

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s)	Brad Moriyama, Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 18, 2019
Subject	Evaluation of Need for a REMS
Established Name	Imipenem, cilastatin, and relebactam
Trade Name	Recarbrio
Name of Applicant	Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc.
Therapeutic Class	Carbapenem antibacterial agent, renal dehydropeptidase inhibitor, beta-lactamase inhibitor
Formulation(s)	Recarbrio 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) vial
Dosing Regimen	Recarbrio 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) by intravenous infusion every 6 hours

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Recarbrio (imipenem, cilastatin, and relebactam) is necessary to ensure the benefits outweigh its risks. Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc. submitted a New Drug Application (NDA) 212819 for imipenem, cilastatin, and relebactam with the proposed indication for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis and complicated intra-abdominal infections (cIAI) caused by susceptible gram-negative bacteria (reserve for use in patients who have limited or no alternative treatment options). The serious risks associated with imipenem, cilastatin, and relebactam include hypersensitivity reactions, seizures and other central nervous system adverse reactions, increased seizure potential due to interaction with valproic acid, *Clostridium difficile*-associated diarrhea, and the development of drug-resistant bacteria. The applicant did not submit a proposed REMS but submitted a risk management plan with this application.

DRISK and DAIP agree that a REMS is not necessary to ensure the benefits of imipenem, cilastatin, and relebactam outweigh its risks. The efficacy of imipenem, cilastatin, and relebactam in cUTI and cIAI was supported by previous studies of imipenem and cilastatin in these infections and the efficacy of relebactam was supported *in vitro* and in animal models of infection. The serious risk associated with imipenem, cilastatin, and relebactam will be addressed in the warnings and precautions section of the label. In addition, approved beta-lactam and beta-lactamase inhibitor combinations also do not have a boxed warning in their respective labels or have required a REMS for approval.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Recarbrio (imipenem, cilastatin, and relebactam) is necessary to ensure the benefits outweigh its risks. Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc. submitted a New Drug Application (NDA) 212819 for imipenem, cilastatin, and relebactam with the proposed indication for the treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis and complicated intra-abdominal infections (cIAI) caused by susceptible gram-negative bacteria (reserve for use in patients who have limited or no alternative treatment options).¹ This application is under review in DAIP. The applicant did not submit a REMS with this application but submitted a risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Recarbrio (imipenem, cilastatin, and relebactam), a NME, is a combination of a carbapenem antibacterial agent, a renal dehydropeptidase inhibitor, and a beta-lactamase inhibitor, proposed for the treatment of patients 18 years of age and older with cUTI including pyelonephritis and cIAI caused by susceptible gram-negative bacteria (reserve for use in patients who have limited or no alternative

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

treatment options). Relebactam is a NME and imipenem and cilastatin (Primaxin) is a 505(b)(2) submission. Relebactam is a diazobicyclooctane beta-lactamase inhibitor that is active against beta-lactamases including AmpC, extended-spectrum beta-lactamase (ESBL), and *Klebsiella pneumoniae* carbapenemase (KPC).² It was developed by the sponsor to restore activity of imipenem in carbapenem-resistant gram-negative bacterial infections. Imipenem, cilastatin, and relebactam is supplied as a 1.25 gram vial for IV injection (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg). The proposed dosing regimen is Recarbrio 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) IV over 30 minutes every 6 hours.^b The combination of imipenem, cilastatin, and relebactam is not currently approved in any jurisdiction. Imipenem, cilastatin, and relebactam was designated as a qualified infectious disease product (QIDP) and fast track designation.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for imipenem, cilastatin, and relebactam NDA 212819 relevant to this review:

- 09/13/2013: Qualified infectious disease product designation and fast track designation granted
- 11/16/2018: NDA 212819 submission for the treatment of patients 18 years of age and older with cUTI including pyelonephritis and cIAI caused by susceptible gram-negative bacteria
- 03/18/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for imipenem, cilastatin, and relebactam

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

3.1.1 Complicated Urinary Tract Infections

Complicated urinary tract infections, as defined by the FDA Guidance for Industry in 2018, are a clinical syndrome of pyuria and a documented pathogen in blood or urine. It involves signs and symptoms of fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness in patients with a functional or anatomical abnormality of the urinary tract or a catheter.³ Pathogens causing cUTI include *Escherichia coli*, *Enterococcus* spp., *Klebsiella pneumoniae*, *Candida* spp., *Staphylococcus aureus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and group B *Streptococcus*.⁴ Bacterial resistance is an important issue with urinary tract infections, especially with the emergence of infections caused by ESBL producing bacteria or carbapenem-resistant Enterobacteriaceae (CRE).⁵ A study from 1997 to 2001 using data from the Group Health Cooperative in Seattle, Washington revealed an annual rate of outpatient and inpatient pyelonephritis in women of 12 to 13 cases per 10,000 population and 3 to 4

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

cases per 10,000 population, respectively.^{6,c} Furthermore, a prevalence survey by the CDC estimated in 2011 that there were 35,600 catheter-associated urinary tract infections in acute care hospitals in the United States.⁷ However, a repeat prevalence survey by the CDC in 2015 revealed a reduction in catheter-associated urinary tract infections which may have been due to preventative strategies.⁸ Catheter-associated urinary tract infections may lead to secondary bloodstream infections and are associated with an increased morbidity and mortality.^{4,d}

