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Recarbrio (imipenem, cilastatin, and relebactam) for Injection Clinical Update

Clinical Update: FDA Approves Merck's Recarbrio (imipenem, cilastatin, and relebactam) for the Treatment of Adults with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP).
FDA approval date: June 4, 2020

Recarbrio (imipenem, cilastatin, and relebactam) is a combination of imipenem, a penem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a betalactamase inhibitor, indicated for the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults.

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-baumanniicomplex, 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.

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%).