



NEWS RELEASE

## Results of Phase 3 Trial Evaluating the Efficacy and Safety of Merck's RECARBRIO™ (Imipenem, Cilastatin, and Relebactam) Versus Piperacillin and Tazobactam in Adult Patients with HABP/VABP Now Available

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U.S. Food and Drug Administration (FDA) Accepted for Review a Supplemental New Drug Application (sNDA) for RECARBRIO in Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia in February 2020

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced results from RESTORE-IMI 2, a randomized, controlled, double-blind Phase 3 clinical trial evaluating RECARBRIO™ (imipenem, cilastatin, and relebactam) for the treatment of adults with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP). The results demonstrated noninferiority of RECARBRIO compared to piperacillin and tazobactam (PIP/TAZ), the active comparator, in the primary and key secondary endpoints of the study, 28-day all-cause mortality and clinical response, respectively. In February 2020, the U.S. Food and Drug Administration (FDA) accepted for review a supplemental New Drug Application (sNDA) for use of RECARBRIO in this patient population. The FDA Prescription Drug User Fee Act (PDUFA) goal date is June 4, 2020. Phase 3 trial data are now available in a compendium of presentations **posted by Merck**, coinciding with **publication of study abstracts** by the 30th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID).

"We are pleased to post results from the RESTORE-IMI 2 clinical trial, which further demonstrate the potential of RECARBRIO to treat HABP/VABP due to certain susceptible Gram-negative pathogens," said Dr. Joan Butterson,

associate vice president, infectious disease clinical research, Merck Research Laboratories. “These data underscore Merck’s commitment to pursuing innovative options for those in need of novel antibiotic treatments.”

## RESTORE-IMI 2 Design

RESTORE-IMI 2 was a Phase 3 multinational, randomized, double-blind, non-inferiority trial evaluating the efficacy and safety of RECARBRIO versus PIP/TAZ in adult patients with HABP/VABP. In the study, 537 patients at 113 clinical trial sites were randomized 1:1 to receive a dose of RECARBRIO (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) or PIP/TAZ (piperacillin 4000 mg/tazobactam 500 mg), each given intravenously every six hours for seven to 14 days. Patients in both treatment groups also received open label empiric linezolid (600 mg) until baseline cultures confirmed absence of methicillin-resistant *Staphylococcus aureus* (MRSA). The primary endpoint was Day 28 all-cause mortality and the key secondary endpoint was clinical response at early follow-up (seven to 14 days after completing therapy).

## RESTORE-IMI 2 Results

RECARBRIO met its primary and key secondary endpoints, demonstrating non-inferiority compared to PIP/TAZ. For patients treated with RECARBRIO, Day 28 all-cause mortality (primary endpoint) was 15.9% (42/264) compared with 21.3% (57/267) in those treated with PIP/TAZ (adjusted treatment difference: 5.3%, 95% confidence interval [CI]: -11.9, 1.2). For patients treated with RECARBRIO, a favorable clinical response at early follow-up (key secondary endpoint) was observed in 60.9% (161/264) compared with 55.8% (149/267) in the PIP/TAZ group (adjusted treatment difference: 5%, 95% CI: -3.2, 13.2).

Rates of overall adverse events (AEs) were similar between treatment groups, with 84.9% (226/266) in the RECARBRIO arm vs. 86.6% (233/269) in the PIP/TAZ arm, reporting at least one AE. AEs classified as drug-related by the investigator were 12% (31/266) in the RECARBRIO arm vs. 10% (26/269) in the PIP/TAZ arm. Additionally, therapy discontinuations due to any AE were similar in both groups, with 6% (15/266) in the RECARBRIO arm vs. 8% (22/269) in the PIP/TAZ arm. Therapy discontinuations due to drug-related AEs were also similar: 2.3% (6/266) in the RECARBRIO arm vs. 1.5% (4/269) in the PIP/TAZ arm. The most frequently reported (>5 patients) drug-related AEs in the RECARBRIO arm were diarrhea and elevated levels of the liver function biomarkers alanine aminotransferase and aspartate aminotransferase (2% each [6/266]).

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

RECARBRIO was initially approved by the 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.

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 is 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.

## **Selected Safety Information for 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 (imipenem, cilastatin, and relebactam) 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):** 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](http://www.merck.com).

## About Merck

For more than 125 years, Merck, 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues

to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit [www.merck.com](http://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 the recent global outbreak of novel coronavirus disease (COVID-19); 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 2019 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](http://www.sec.gov)).

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

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