3.1.2 Complicated Intra-abdominal Infections

Complicated intra-abdominal infections are infections that extend beyond the hollow viscus of origin into the peritoneal space and are associated with abscess formation or peritonitis.⁹ The clinical diagnosis of cIAI, listed in the FDA Guidance for Industry in 2018, include intra-abdominal abscess, perforation of intestine, peritonitis, appendicitis with perforation or periappendiceal abscess, cholecystitis with perforation or abscess, and diverticulitis with perforation, peritonitis, or abscess.¹⁰ Bacterial pathogens causing cIAI include gram-negative aerobic bacteria, anaerobic bacteria, and gram-positive bacteria. As with cUTI, the emergence of bacterial resistance is an important issue with cIAI. A common cause of cIAI is appendicitis.¹¹ A summary of the National Hospital Discharge Survey by the CDC estimated in 2006 that 318,000 inpatients were discharged from short stay hospitals in the United States with the diagnosis of appendicitis.^{12c} Complicated intra-abdominal infections are also associated with an increased morbidity and mortality.¹¹ A worldwide multicenter observational study from October 2012 to March 2013 revealed an overall mortality rate of 10.5% with cIAI.^d

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The Antibiotic Resistance Threats in the United States report by the CDC in 2013 listed CRE, including carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *E. coli*, as an urgent threat and multidrug-resistant *P. aeruginosa* as a serious threat.¹³ A common mechanism of carbapenem resistance in CRE is the production of KPC.^{14,15} *Klebsiella pneumoniae* carbapenemase producing bacterial infections including cUTI and cIAI may be associated with a high mortality rate and treatment options in the past were limited. Antibacterial agents that were used for treatment of KPC producing bacterial infections, depending on the site of infection, included colistin, polymyxin B, tigecycline, and aminoglycosides.^{16,17,18}

Recently, three antibacterial agents with *in vitro* activity against KPC producing bacteria including ceftazidime and avibactam (Avycaz), meropenem and vaborbactam (Vabomere), and plazomicin (Zemdri) have been approved by the FDA.^{19,20,21} Ceftazidime and avibactam, a combination of a cephalosporin and a beta-lactamase inhibitor, was approved by the FDA in 2015 for the treatment of cIAI, cUTI including pyelonephritis, hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP). Meropenem and vaborbactam, a combination of a carbapenem

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

and a beta-lactamase inhibitor, was approved by the FDA in 2017 for the treatment of cUTI including pyelonephritis. Neither beta-lactam and beta-lactamase inhibitor combination has a boxed warning in their respective labels or have required a REMS for approval. Plazomicin, an aminoglycoside antibacterial agent, was approved by the FDA in 2018 for the treatment of cUTI including pyelonephritis. As with other aminoglycosides, plazomicin has a boxed warning for nephrotoxicity, ototoxicity, neuromuscular blockage, and fetal harm.

Antimicrobial agents that are treatment options for KPC producing bacterial infections are summarized in Table 1 in the appendix.¹⁸

4 Benefit Assessment

The trials supporting this application for imipenem, cilastatin, and relebactam consisted of two Phase 2 studies for the efficacy and safety in cUTI (NCT 01505634) and cIAI (NCT 01506271), and a Phase 3 study for the efficacy and safety in imipenem nonsusceptible infections including HABP, VABP, cIAI, and cUTI (NCT 02452047).²²

Study NCT 01505634 (PN003) was a multicenter, randomized, double-blind, placebo controlled, and active-controlled trial. The primary efficacy endpoint was clinical-microbiological response. Patients could be switched to oral ciprofloxacin after a minimum of four days of IV therapy. Patients (N=302) were randomized to imipenem 500 mg/cilastatin 500 mg + relebactam 250 mg IV every 6 hours (N= 74 MITT population), imipenem 500 mg/cilastatin 500 mg + relebactam 125 mg IV every 6 hours (N= 82 MITT population), or imipenem 500 mg/cilastatin 500 mg + placebo IV every 6 hours (N= 81 MITT population). The success rate for the primary efficacy endpoint at the discontinuation of IV trial treatment (DCIV) visit was 85.1% in the imipenem, cilastatin + relebactam 250 mg group, 86.6% in the imipenem, cilastatin + relebactam 125 mg group, and 92.6% in the imipenem and cilastatin group. The success rate for the primary efficacy endpoint at the early follow-up (EFU) visit was 54.1% in the imipenem, cilastatin + relebactam 250 mg group, 59.8% in the imipenem, cilastatin + relebactam 125 mg group, and 61.7% in the imipenem and cilastatin group.

Study NCT 01506271 (PN004) was a multicenter, randomized, double-blind, placebo controlled, and active-controlled trial. The primary efficacy endpoint was global response. Patients (N=351) were randomized to imipenem 500 mg/cilastatin 500 mg + relebactam 250 mg IV every 6 hours (N= 89 MITT population), imipenem 500 mg/cilastatin 500 mg + relebactam 125 mg IV every 6 hours (N= 96 MITT population), or imipenem 500 mg/cilastatin 500 mg + placebo IV every 6 hours (N= 92 MITT population). The success rate for the primary efficacy endpoint at the global follow-up (GFU) visit was 86.5% in the imipenem, cilastatin + relebactam 250 mg group, 89.6% in the imipenem, cilastatin + relebactam 125 mg group, and 84.8% in the imipenem and cilastatin group.

