FDA Approves Merck’s RECARBRIO™ (imipenem, cilastatin, and relebactam) For the Treatment of Adults with Complicated Urinary Tract and Complicated Intra-Abdominal Bacterial Infections Where Limited or No Alternative Treatment Options Are Available

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KENILWORTH, N.J.--(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection, 1.25 grams, a new combination antibacterial. RECARBRIO is indicated in patients 18 years of age and older who have limited or no alternative treatment options, for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: Enterobacter cloacae, Escherichia coli, Klebsiella aerogenes, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

RECARBRIO is also indicated in patients 18 years of age or older who have limited or no alternative treatment options, for the treatment of complicated intra-abdominal infections (cIAI) caused by the following susceptible Gram-negative microorganisms: Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Fusobacterium nucleatum, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Parabacteroides distasonis and Pseudomonas aeruginosa.

Approval of these indications is based on limited clinical safety and efficacy data for RECARBRIO.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RECARBRIO and other antibacterial drugs, RECARBRIO 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.

Relebactam received FDA’s Qualified Infectious Disease Product (QIDP) designation for the treatment of cUTI and cIAI. The New Drug Application (NDA) for RECARBRIO received Priority Review designation from the FDA. Merck anticipates making RECARBRIO available later this year.

RECARBRIO is contraindicated in patients with a history of known severe hypersensitivity (severe systemic allergic reaction such as anaphylaxis) to any component of RECARBRIO. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. Central nervous system (CNS) adverse reactions, such as seizures, confusional states, and myoclonic activity, have been reported during treatment with imipenem/cilastatin, a component of RECARBRIO, especially when recommended dosages of imipenem were exceeded. These reactions have been reported most commonly in patients with CNS disorders (such as brain lesions or a history of seizures) and/or compromised renal function. Concomitant use of RECARBRIO, with valproic acid or divalproex sodium may increase the risk of breakthrough seizures. Additionally, Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including imipenem/cilastatin plus relebactam and may range in severity from mild diarrhea to fatal colitis. See Important Safety Information below.

RECARBRIO is a combination of imipenem/cilastatin and relebactam. Imipenem is a penem antibacterial drug, cilastatin sodium is a renal dehydropeptidase inhibitor, and relebactam is a beta lactamase inhibitor. Cilastatin limits the renal metabolism of imipenem and does not have antibacterial activity. The bactericidal activity of imipenem results from binding to PBP 2 and PBP 1B in Enterobacteriaceae and Pseudomonas aeruginosa and the subsequent inhibition of penicillin binding proteins (PBP). Inhibition of PFBs leads to the disruption of bacterial cell wall synthesis. Imipenem is stable in the presence of some beta lactamases. Relebactam has no intrinsic antibacterial activity. Relebactam protects imipenem from degradation by certain serine beta lactamases such as Sulhydryl Variable (SHV), Temoneira (TEM), Cefotaximase-Munich (CTX-M), Enterobacter cloacae P99 (P99), Pseudomonas-derived cephalosporinase (PDC), and Klebsiella-pneumoniae carbapenemase (KPC).
“RECARBRIO provides an important addition to our toolkit in the ongoing fight against infections caused by certain Gram-negative pathogens,” said Dr. Keith Kaye, professor of medicine and director of research for the division of infectious diseases, University of Michigan Health System, and a principal investigator in the clinical program. “RECARBRIO offers an additional treatment option for patients with cIAI and cUTI who have limited and, in some cases, no alternative therapeutic options.”

“Today’s announcement is a great example of Merck’s longstanding commitment to infectious diseases research and development, as we continue to search for novel ways to approach difficult-to-treat pathogens,” said Dr. Nick Kartsonis, senior vice president, infectious diseases and vaccines, Merck Research Laboratories.

Important Safety Information about RECARBRIO (imipenem, cilastatin, and relebactam)

CONTRAINDICATIONS

RECARBRIO is contraindicated in patients with a history of known severe hypersensitivity (severe systemic allergic reaction such as anaphylaxis) to any component of RECARBRIO.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta lactams. Before initiating therapy with RECARBRIO, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta lactams, and other allergens. If a hypersensitivity reaction to RECARBRIO occurs, discontinue the therapy immediately.

Seizures and Other Central Nervous System (CNS) Adverse Reactions: CNS adverse reactions, such as seizures, confusional states, and myoclonic activity, have been reported during treatment with imipenem/cilastatin, a component of RECARBRIO, especially when recommended dosages of imipenem were exceeded. These have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions including seizures occur, patients should undergo a neurological evaluation to determine whether RECARBRIO should be discontinued.

Increased Seizure Potential Due to Interaction with Valproic Acid: Concomitant use of RECARBRIO, with valproic acid or divalproex sodium may increase the risk of breakthrough seizures. Avoid concomitant use of RECARBRIO with valproic acid or divalproex sodium or consider alternative antibacterial drugs other than carbapenens.

Clostridium difficile-Associated Diarrhea (CDAD): Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including imipenem/cilastatin plus relebactam, 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 strains 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.

Development of Drug-Resistant Bacteria: Prescribing RECARBRIO in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adverse Reactions: The most frequently reported adverse reactions occurring in ≥2% of patients treated with imipenem/cilastatin plus relebactam 250 mg were diarrhea, nausea, headache, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, phlebitis/infusion site reactions, pyrexia, and hypertension.

About Merck

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world’s most challenging diseases. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.
Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2018 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information for RECARBRIÒ (imipenem, cilastatin, and relebactam) at https://www.merck.com/product/usa/pi_circulars/r/recarbrio/recarbrio_pi.pdf

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