during the first infusion of meropenem-vaborbactam. Otherwise, no significant changes in vital signs and ECG parameters including changes in PR, QRS and QT intervals were observed during the meropenem-vaborbactam clinical program. A thorough QT study will be conducted as a postmarketing requirement.

Hypersensitivity reactions were reported in 5 (1.8%) of subjects in both treatment groups. In the meropenem-vaborbactam group, one subject had an event described as anaphylactic reaction. The event occurred during the second infusion of meropenem-vaborbactam and was described as dizziness, headache, general weakness, and “pins and needles” in the scalp. Vital signs remained within normal ranges. Study drug was discontinued and the event resolved the next day. Overall, the description of the event did not meet criteria for an anaphylactic reaction.



Reference ID: 4146227

The proportion of subjects who experienced at least one TEAE was similar in the meropenem-vaborbactam and piperacillin-tazobactam groups, 39% (106/272) and 35.5% (97/273) respectively. The most frequent TEAE in the meropenem-vaborbactam and piperacillin-tazobactam groups included headache (8.8% and 4.4%), diarrhea (3.3% and 4.4%), infusion site reaction (2.2% and 0.7%), nausea (1.8% and 1.5%), and alanine aminotransferase increased (1.8% and 0.4%). There were no relevant differences between meropenem-vaborbactam and piperacillin-tazobactam groups for clinical laboratory parameters. Seizure, an event associated with the use of carbapenems, was not reported in meropenem-vaborbactam-treated subjects in this study.

Safety findings in Study 506 will not be discussed in detail in this review because the results of this study are not used to support the cUTI indication and will not be included in the product label. The severity of infections and underlying comorbidities were greater in Study 506 as compared to Study 505. Eight deaths were reported, including 5 (21.7%) in the meropenem-vaborbactam group and 3 (18.8%) in the BAT group. In subjects with cUTI, 20% (3/15) died in the meropenem-vaborbactam group as compared to 0% (0/8) in the BAT group. Two subjects with cUTI died of septic shock and the deaths could potentially be related to low efficacy of study drug.

The proportion of subjects who discontinued study drug or were discontinued from the study was similar in the meropenem-vaborbactam and BAT groups, 34.8% (8/23) and 31.2% (5/16), respectively. The proportion of subjects with at least one TEAE was similar in the meropenem-vaborbactam and BAT groups, 87.0% and 87.5%, respectively. Diarrhea and sepsis/septic shock were the most frequent TEAEs in both groups.

We agree with Dr. Kapoor’s assessment that the Applicant has provided sufficient information to support the safety of meropenem-vaborbactam for the treatment of cUTI including pyelonephritis in subjects 18 years and older.

# 9. Advisory Committee Meeting

This NDA was not discussed at an advisory committee meeting as there were no specific questions that needed input from the committee.

# 10. Pediatrics

The Applicant requested deferral of pediatric studies because the adult trial of cUTI was completed and the product is ready for approval. No waivers for any age cohort were requested. Extrapolation of efficacy from adults to the pediatric population is considered appropriate for the cUTI indication due to the similar pathogenesis of disease in adult and pediatric patients, and a similar expected response to treatment. Because of concerns regarding poor localization of infection and the risk of CNS infection in the neonatal population, a separate safety study for the neonatal population (0-3 months of age) is proposed.



Reference ID: 4146227

The pediatric plan was discussed at the Pediatric Review Committee (PeRC) and found to be acceptable. The proposed pediatric studies will be postmarketing requirements (PMRs). The Applicant has agreed to the following PMRs and proposed timelines.