Study NCT 02452047 (PN013) was a multicenter, randomized, double-blind, placebo controlled, and active-controlled trial. The primary efficacy endpoint was favorable overall response. Patients (N=47) were randomized to imipenem 500 mg/cilastatin 500 mg, and relebactam 250 mg IV every 6 hours + placebo (N= 21 mMITT population) or imipenem 500 mg/cilastatin 500 mg IV every 6 hours + colistin (N= 10 mMITT population). Three patients also received imipenem, cilastatin, and relebactam in the open

label arm of the trial. The success rate for the primary efficacy endpoint was 71.4% in the imipenem, cilastatin, and relebactam group and 70% in the imipenem and cilastatin + colistin group.

The FDA clinical reviewer concluded the efficacy of imipenem, cilastatin, and relebactam in cUTI and cIAI was supported by previous studies of imipenem and cilastatin in these infections and the efficacy of relebactam was supported *in vitro* and in animal models of infection.^e They concluded that studies PN003, PN004, and PN013 were not designed for formal hypothesis for inferential testing. Study PN003 and PN004 were designed to assess safety and dose selection and Study PN013 was designed for estimation.

5 Risk Assessment & Safe-Use Conditions^f

The safety of imipenem, cilastatin, and relebactam was evaluated in two Phase 2 clinical trials for the treatment of cUTI (NCT 01505634, PN003) and cIAI (NCT 01506271, PN004) and a Phase 3 trial for the treatment of imipenem nonsusceptible infections including HABP, VABP, cIAI, and cUTI (NCT 02452047, PN013).²² In the combined safety population from PN003 and PN004, 431 patients received imipenem, cilastatin, and relebactam and 214 patients received imipenem and cilastatin. Discontinuation from treatment due to an adverse event occurred in 4/216 (1.9%) in the imipenem, cilastatin, and relebactam 250 mg group, 6/215 (2.8%) in the imipenem, cilastatin, and relebactam 125 mg group, and 5/214 (2.3%) in the imipenem and cilastatin group. Common treatment emergent adverse events reported with imipenem, cilastatin, and relebactam included nausea, diarrhea, vomiting, headache, increased alanine aminotransferase, and increased aspartate aminotransferase.

In the safety population from PN013, 31 patients received imipenem, cilastatin, and relebactam (randomized treatment group), 16 patients received imipenem and cilastatin + colistin (randomized treatment group), and three patients received imipenem, cilastatin, and relebactam in the open label treatment group. Adverse reactions reported with imipenem, cilastatin, and relebactam in the randomized treatment group included increased aspartate aminotransferase, increased alanine aminotransferase, pyrexia, infusion site reactions, nausea, decreased hemoglobin, creatinine change/renal injury, and dyspnea.

There were 11 deaths in the imipenem, cilastatin, and relebactam development program. In Study PN004, three deaths occurred in the randomized phase in the imipenem, cilastatin, and relebactam 125 mg group due to ventricular fibrillation, intestinal infarction, and septic shock. In Study PN003, two deaths occurred after the 14 day follow-up period in the imipenem, cilastatin, and relebactam 250 mg group due to progression of renal cancer and cardiac arrest. Six deaths were reported in Study PN013.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

Two deaths occurred in the randomized phase in the imipenem, cilastatin, and relebactam group due to worsening pneumonia/systemic inflammatory response syndrome and lung infection. One death occurred in the open label imipenem, cilastatin, and relebactam group due to septic shock. In addition, three deaths occurred in the randomized phase in the imipenem and cilastatin + colistin group due to septic shock, subarachnoid hemorrhage, and ventricular tachycardia. The deaths during the randomized phase in these studies were deemed unrelated by the clinical reviewer to the study drug or comparator.

The serious risk⁹ associated with imipenem, cilastatin, and relebactam which include hypersensitivity reactions, seizures and other central nervous system adverse reactions, increased seizure potential due to interaction with valproic acid, *Clostridium difficile*-associated diarrhea, and the development of drug resistant bacteria are summarized in the sections below. These risks are also listed in the warnings and precautions section in the imipenem and cilastatin label.²³

5.1 HYPERSENSITIVITY REACTIONS

Imipenem, cilastatin, and relebactam is contraindicated in patients with severe hypersensitivity to any of the components of imipenem, cilastatin, and relebactam. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 SEIZURES AND OTHER CENTRAL NERVOUS SYSTEM ADVERSE REACTIONS

Seizures, confusional states, and myoclonic activity have been reported with imipenem, cilastatin, and relebactam and imipenem and cilastatin. One patient in the imipenem, cilastatin, and relebactam open label group in Study PN013 experienced a generalized tonic clonic seizure. The patient received an additional dose of non study drug imipenem and cilastatin. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 INCREASED SEIZURE POTENTIAL DUE TO INTERACTION WITH VALPROIC ACID

The concomitant use of imipenem and cilastatin with valproic acid/divalproex sodium may lead to a decrease in valproic acid concentrations and an increase risk of breakthrough seizures. The administration of imipenem, cilastatin, and relebactam with valproic acid/divalproex sodium is not recommended. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4 CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA

The use of antibacterial agents is a risk factor for *C. difficile* infection. This infection may be serious with an increased morbidity and mortality. Three patients in the imipenem, cilastatin, and relebactam

⁹ Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

groups in PN003 and PN004 experienced *C. difficile* colitis and infection, with one case thought to be related to imipenem, cilastatin, and relebactam by the study investigators. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.5 DEVELOPMENT OF DRUG-RESISTANT BACTERIA

As with other antibacterial agents, using imipenem, cilastatin, and relebactam in the absence of a proven or suspected bacterial infection may increase the risk of bacterial resistance. If approved, this risk will be communicated in the warnings and precautions section of the label.



