



NEWS RELEASE

Merck Receives Positive EU CHMP Opinion for RECARBRIO™ (imipenem, cilastatin, and relebactam) for the Treatment of Infections Due to Aerobic Gram-Negative Organisms in Adults with Limited Treatment Options

12/16/2019

Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending RECARBRIO™ (imipenem, cilastatin, and relebactam), a new combination antibacterial agent, for approval. If approved by the European Commission, RECARBRIO would be indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

“Merck remains focused on developing new antibacterial medicines that provide meaningful benefit to patients fighting serious bacterial infections,” said Dr. Nicholas Kartsonis, senior vice president, infectious diseases and vaccines, Merck Research Laboratories. “The CHMP positive opinion marks an important milestone as we seek to provide European medical professionals an additional option for critically ill patients with Gram-negative bacterial infections.”

The CHMP positive opinion will now be considered by the European Commission. If the European Commission affirms the CHMP opinion, it will grant the centralized marketing authorization with unified labeling that is valid in the 28 countries that are members of the European Union, as well as European Economic Area members, Iceland, Liechtenstein and Norway.

RECARBRIO was approved by the U.S. Food and Drug Administration (FDA) in July 2019 for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI) caused by susceptible Gram-negative bacteria, in adults who have limited or no alternative treatment options. See full indication below.

About RECARBRIO™ (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg)

In the United States, 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 stercoris*, *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.

RECARBRIO is a combination of imipenem/cilastatin and relebactam, and is administered intravenously. 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 (PBPs). Inhibition of PBPs 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).

Selected Safety Information about RECARBRIO™ (imipenem, cilastatin, and relebactam)

Hypersensitivity Reactions: 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. 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 carbapenems.

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. 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.

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 $\geq 2\%$ of patients treated with

RECARBRIO were diarrhea (6%), nausea (6%), headache (4%), vomiting (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), phlebitis/infusion site reactions (2%), pyrexia (2%), and hypertension (2%).

Merck's Commitment to Infectious Diseases

For more than 100 years, Merck has contributed to the discovery and development of novel medicines and vaccines to combat infectious diseases. In addition to a combined portfolio of vaccines and antibacterial, antiviral and antifungal medicines, Merck has multiple programs that span discovery through late-stage development. To learn more about Merck's infectious diseases pipeline, visit www.merck.com.

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).

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Please see Prescribing Information for RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection (1.25 g) at

https://www.merck.com/product/usa/pi_circulars/r/recarbrio/recarbrio_pi.pdf

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