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Date of request: October 1st, 2018

NCCN Guidelines Panel: NCCN Prevention and Treatment of Cancer-Related Infections

On behalf of Melinta Therapeutics, Inc., I respectfully request the *NCCN Prevention and Treatment of Cancer-Related Infections Panel* to review the enclosed data supporting the inclusion of VABOMERE[®] (meropenem and vaborbactam) for Injection as a treatment option for patients with cancer and serious infections due to gram-negative bacteria, including complicated urinary tract infection (cUTI), acute pyelonephritis (AP), complicated intra-abdominal infections (cIAI), hospital-acquired bacterial pneumonia (HABP), ventilator-acquired bacterial pneumonia (VABP), and bacteremia, suspected or known to be caused by CRE

Specific Changes Requested: Inclusion of VABOMERE as a therapeutic option for the treatment of serious infections by: (1) adding VABOMERE to the FEV-5 *Initial Empiric Therapy for Fever and Neutropenia; IV Antibiotic Therapy*; and (2) adding VABOMERE to the FEV-A *Antibacterial Agents: Anti-Pseudomonal Agents* table.

FDA Indication and Usage (approved August 29, 2017): 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

Rationale: Patients with underlying malignancies, particularly hematologic malignancies, as well as transplantation recipients, are at increased risk for CRE infections due to many factors, including chemotherapy-induced gastrointestinal mucositis, underlying immunosuppression, prolonged hospital stay, and empiric and/or prophylactic use of broad-spectrum antimicrobial agents.² Mortality rates associated with CRE infections approach 40% in solid organ transplant recipients and 65% in patients with hematologic malignancies.

Overall, clinical and economic outcomes associated with CRE infections are extremely poor and are associated with high clinical failure and mortality rates, particularly in vulnerable patient populations. One recently published model estimated the US CRE infection incidence of 2.93 per 100,000 population (9,418 infections annually) and may cost hospitals approximately \$275 million annually (nearly \$30,000 per patient).³ Key cost drivers are adverse events including renal failure, inappropriate empiric therapy, and duration of hospital stay. When applied to patients with underlying malignancies, clinical failures, mortality rates and overall poor outcomes are expected to be at a greater magnitude due to the additional complexities associated with this patient population.

The current antimicrobial armamentarium to combat CRE is extremely limited. Patients with underlying malignancies must rely on timely, active antibacterial therapy to combat gram-negative infections with an CRE-active therapy. Beta-lactam antibiotics are among the most useful classes of antibiotics to treat infections caused by gram-negative bacteria.⁴ In 2013, the Centers for Disease Control and Prevention prioritized resistance to beta-lactam antibiotics as a serious or urgent antimicrobial resistance threat.

The Targeting Antibiotic Non-susceptible Gram-negative Organisms (TANGO) II trial was a pathogen-directed Phase 3 trial to evaluate the efficacy, safety, and tolerability of VABOMERE 4 g (meropenem 2 g and vaborbactam 2 g) as monotherapy compared to best available therapy (BAT) in the treatment of subjects with severe gram-negative infections suspected or known to be caused by KPC-producing CRE.⁵ VABOMERE as

monotherapy in the treatment of serious CRE infections such as cUTI/AP, cIAI, HABP/VABP, and bacteremia, was associated with significantly higher clinical cure rates, lower nephrotoxicity rates, and numerically lower mortality than BAT (individualized single or combination antibiotic therapy) in the overall study population. TANGO II included patients with underlying and active malignancy, including immunocompromised patients, patients with hematological malignancies, and hematopoietic stem cell transplant recipients.⁶ In this analysis of 72 patients randomized (VABOMERE:47; BAT:25), 22 (30.6%) patients had a prior diagnosis of malignancy of which 15 of these patients presented with a CRE pathogen (mCRE-MITT; microbiological carbapenem-resistant Enterobacteriaceae Modified Intent to Treat) and infection types of: bacteremia (53.3%; 8/15), cUTI/AP (20.0%; 3/15), HABP/VABP (13.3%; 2/15), and cIAI (13.3%; 2/15).