(b) (4) The imipenem, cilastatin, and relebactam proposed label is being revised to mitigate the risk of preparation errors. The review division is also planning to work with the applicant to update the imipenem and cilastatin label. Revisions should include instructions for preparation of doses that do not correspond to the vial size (doses for CLcr < 90 mL/min, 1000 mg doses, and pediatric dosages) to mitigate the risk of preparation errors.

6 Expected Postmarket Use

If approved, imipenem, cilastatin, and relebactam will primarily be used in both inpatient and outpatient (such as infusion centers or home infusion) settings. The likely prescribers will be internal medicine practitioners, critical care medicine practitioners, and infectious diseases specialists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for imipenem, cilastatin, and relebactam beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of imipenem, cilastatin, and relebactam on the basis of the efficacy and safety information currently available. Imipenem, cilastatin, and relebactam is a combination of a carbapenem antibacterial agent, a renal dehydropeptidase inhibitor, and a beta-lactamase inhibitor with *in vitro* activity against KPC producing CRE and may be an additional treatment option for cUTI including pyelonephritis and cIAI caused by KPC producing CRE. The efficacy of imipenem, cilastatin, and relebactam in cUTI and cIAI was supported by previous studies of imipenem

and cilastatin in these infections and the efficacy of relebactam was supported *in vitro* and in animal models of infection.

The serious risk associated with imipenem, cilastatin, and relebactam which include hypersensitivity reactions, seizures and other central nervous system adverse reactions, increased seizure potential due to interaction with valproic acid, *Clostridium difficile*-associated diarrhea, and the development of drug-resistant bacteria will be addressed in the warnings and precautions section of the label. These serious risks are also listed in the warnings and precautions section in the imipenem and cilastatin label. No new major safety issues were identified with imipenem, cilastatin, and relebactam when compared to imipenem and cilastatin.²²

Complicated urinary tract infections and cIAI are serious infections that may be associated with increased morbidity and mortality. Furthermore, KPC producing CRE infections may be life threatening and are associated with a high mortality rate. The likely prescribers of imipenem, cilastatin, and relebactam are internal medicine practitioners, critical care medicine practitioners, and infectious diseases specialists who should have experience prescribing beta-lactam and beta-lactamase inhibitor combination antimicrobial agents. Based on the efficacy and risk associated with imipenem, cilastatin, and relebactam for the treatment of cUTI including pyelonephritis and cIAI, this reviewer's recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for imipenem, cilastatin, and relebactam to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 TABLE 1: TREATMENT OPTIONS FOR KPC PRODUCING BACTERIAL INFECTIONS

Generic Name	Trade Name	Boxed Warning/Major Safety and Tolerability Issues	Risk Management Approaches
ceftazidime and avibactam ¹⁹	Avycaz	Decreased clinical response in adult cIAI patients with baseline CrCl of 30 to \leq 50 mL/min, central nervous system reactions	Warnings and precautions in label
meropenem and vaborbactam ²⁰	Vabomere	Seizure potential, risk of breakthrough seizures due to drug interaction with valproic acid, thrombocytopenia, potential for neuromotor impairment	Warnings and precautions in label
plazomicin ²¹	Zemdri	Boxed warning: nephrotoxicity, ototoxicity, neuromuscular blockade, fetal harm	Boxed warning, warnings and precautions in label
colistin ²⁵		nephrotoxicity, neurotoxicity	Warnings and precautions in label
polymyxin B ²⁶		Boxed warning: nephrotoxicity, neurotoxicity, neuromuscular blockade, safety in pregnancy not established	Boxed warning, warnings and precautions in label
tigecycline ²⁷	Tygacil	Boxed warning: All-cause mortality Mortality imbalance and lower cure rates in hospital-acquired pneumonia, hepatic adverse effects, pancreatitis, fetal harm, tooth discoloration, sepsis/septic shock in patients with intestinal perforation, tetracycline class adverse effects (photosensitivity, pseudotumor cerebri, anti-anabolic action)	Boxed warning, warnings and precautions in label
amikacin ²⁸		Boxed warning: nephrotoxicity, ototoxicity, neurotoxicity, neuromuscular blockade and respiratory paralysis Fetal harm	Boxed warning, warnings and precautions in label
gentamicin ²⁹		Boxed warning: nephrotoxicity, ototoxicity, neurotoxicity, fetal harm Neuromuscular blockade and respiratory paralysis	Boxed warning, warnings and precautions in label

10.2 REFERENCES

¹ Proposed prescribing information for imipenem, cilastatin, and relebactam as currently edited by FDA, Accessed 5/24/2019.

² Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc. Imipenem/relebactam. Module 2.5. clinical overview. November 16, 2018.

³ Refer to Guidance for Industry Complicated Urinary Tract Infections: Developing Drugs for Treatment for more information (<https://www.fda.gov/media/71313/download>)

⁴ Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol*. 2015;13(5):269-84.

⁵ Steiger SN, Comito RR, Nicolau DP. Clinical and economic implications of urinary tract infections. *Expert Rev Pharmacoecon Outcomes Res*. 2017;17(4):377-383.

⁶ Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clin Infect Dis*. 2007;45(3):273-80.

