



## NEWS RELEASE

# FDA Approves Merck's RECARBRIO™ (imipenem, cilastatin, and relebactam) for the Treatment of Adults with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

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## RECARBRIO is Indicated to Treat Multiple Infections Caused by Susceptible Gram-Negative Bacteria in Adults

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, announced today that the U.S. Food and Drug Administration (FDA) has approved a supplemental New Drug Application (sNDA) for RECARBRIO™ (imipenem, cilastatin, and relebactam) for the treatment of patients 18 years of age and older with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms: *Acinetobacter calcoaceticus-baumannii* complex, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia marcescens*. 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. RECARBRIO is contraindicated in patients with a history of known severe hypersensitivity to any component of RECARBRIO. See Selected Safety Information below.

"Hospital-acquired infections continue to be a significant cause of illness and death despite advances in our understanding of the contributing factors and prevention of these diseases," 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. “Because these infections are often caused by difficult to treat Gram-negative organisms, new therapeutic options such as RECARBRIO are urgently needed for patients.”

RECARBRIO is a combination of imipenem, a carbapenem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor. Relebactam protects imipenem from degradation by certain serine beta-lactamases such as SHV (Sulfhydryl Variable), TEM (Temoneira), CTX-M (Cefotaximase-Munich), P99 (Enterobacter cloacae P99), PDC (Pseudomonas-derived cephalosporinase), and KPC (Klebsiella-pneumoniae carbapenemase).

The additional indication in HABP/VABP is based on results of the pivotal Phase 3 RESTORE-IMI 2 trial that compared RECARBRIO 1.25 grams (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) to piperacillin/tazobactam 4.5 grams (PIP/TAZ, piperacillin 4000 mg/tazobactam 500 mg), each administered intravenously every six hours for seven to 14 days, for the treatment of adult patients with HABP/VABP. RECARBRIO met the primary and key secondary endpoints, demonstrating non-inferiority to PIP/TAZ in 28-day all-cause mortality and clinical response at early follow-up, respectively. The RESTORE-IMI 2 study abstract was published by the 30th European Congress of Clinical Microbiology & Infectious Diseases (ECCMID).

“At a time of great public health concern about the need for new treatments to meet the evolving challenges posed by Gram-negative bacteria, we are proud to continue bringing new therapeutic options to health care practitioners in an effort to help them overcome the challenges in patient care,” said Dr. Nicholas Kartsonis, senior vice president, clinical research, infectious diseases and vaccines, Merck Research Laboratories. “Today’s approval is further affirmation of Merck’s steadfast commitment to meeting the needs of the health care community.”

RECARBRIO is also indicated in adults who have limited or no alternative treatment options for complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI) caused by susceptible Gram-negative bacteria, as described below. RECARBRIO is administered via intravenous injection.

## Clinical Data Supporting Use of RECARBRIO (imipenem, cilastatin, and relebactam) in HABP/VABP

The FDA approval of the use of RECARBRIO in HABP/VABP was based on the RESTORE-IMI 2 trial (NCT02493764), a Phase 3, multinational, randomized, double-blind, non-inferiority study evaluating the efficacy and safety of RECARBRIO (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) compared with PIP/TAZ (piperacillin 4000 mg/tazobactam 500 mg) in adults with HABP/VABP. In the study, 535 hospitalized adults with HABP/VABP in 113 trial sites were randomized 1:1 to receive a dose of RECARBRIO or PIP/TAZ, each given intravenously every six hours for seven to 14 days. The primary efficacy endpoint was incidence of all-cause mortality through Day 28 in the modified intent-to-treat (MITT) population, which is defined as all randomized participants who received at least

one dose of trial treatment and did not have only Gram-positive cocci on Gram stain of a baseline lower respiratory tract (LRT) specimen. The key secondary endpoint was clinical response at early follow-up (seven to 14 days after completing therapy) in the MITT population.

The mean age of patients in the study was 60 years, 43% of patients were 65 years of age and older, 31% were female, and 22% had polymicrobial infection. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 15, and 48% of patients had an APACHE II score greater than or equal to 15 at baseline. Overall, 260 (49%) patients were ventilated at enrollment, including 194 (36%) patients with VABP and 66 (12%) patients with ventilated HABP. Concurrent bacteremia was present at baseline in 5.8% of patients.

RECARBRIO met the primary and key secondary endpoints, demonstrating non-inferiority to PIP/TAZ. For patients treated with RECARBRIO, 28-day all-cause mortality was 15.9% (42/264) and 21.3% (57/267) in those treated with PIP/TAZ, for a treatment difference of -5.3% (95% confidence interval [CI]: -11.9, 1.2). Clinical response at early follow-up was 61% (161/264) for RECARBRIO and 55.8% (149/267) for PIP/TAZ group, for a treatment difference of 5% (95% CI: -3.2, 13.2).

In the subgroup of patients with ventilated HABP/VABP at enrollment, a favorable response in 28-day all-cause mortality was observed at 19.7% (24/122) for RECARBRIO and 30.9% (42/136) for PIP/TAZ, for a treatment difference of -11.2% (95% CI: -21.6, -0.5). In the subgroup of patients with non-ventilated HABP at enrollment, 28-day all-cause mortality was 12.7% (18/142) for RECARBRIO and 11.5% (15/131) for PIP/TAZ, for a treatment difference of 1.2% (95% CI: -6.8, 9.1).

Serious adverse reactions occurred in 27% (71/266) of patients receiving RECARBRIO and 32% (86/269) of patients receiving PIP/TAZ. Deaths were reported in 15% (40/266) of patients receiving RECARBRIO and 21% (57/269) of patients receiving PIP/TAZ. Adverse reactions leading to discontinuation occurred in 5.6% (15/266) of patients receiving RECARBRIO and 8.2% (22/269) of patients receiving PIP/TAZ. The most frequently reported adverse reactions occurring in 4% or greater of patients treated with RECARBRIO were increased aspartate aminotransferase (11.7%), anemia (10.5%), increased alanine aminotransferase (9.8%), diarrhea (7.9%), hypokalemia (7.9%), hyponatremia (6.4%), constipation (4.1%), pyrexia (4.1%) and rash (4.1%).

RECARBRIO was also studied in patients with cIAI, cUTI, and HABP/VABP caused by imipenem-nonsusceptible pathogens, in a non-inferential trial which used colistin (loading dose to achieve 300 mg colistin base activity, followed by maintenance doses up to 150 mg colistin base activity, every 12 hours) plus imipenem (500 mg every 6 hours) as the active comparator (RESTORE-IMI 1; NCT02452047). This trial, which included 47 patients, provided only limited efficacy and safety information.

## 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.

**Clostridioides difficile-Associated Diarrhea (CDAD):** Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including RECARBRIO, 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:** In the cUTI and cIAI trials, 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%). In the HABP/VABP study, the most frequently reported adverse reactions occurring in  $\geq 4\%$  of patients treated with RECARBRIO were increased aspartate aminotransferase (11.7%), anemia

(10.5%), increased alanine aminotransferase (9.8%), diarrhea (7.9%), hypokalemia (7.9%), hyponatremia (6.4%), constipation (4.1%), pyrexia (4.1%) and rash (4.1%).

## About RECARBRIO (imipenem, cilastatin, and relebactam)

RECARBRIO is indicated for the treatment of patients 18 years of age and older with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, caused by the following susceptible Gram-negative microorganisms: *Acinetobacter calcoaceticus-baumannii* complex, *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Serratia marcescens*.

RECARBRIO is also 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 and 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 the cUTI and cIAI indications are 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.

## 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) 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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