- Of the 15 patients with prior malignancy in the mCRE-MITT population, 8 patients received VABOMERE and 7 patients received BAT.⁶
 - Patients with underlying malignancy included solid tumor with/without metastases (n=9), leukemia (n=4), and lymphoma (n=2).⁶
 - 10 out of the 15 patients had active malignancy of which 7 received VABOMERE and 3 received BAT.⁷
- For patients with cancer in the VABOMERE treatment arm, the clinical cure rate at EOT (end of therapy; last dose up to 14 days) was 87.5% (7/8) versus 14.3% (1/7) for patients treated with BAT (difference, 73.2% [95% CI, 21.0, 96.4]).⁶ At TOC (test of cure; 7 days ± 2 days from EOT) patients treated with VABOMERE had a clinical cure rate of 75.0% (6/8) while those for BAT had a clinical cure rate of 0% (0/7) (difference, 75.0% [95% CI, 27.1, 96.8]).
- VABOMERE treatment was associated with a significant decrease in Day 28 mortality (absolute risk reduction 44.6%).⁶ Day 28 all-cause mortality in the VABOMERE and BAT treatment arms occurred in 12.5% (1/8) and 57.1% (4/7), respectively in cancer patients.
- Among patients with cancer, VABOMERE was associated with fewer drug-related treatment emergent adverse events (16.7% vs. 33.3%), fewer severe adverse events (25.0% vs. 77.8%), and fewer renal adverse events (8.3% vs. 22.2%) compared to BAT.⁶

Vaborbactam is the first beta-lactamase inhibitor from a novel chemical class of cyclic boronates for potent inhibition of Class A serine carbapenemases, including KPC enzymes.¹ Vaborbactam restores the activity of carbapenems against KPC-producing CRE in vitro and in nonclinical models of infection.^{1,4}

Vaborbactam significantly enhanced the activity of meropenem against KPC-producing strains with MIC-90 values ranging from 0.5 mg/L to 2 mg/L for VABOMERE versus ≥ 32 mg/L for meropenem alone.⁴ In vitro studies indicate that VABOMERE inhibited 99.5% of 10,426 Enterobacteriaceae clinical isolates collected worldwide during 2014 at ≤ 4 mg/L (FDA and CLSI breakpoints).⁸

VABOMERE also demonstrates in vitro activity against: *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Morganella morganii*, *Proteus mirabilis*, *Providencia* spp., *Pseudomonas aeruginosa*, and *Serratia marcescens*.¹

I respectfully request your consideration for inclusion of VABOMERE within the *NCCN Prevention and Treatment of Cancer-Related Infections Panel* guidelines as a treatment option for serious infections due to gram-negative bacteria, including cUTI/AP, cIAI, HABP/VABP, and bacteremia suspected or known to be caused by CRE due to the demonstrated efficacy of VABOMERE in this setting.

Sincerely,
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References (also included as enclosures):

1. VABOMERE Prescribing Information; Melinta Therapeutics.
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3. Bartsch SM, McKinnell JA, Mueller LE, et al. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. *Clin Microbiol Infect*. 2017;23(1):48.e49-48.e16.
4. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. <http://www.cdc.gov/drugresistance/threat-report-2013/>. Accessed July 2017.
5. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: The TANGO II randomized clinical trial. *Infect Dis Ther*. 2018; <https://doi.org/10.1007/s40121-018-0214-1>.
6. Viale P, Giamarellos-Bourboulis EJ, Humphries RM, Golan Y, Daikos GL, Loutit J, Spindler E, Zhang S, Walsh TJ, Alexander EL. Meropenem-vaborbactam versus best available therapy for carbapenem-resistant Enterobacteriaceae infections in TANGO II: Outcomes in patients with cancer. Poster P0285 presented at ECCMID; April, 2018; Madrid, Spain.
7. Data on File; Melinta Therapeutics.
8. Castanheira M, Huband M, Mendes R, Flamm R. Meropenem-vaborbactam tested against contemporary gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant Enterobacteriaceae. *Antimicrob Agents Chemother*. 2017;61(9):e00567-17.