⁷ Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370(13):1198-208.

⁸ Magill SS, O'Leary E, Janelle SJ, et al. Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. *N Engl J Med*. 2018;379(18):1732-1744.

⁹ Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133-64.

¹⁰ Refer to Guidance for Industry Complicated Intra-Abdominal Infections: Developing Drugs for Treatment for more information (<https://www.fda.gov/media/84691/download>)

¹¹ Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. *World J Emerg Surg*. 2014;9:37.

¹² Buie VC, Owings MF, DeFrances CJ, Golosinskiy A. National hospital discharge survey: 2006 annual summary. *Vital Health Stat 13*. 2010;168:1-79.

¹³ Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>. Accessed April 16, 2019.

¹⁴ Woodworth KR, Walters MS, Weiner LM, et al. Vital Signs: Containment of Novel Multidrug-Resistant Organisms and Resistance Mechanisms - United States, 2006-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(13):396-401.

¹⁵ Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J Infect Dis*. 2017;215(suppl_1):S28-S36.

¹⁶ Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis*. 2009;9(4):228-36.

¹⁷ Meropenem/vaborbactam (Vabomere) for complicated urinary tract infection. *Med Lett Drugs Ther*. 2018;60(1549):103-105.

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- ¹⁸ Plazak ME, Tamma PD, Heil EL. The antibiotic arms race: current and emerging therapy for *Klebsiella pneumoniae* carbapenemase (KPC) - producing bacteria. *Expert Opin Pharmacother*. 2018;19(18):2019-2031.
- ¹⁹ Avycaz (ceftazidime and avibactam) package insert. Madison, NJ: Allergan USA, Inc.; 2019 March.
- ²⁰ Vabomere (meropenem and vaborbactam) package insert. Lincolnshire, IL: Melinta Therapeutics, Inc.; 2018 July.
- ²¹ Zemdri (plazomicin) package insert. South San Francisco, CA: Achaogen, Inc.; 2018 June.
- ²² Imipenem, cilastatin, and relebactam multi-disciplinary review and evaluation. Accessed 6/6/2019.
- ²³ Primaxin (imipenem and cilastatin) package insert. Whitehouse Station, NJ: Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc.; 2018 December.
- ²⁴ Division of Medication Error Prevention and Analysis. Recarbrio NDA 212819 internal meeting. Discussion re: preparation in renal insufficient patients, April 9, 2019.
- ²⁵ Colistimethate package insert. Schaumburg, IL: Sagent Pharmaceuticals; 2018 March.
- ²⁶ Polymyxin B package insert. Schaumburg, IL: Athenex; 2018 December.
- ²⁷ Tygacil (tigecycline) package insert. Philadelphia, PA: Wyeth Pharmaceuticals LLC; 2018 April.
- ²⁸ Amikacin package insert. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2018 July.
- ²⁹ Gentamicin package insert. Lake Zurich, IL: Fresenius Kabi; 2015 November.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRAD T MORIYAMA
06/18/2019 05:17:43 PM

ELIZABETH E EVERHART
06/19/2019 08:53:43 AM
I concur.

CYNTHIA L LACIVITA
06/20/2019 02:14:45 PM
Concur

Clinical Inspection Summary

Date	June 5, 2019
From	Aisha Johnson, MD, MPH, MBA, Medical Officer Min Lu, MD, Acting Team Leader Kassa Ayalew, MD, MPH, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shrimant Mishra, MD, Medical Officer Meklit Workneh, MD, Clinical Team Leader Christopher Smith, Pharm D, Regulatory Project Manager Division of Anti-Infective Products (DAIP)
NDA #	212,819
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.
Drug	Imipenem/cilastatin/relbactam (IMI/REL, MK-7655A)
NME (Yes/No)	Yes
Therapeutic Classification	Antibacterial- Systemic
Proposed Indication(s)	Treatment infections due to gram-negative bacteria, including complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI).
Consultation Request Date	11 January 2019
Summary Goal Date	16 May 2019; Extended to 16 June, 2019
Action Goal Date	16 July 2019
PDUFA Date	16 July 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from three studies were submitted as the primary efficacy and safety studies in support of this 505(b)(1) NDA for imipenem/cilastatin/relbactam (IMI/REL). Two Phase 2, dose-ranging studies were conducted in patients with complicated urinary tract infection (Study 003) and complicated intra-abdominal infection (Study 004). Both Phase 2 studies evaluated IMI + REL compared with IMI + placebo to establish non-inferiority. A single Phase 3 study (Study 013) was conducted to evaluate the efficacy and safety of the FDC IMI/REL (500 mg/250 mg) in patients with gram-negative imipenem-nonsusceptible bacterial infections, specifically complicated urinary tract infection (cUTI), complicated intrabdominal infection (cIAI), and hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP).

Seven study sites were selected for clinical inspection as part of PDUFA pre-approval clinical investigation and data validation.

The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the proposed indication.

The final regulatory compliance classification for the sites of Dr. Dzintra Litavniece, Dr. Valeri Mariyanovski, Dr. Christopher Lucasti, Dr. Joahann Motsch, and Dr. Kadri Tamme is no action indicated (NAI). The preliminary regulatory compliance classification for Dr. Ülo Kivistik's site is VAI.

The preliminary regulatory classification for Dr. Liviu Vasile's site is NAI.

A clinical inspection summary addendum will be generated if conclusions change upon receipt and review of the final Establishment Inspection Reports (EIRs). Preliminary classification is based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity.

