Venatorx and Melinta Provide Update on Status of U.S. New Drug Application for Cefepime-Taniborbactam

No Clinical Safety or Efficacy Issues Identified

No Requirement for Further Clinical Data or Trials

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MALVERN, Pa. & PARSIPPANY, N.J.--(BUSINESS WIRE)--Venatorx Pharmaceuticals (Venatorx) and Melinta Therapeutics (Melinta) announced today that the U.S. Food and Drug Administration (FDA) issued a Complete Response Letter (CRL) regarding the New Drug Application (NDA) for cefepime-taniborbactam, a beta-lactam/beta-lactamase inhibitor (BL/BLI) combination antibiotic under review as a potential treatment for adult patients with complicated urinary tract infections (cUTI), including acute pyelonephritis caused by susceptible gram-negative microorganisms.

The CRL did not identify clinical safety or efficacy issues in the NDA, and the FDA did not request any new clinical trials to support the approval of cefepime-taniborbactam. The FDA requested additional chemistry, manufacturing, and controls (CMC) and related data about the drug, testing methods, and manufacturing process.

“While we are disappointed with this setback, we maintain utmost confidence in cefepime-taniborbactam. We are already hard at work generating the additional requested CMC data, and we will continue to work closely with the FDA so that we can make this important new medicine available to patients as quickly as possible,” said Christopher J. Burns, Ph.D., Chief Executive Officer of Venatorx.

Melinta Chief Executive Officer and President, Christine Ann Miller added, “We are committed to our plans of supporting the US commercialization of this drug, which we believe when approved, will offer healthcare providers an important therapy for adult patients suffering from complicated urinary tract infections including acute pyelonephritis caused by susceptible gram-negative microorganisms.”

About Cefepime-Taniborbactam
Cefepime-taniborbactam is an investigational intravenous (IV) beta-lactam/beta-lactamase inhibitor (BL/BLI) antibiotic combination being developed for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults.

Cefepime, a fourth-generation cephalosporin, is a widely used beta-lactam (BL) antibiotic with more than two decades of proven safety and clinical utility against susceptible gram-negative and gram-positive bacteria. Taniborbactam is a beta-lactamase inhibitor (BLI) that, in combination with

cefepime, is being studied as a potential treatment option for patients with serious bacterial infections caused by antibiotic resistant gram-negative bacteria, most notably Extended Spectrum Beta-lactamase (ESBL)-expressing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), and multidrug-resistant (MDR) *Pseudomonas aeruginosa* (MDR-PA), which can include carbapenem-resistant *P. aeruginosa* (CRPA).

Cefepime-taniborbactam has been granted Qualified Infectious Disease Product (QIDP) and Fast Track designations by the U.S. Food and Drug Administration (FDA). Fast Track designation is designed to facilitate the development, and to expedite the review of drugs to treat serious conditions that do not have sufficient treatment options. QIDP designation provides certain incentives for the development of new antibiotics, including priority review, as well as a five-year regulatory exclusivity extension. QIDP was authorized under the Generating Antibiotic Incentives Now (GAIN) Act of 2012, as part of the FDA Safety and Innovation Act, to underscore the urgency in development of new antibiotics.

About Gram-Negative Infections and Antimicrobial Resistance (AMR)
In a recent report on AMR, the U.S. Centers for Disease Control and Prevention (CDC) reported rates of resistance have increased significantly in the U.S. among bacterial pathogens including those commonly causing cUTI, pyelonephritis, and bacteremia. The CDC also cited that there are more than 2.8 million AMR infections annually in the U.S., which are directly related to more than 35,000 deaths.[1]

Between 2014 and 2019, an analysis of U.S. UTI patients determined that 4.4% of cases were carbapenem resistant (CR) and 24.5% of U.S. UTI patients were bacteremic with 1.7% of cases caused by a CR pathogen. Patients with CR infections had a significantly longer hospital length of stay (LOS), were less likely to be discharged home, had a higher readmission rate, and had greater LOS-associated charges than patients with carbapenem-susceptible infections. Additionally, patients with bacteremia (urosepsis) due to CR pathogens had a significantly higher rate of mortality than those with carbapenem susceptible pathogens.[2]

Gram-negative bacteria have multiple AMR mechanisms that continue to adapt in response to increases in antibiotic usage. Carbapenems are broad-spectrum antibiotics that have been widely used to treat infections caused by multidrug-resistant gram-negative bacteria, including Enterobacterales. With the increased global use of carbapenems, CRE have emerged, which have limited treatment options and are associated with increased morbidity and mortality. Resistance to carbapenems among Enterobacterales is primarily achieved by production of carbapenemases, which are enzymes capable of hydrolyzing carbapenem antibiotics and most other beta-lactams and fall into two distinct families: serine beta-lactamases and metallo-beta-lactamases (MBLs). K*lebsiella pneumoniae* carbapenemase (KPC), a class-A serine beta-lactamase, is one of the most prevalent carbapenemases, and New Delhi MBL (NDM) and Verona Integron-encoded MBL (VIM) are common variants of MBLs identified in gram-negative infections due to Enterobacterales and *P. aeruginosa.* According to an IHMA surveillance study in 2018-2019 and a JMI U.S. Surveillance study from 2021, MBLs were the most commonly identified carbapenem resistance mechanism globally among Enterobacterales isolates, with ~16 to 18% of U.S. CRE isolates carrying MBLs.[3,4]