**PMR 3248-1**: Conduct an open-label, sequential study to assess the pharmacokinetics (PK), safety, and tolerability of Vabomere and the PK of meropenem-vaborbactam in children from birth to < 18 years of age with selected serious bacterial infections.

| | |
|---|---|
| Final Protocol Submission: | Submitted November 2, 2015 |
| Study Completion: | 09/2019 |
| Final Report Submission: | 03/2020 |

**PMR 3248-2**: Conduct a randomized, single-blind, active comparator study to evaluate the safety, tolerability, and PK of Vabomere versus piperacillin-tazobactam for the treatment of pediatric subjects from 3 months to < 18 years of age with complicated urinary tract infections (cUTI) including acute pyelonephritis.

| | |
|---|---|
| Draft Protocol Submission: | 05/2018 |
| Final Protocol Submission: | 09/2018 |
| Study/Trial Completion: | 09/2021 |
| Final Report Submission: | 03/2022 |

**PMR 3248-3**: Conduct an open-label, active comparator study to evaluate the PK, safety, and tolerability of multiple doses of Vabomere versus comparator in neonates (≤ 90 days of age) with late onset sepsis.

| | |
|---|---|
| Draft Protocol Submission: | 11/2019 |
| Final Protocol Submission: | 03/2020 |
| Study Completion: | 12/2024 |
| Final Report Submission: | 06/2025 |

# 11. Other Relevant Regulatory Issues

John Lee, MD from the Office of Scientific Investigations (OSI) provided a clinical inspection summary for this NDA. Five inspections for Study 505 were conducted. The inspections included 4 clinical sites with the largest enrollment (three sites in Ukraine and one in Greece) and a contract research organization in the US. No significant deficiencies were observed during the inspections. The study conduct was found to be adequate, including the Applicant's oversight of study conduct. Dr. Lee notes that all audited data were adequately verifiable and appear reliable as reported in the NDA.

Two clinical sites in Study 505 were closed by the Applicant after significant quality issues were identified related to protocol noncompliance and insufficient documentation for data verification. The site closures were reported to FDA. Subjects enrolled at these sites were



Reference ID: 4146227

excluded from FDA efficacy analyses. OSI concurred with exclusion of these two sites from efficacy evaluations.

# 12. Labeling

Labeling recommendations provided by the review team, including OPDP and DMEPA have been incorporated in labeling. The trade name Vabomere was considered acceptable by DMEPA. Only the results of the cUTI trial are included in the Adverse Reactions and Clinical Studies section of the label. The interim results of Study 506 for the treatment of CRE infections are not included in the label because the study was not used to support the cUTI indication and it does not provide significant safety information in addition to safety data collected in Study 505. Labeling also includes warnings, adverse reactions, and drug-drug interaction information from the meropenem label.

# 13. Postmarketing Recommendations

*Risk Evaluation and Management Strategies (REMS)*

The Division of Risk Management (DRISK) determined that a risk evaluation and mitigation strategy (REMS) was not necessary to ensure that the benefits of meropenem-vaborbactam outweigh its risks.

*Postmarketing Requirements (PMRs) and Commitments (PMCs)*

Postmarketing requirements under Pediatric Research Equity Act (PREA) are outlined in Section 10 of this review. In addition, the Applicant has agreed to the following postmarketing requirements and commitment:

**PMR 3248-4**: Conduct a US surveillance study for five years from the date of marketing to determine if resistance to Vabomere has developed in those organisms specific to the indications in the label.

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|---|---|
| Final Protocol Submission: | 09/2017 |
| Interim Study Report: | 06/2018 |
| Interim Study Report: | 06/2019 |
| Interim Study Report: | 06/2020 |
| Interim Study Report: | 06/2021 |
| Interim Study Report: | 06/2022 |
| Study/Trial Completion: | 03/2023 |
| Final Report Submission: | 06/2023 |

**PMR 3248-5**: Conduct a “Thorough QT/QTc Study” to evaluate whether Vabomere has a threshold pharmacologic effect on cardiac repolarization.

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|---|---|
| Draft protocol submission: | 11/2017 |
| Final protocol submission: | 01/2018 |



Reference ID: 4146227

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| Study completion: | 08/2018 |
| Final report submission: | 01/2019 |

**PMC 3248-6**: Conduct extractable/leachable studies on the drug product commercial container-closure system.

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| Protocol Submission: | 12/2017 |
| Interim Report: | 09/2018 |
| Study Completion: | 02/2019 |
| Final Report Submission: | 04/2019 |

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/s/

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