II. BACKGROUND

The proposed product is a fixed dose combination (FDC) of IMI (imipenem/cilastatin) and relebactam (REL, also known as MK-7655). Relebactam (REL) is a small-molecule non- β -lactamase inhibitor. IMI is a carbapenem β -lactam antibiotic that has been approved for over 30 years (marketed as PRIMAXIN in the United States). REL has demonstrated the ability to restore antibacterial activity of imipenem/cilastatin against some imipenem-nonsusceptible organisms.

The proposed indication of IMI/REL is the treatment infections due to gram-negative bacteria, including complicated urinary tract infections (cUTI), including pyelonephritis, and complicated intra-abdominal infections (cIAI).

IMI/REL received designation as a Qualified Infectious Disease Product (QIDP) and has also received Fast Track Designation for the proposed indication.

As described briefly above, data from two Phase 2 studies and a single Phase 3 study form the basis for the regulatory decision-making for this application

Protocol 003

A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Urinary Tract Infection

The primary objectives of this study were:

1. To evaluate the efficacy of 2 doses of MK-7655 + imipenem/cilastatin (250 mg and 125 mg) with respect to the microbiological response assessment profile in the treatment of

- adult patients with cUTI, as compared to imipenem/cilastatin at completion of IV study therapy (DCIV).
2. To evaluate the safety and tolerability profile of 2 doses of MK-7655 + imipenem/cilastatin (250 mg and 125 mg).

Patients were randomized in a 1:1:1 ratio to receive the following:
Treatment group 1- REL (250 mg) + imipenem/cilastatin (500 mg)
Treatment group 2- REL (125 mg) + I imipenem/cilastatin MP/CIL (500 mg)
Treatment group 3- matching placebo + imipenem/cilastatin (500 mg)

The dose of imipenem/cilastatin (500 mg) used for this study is one of the approved doses for the cUTI indication.

The primary efficacy endpoint was the proportion of subjects achieving favorable microbiological response at the completion of IV study therapy (DCIV visit).

A total of 302 subjects were enrolled and randomized in a 1:1:1 to receive IPM/CIL + 250 mg of MK-7655 (101 subjects), IPM/CIL + 125 mg of MK-7655 (101 subjects), or Placebo + IPM/CIL (100 subjects).

In this multicenter study, 34 sites enrolled subjects: 2 in the United States; 8 in Ukraine; 5 in Romania; 4 in Bulgaria; 4 in Latvia; 2 in Peru; 2 in Russia; 2 in Turkey; 2 in Greece; 2 in South Korea; and 1 in Poland.

The first subject was enrolled in the study on 03 December 2012. The last subject completed the study on 07 March 2016.

Protocol 004

A Phase II, Randomized, Active Comparator-Controlled Clinical Trial to Study the Safety, Tolerability, and Efficacy of MK-7655 + Imipenem/Cilastatin Versus Imipenem/Cilastatin Alone in Patients with Complicated Intra-Abdominal Infection (cIAI)

The primary objectives of this study were:

1. To evaluate the efficacy of two doses of MK-7655 (250 mg and 125 mg) + imipenem/cilastatin as compared with imipenem/cilastatin alone, with respect to the clinical response assessment profile in the treatment of adult subjects with cIAI at completion of IV study therapy (DCIV).
2. To evaluate the safety and tolerability profile of two doses of MK-7655 + imipenem/cilastatin (250 mg and 125 mg).

Patients were randomized in a 1:1:1 ratio to receive the following:
Treatment group 1- REL (250 mg) + imipenem/cilastatin (500 mg)
Treatment group 2- REL (125 mg) + imipenem/cilastatin (500 mg)
Treatment group 3- imipenem/cilastatin (500 mg) + matching placebo for REL

The dose of imipenem/cilastatin used for this study is one of the approved doses for the cUTI indication.

The primary efficacy endpoint for this study was the clinical response at the DCIV visit. Clinical responses at the completion of IV study therapy (DCIV visit) were assessed as “favorable” (cure) or “unfavorable” (failure).

A total of 351 subjects were enrolled and randomized 1:1:1 ratio to receive IPM/CIL + 250 mg of MK-7655 (118 subjects), IPM/CIL + 125 mg of MK-7655 (116 subjects), or IPM/CIL + placebo (117 subjects).

In this multicenter study, 45 sites enrolled subjects: 4 in the United States; 1 in Mexico; 2 in Argentina; 1 in Colombia; 1 in Brazil; 2 in Peru; 1 in Bulgaria; 1 in Estonia; 2 in Greece; 3 in Latvia; 4 in Lithuania; 1 in Poland; 1 in Germany; 1 in Portugal; 5 in Romania; 2 in Turkey; 2 in Russia; 7 in Ukraine; 2 in South Africa; and 2 in Taiwan.

The first subject was enrolled in the study on 16 November 2012. The last subject completed the study on 12 August 2014.

Protocol 013

A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial to Estimate the Efficacy and Safety of Imipenem/Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem/Cilastatin in Subjects with Imipenem-Resistant Bacterial Infection

The primary objectives of this study were:

1. To estimate the proportion of subjects with favorable overall response to IMI/REL (Treatment Group 1 only) and to CMS + IMI (Treatment Group 2).
The overall response was estimated based on the following: (a) survival (based upon all-cause mortality) through Day 28 post-randomization in subjects with HABP/VABP, (b) clinical response at Day 28 post-randomization for subjects with cIAI, and (c) the composite clinical and microbiological response at the EFU Visit for subjects with cUTI.
2. To evaluate the safety and tolerability profile of IMI/REL (Treatment Group 1 only).