While CRPA is also increasing in some geographies due to emergence of MBLs, MDR-PA, which may exhibit resistance to carbapenems, represents an increasing challenge for clinicians and their patients in the U.S. and globally due to the paucity of treatment options for this primarily hospital-associated pathogen. Especially outside the U.S., CRPA may carry carbapenemases including MBLs (i.e., VIM); however, non-carbapenemase resistance mechanisms (i.e., efflux pumps, porins) also contribute to the growing global resistance of MDR-PA and CRPA.[5]

If AMR infections continue on this trajectory, it has been projected that an estimated 10 million people will die per year of resistant infections by 2050—a number that surpasses the projected annual number of deaths (8.2 million) caused by cancer—and the cumulative cost to the global economy could be as high as U.S. $100 trillion.[6] In the U.S., estimates have reached as high as U.S. $20 billion in excess direct healthcare costs, with an additional U.S. $35 billion associated with lost productivity.[7] By 2050, the world is at risk of losing up to 3.8% of its annual gross domestic product with an annual shortfall of up to U.S. $3.4 trillion by 2030, a figure on par with losses attributable to the 2008 global financial crisis.[8]

The Infectious Disease Society of America (IDSA) maintains updated guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections online at https://www.idsociety.org/practice-guideline/amr-guidance/.[9] For those patients who do not respond to current treatment, new antibiotic therapies are needed to combat AMR.

About Complicated Urinary Tract Infections
Complicated UTIs, which include pyelonephritis, are defined as urinary tract infections ascending from the bladder accompanied by local and systemic signs and symptoms, including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness, that usually occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Bacteremia can arise secondary to infections like cUTI and can result in substantial morbidity and mortality. [1] Annually in U.S., it is estimated that more than 3 million cUTI patients will be diagnosed and require antibiotic therapy leading to over $6 billion in annualized 30-day costs.[10]

About Venatorx Pharmaceuticals
Venatorx is a private, late-stage clinical pharmaceutical company focused on improving health outcomes for patients with multidrug-resistant bacterial infections and hard-to-treat viral infections. Venatorx's lead program, cefepime-taniborbactam, is a clinical-stage antibiotic that completed a Phase 3 study in adults with complicated urinary tract infections (cUTI), including pyelonephritis. In October 2022, BARDA awarded a contract of up to $318M for development and procurement of cefepime-taniborbactam for the treatment of melioidosis and multi-drug resistant infections. Cefepime-taniborbactam is currently under review by the FDA for the treatment of cUTI, including acute pyelonephritis. Venatorx is also developing an oral antibacterial, ceftibuten-ledaborbactam (formerly known as VNRX-7145), for the treatment of cUTI, including pyelonephritis, caused by certain bacteria in adult patients with limited treatment options; this product is completing Phase 1 and will advance directly to a global Phase 3 cUTI clinical trial. For more information about Venatorx and its anti-infectives portfolio, please visit www.venatorx.com.

About Melinta Therapeutics LLC
Melinta Therapeutics is a biopharmaceutical company dedicated to providing innovative therapies to people impacted by acute and life-threatening illnesses. We focus our expanding portfolio on serving patients with an unmet need because that's how we make the most meaningful impact. At Melinta, we're visionaries dedicated to innovation while staying grounded in what matters most: patients. Our portfolio currently includes seven commercial-stage products: BAXDELA® (delafloxacin), KIMYRSA® (oritavancin), MINOCIN® (minocycline) for Injection, ORBACTIV® (oritavancin), REZZAYO® (rezafungin for injection), TOPROL-XL® (metoprolol succinate) and VABOMERE® (meropenem and vaborbactam). For more information about Melinta Therapeutics, our commitment to patients, and to learn about our portfolio of therapies, visit www.melinta.com.

Funding Partners and Collaborators for Cefepime-Taniborbactam
This project has been funded in part with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under

contract number HHSN272201300019C, and Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z, and has continued with federal funds from the Department of Health and Human Services; Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract numbers HHSO100201900007C and 75A50122C00080.

In September 2018, Venatorx entered into an exclusive license agreement with Everest Medicines to support the development, registration, and commercialization of cefepime-taniborbactam in Greater China, South Korea, and select countries in Southeast Asia. Everest will be solely responsible for the commercialization of cefepime-taniborbactam in its territory and Venatorx will be eligible to receive royalties on net sales.

In April 2020, Venatorx and the GARDP Foundation (GARDP) announced a collaboration to accelerate the development of, and access to, cefepime-taniborbactam for adult and pediatric populations. Venatorx has granted GARDP exclusive rights to distribute and sub-distribute cefepime-taniborbactam, once it is approved for clinical use, in low- and lower-middle-income countries.

In November 2023, Venatorx and Melinta entered into an exclusive License Agreement to facilitate a strategic partnership in the U.S. to commercialize cefepime-taniborbactam, a beta-lactam / beta-lactamase inhibitor (BL/BLI) combination antibiotic being developed for the treatment of complicated urinary tract infections (cUTI) and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults.

In December 2023, Venatorx entered into an agreement with Menarini Group, who acquired the exclusive rights to commercialize, upon approval of relevant health authorities, cefepime-taniborbactam in 96 countries in Europe, Latin America, Middle East, Turkey and North Africa and the Commonwealth of Independent States (CIS).

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