Patients were randomized in a 2:1 ratio to Treatment Group 1 or Treatment Group 2:

- Treatment Group 1- REL (250 mg) + imipenem/cilastatin (500 mg) + placebo for colistin (in the form of Colistimethate sodium, CMS, (300 mg) every six hours
- Treatment Group 2- CMS 300 mg every 12 hours, imipenem/cilastatin (500 mg) every 6 hours

The primary efficacy endpoint for this study was the proportion of subjects with a favorable overall response as assessed for each of the 3 infection types.

Defined as follows:

- HABP/VABP: survival at Day 28
- cIAI: sustained cure or cure at Day 28
- cUTI: at EFU
 - Clinical response: sustained cure or cure, and
 - Microbiological response: sustained eradication

A total of 50 subjects were enrolled and 47 subjects randomized in a 2:1 ratio into Treatment Group 1 (31 subjects) or Treatment Group 2 (16 subjects). See above for a description of the treatment groups. The remaining three subjects received IMI/REL in open-label treatment.

In this multicenter study, 16 centers in 11 countries (United States, Lithuania, Ukraine, Estonia, Romania, Germany, Mexico, Brazil, Peru, Colombia, and Turkey).

The first subject was enrolled in the study on 31 October 2012. The last subject completed the study on 18 September 2017+.

Rationale for Site Selection

The clinical sites for inspection were chosen using the Clinical Investigator Site Selection Tool. Two sites were chosen for Protocol 003 and Protocol 013. Three sites were chosen for Protocol 004 including one site in United States.

III. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Dr. Dzintra Litavniece Liepaja Regional Hospital Ltd., Slimnīcas Street 25, Liepaja, LV-3414, Latvia	Site # 36 Protocol 003 8 subjects	April 15-18, 2019	NAI
Dr. Valeri Mariyanovski University Multiprofile Hospital for Active Treatment and Emergency Medicine "N.I.Pirogov" Clinic of Urology 21 Totleben Boulevard Sofia 1606 Bulgaria	Site # 21 Protocol 003 27 subjects	April 22-25, 2019	NAI
Dr. Ülo Kivistik North Estonian Medical Centre Foundation, Sütiste tee 19, Tallinn, Harjumaa 13419 Estonia	Site # 33 Protocol 004 14 subjects	April 8-18, 2019	VAI*

Dr. Christopher Lucasti South Jersey Infectious Disease, 730 Shore Road, Somers Point, NJ 08244	Site # 4 Protocol 004 15 subjects	January 18-25, 2-10	NAI
Dr. Liviu Vasile Str. Tabaci nr. 1 Craiova, 200642 Romania	Site # 71 Protocol 004 29 subjects	May 6-10, 2019	NAI*
Dr. Joahann Motsch Im Neuenheimer Feld 100 Klinik fuer Anaesthesiologie Heidelberg, NA 69120 Germany	Site # 502 Protocol 013 8 subjects	March 18-21, 2019	NAI
Dr. Kadri Tamme Puusepa 8 Anaesthesiology and Intensive Care Clinic Tartu, NA 51014 Estonia	Site # 400 Protocol 013 2 subjects	April 22-23, 2019	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Dzintra Litavniece/ Site #36/ Protocol 003

This inspection was the first FDA inspection of this clinical investigator. At this site, there were eight subjects screened, eight subjects enrolled, and eight subjects completed the study. All eight records were reviewed in full. Subject 300012 completed the study (including all follow-up visits) and subsequently died of metastatic renal cancer.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. No items were discussed during the inspection close-out meeting. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Dr. Valeri Mariyanovski/ Site # 21/ Protocol 003

At this site, there were 28 subjects screened, 27 subjects enrolled, and 25 subjects completed the study. There were no deaths reported during the study. Twenty-eight subject records were reviewed.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

One item was discussed with the principal investigator during the close-out meeting. Subject 300011 had a negative urine pregnancy test and a serum β -hCG was taken, per protocol. However, the serum β -hCG hemolyzed and there was no repeat test done. The protocol deviation was not reported to the NDA.

Other than described above, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

OSI Reviewer Comment:

The issue of unreported protocol deviations does not appear to be a widespread practice at this site. Although the serum β -hCG was not repeated as required by the protocol, the subject was not subsequently reported as pregnant during the study. Therefore, the reported deviation has no impact on patient safety.

3. Dr. Ülo Kivistik / Site # 33/ Protocol 004

At this site, there were 17 subjects screened, 14 subjects enrolled, 12 subjects completed the study. The records of all 14 enrolled subjects were reviewed during the inspection.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, source data evaluation, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

Subject 509 was enrolled and received study drug despite meeting Exclusion Criterion #19 (total bilirubin value ≥ 2 times upper limit of normal (ULN)). One day before screening, the subject's total bilirubin value was normal (65 $\mu\text{mol/L}$, ULN 17.1). The subject was enrolled prior to the subject's final total bilirubin value being available for review. It was assumed by study staff that the result would be within normal limits given the normal lab value the day prior to screening. The subject was enrolled and randomized to receive study drug. The subject's final total bilirubin result was reported as 65 $\mu\text{mol/L}$.

Concomitant medications were omitted from the eCRFs for two subjects--Subject 022 (paracetamol, magnesium sulfate, potassium chloride) and Subject 025 (calcium chloride, paracetamol, metoclopramide, vitamins B1 and B6, potassium chloride, and magnesium sulfate).

In addition, adverse events were omitted from the eCRF—Subject 013 (moderate delirium, resolved) and Subject 510 (mild tachyarrhythmia, ongoing).

The primary and secondary endpoint data were verifiable.

Other than mentioned above, the inspection revealed adequate adherence to the regulations and the investigational plan. There was no Form FDA-483, Inspectional Observations, issued.

OSI Reviewer Comment: Randomizing subjects who met one or more of the exclusion criteria occurred in at least two subjects enrolled at this site. One instance was reported as a protocol deviation (Subject 511) and one instance was not reported (Subject 509, described above). These protocol deviations had the potential to result in significant harm. Further, concomitant medications and adverse events were omitted from eCRFs (two subjects for each omission). A VAI regulatory classification is appropriate for this site.

4. Dr. Christopher Lucasti/ Site # 4/ Protocol 004

At this site, there were 16 subjects screened and 15 subjects enrolled (one screen failure). All 15 subjects completed the study.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, ethics committee approvals, financial disclosures, informed consent forms, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary and secondary endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

One item was discussed at the closeout meeting with the principal investigator—discrepancy between EDC and source data in screening medical history for Subject 013. The EDC showed that Subject 013 had a history of 'possible multiple sclerosis' diagnosed in 2005. However, this information was not in the source document.

Other than mentioned above, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

OSI Reviewer Comment:

Discrepancy in past medical history between source documents and EDC appears to have been an isolated occurrence at this site. It is unlikely that this incident will affect the overall safety and efficacy conclusions of the study data derived from this site.

5. Dr. Liviu Vasile/ Site # 71/ Protocol 004

At this site, there were 30 subjects screened and 29 subjects enrolled (one screen failure). All 29 subjects completed the study. All 30 subject records were reviewed during the inspection.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, ethics committee approvals, financial disclosures, informed consent forms, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued.

6. Dr. Johann Motsch/ Site #502/ Protocol 013

At this site, there were 9 subjects screened and 8 subjects enrolled (one screen failure). All 29 subjects completed the study. All 9 subject records were reviewed during the inspection.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, ethics committee approvals, financial disclosures, informed consent forms, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

During the close-out meeting, the discrepancy between source documents and the eCRF entries regarding study drug infusion times was discussed. The planned start and stop times for study

drug infusion was found to be recorded even if the plan was not followed (Subjects 10005, 10009, 100013). Further, the administration time for Subject 100013 was entered into the electronic medical record four days after the study drug administration. Administration times of 20 minutes were also noted in the EMR (protocol specified 30-minute infusion time). There was also no documentation of the infusion pumps being set to an automatic 30-minute schedule.

Other than mentioned above, the inspection revealed adequate adherence to the regulations and the investigational plan except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued.

OSI Reviewer Comment:

The issue of inaccurate documentation of actual infusion times at this site appears to be relatively widespread occurring in at least three of the eight subjects enrolled. However, it is unlikely that this inaccurate documentation will affect the overall safety and efficacy conclusions of the study data derived from this site.

7. Dr. Kadri Tamme/ Site # 400/ Protocol 013

At this site, there were 2 subjects screened and 2 subjects enrolled. Neither subject completed the study as both subjects died prior to the final study visit.

Subject 010 (IMI/REL + placebo for CMS, 11 days) completed study dosing; however, the subject died on Study Day 17 due to pulmonary infection and respiratory failure. Subject 201 (IMI/REL) died on Study Day 8 prior to the completion of study dosing. The cause of death was listed as septic shock and pneumonia. The events of both subjects were considered unlikely related to investigational therapy by the investigator. An audit was conducted for both subjects for protocol compliance and data listing verification.

The records reviewed included: subject selection criteria and informed consent forms, test article controls including accountability and blinding, ethics committee approvals, financial disclosures, informed consent forms, concomitant medication and procedures, site monitoring records, source documentation, case report forms, adverse events, and laboratory reports.

The primary efficacy endpoint data was verifiable. There was no evidence of under-reporting of adverse events.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan except the items described as above. A Form FDA 483 (Inspectional Observations) was not issued.

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{ See appended electronic signature page }

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OSI/DCCE/GCP Reviewer/ Aisha Johnson
OSI/ GCP Program Analysts/ Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters

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/s/

AISHA P JOHNSON
06/05/2019 11:05:12 PM

MIN LU
06/05/2019 11:26:05 PM

KASSA AYALEW
06/06/2019 10:30:27 AM

NDA 212819 for imipenem, cilastatin, and relebactam for injection

Container and Carton Label Review

1. Container and Carton Labeling

1) Immediate Container Label



Text of Vial Label

[Left hand side of vial label]

NDC 0006-3856-01

MUST BE CONSTITUTED (b) (4) **FURTHER DILUTED.** See enclosed package insert for preparation instructions.

USUAL DOSAGE: See package insert.

Store vial at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Keep vial in the outer carton.

See package insert for storage of constituted product.

Inactive ingredient: 20 mg sodium bicarbonate

Merck Sharp & Dohme Corp., a subsidiary of

Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

[Right hand side of vial label]

NDC 0006-3856-01

Trademark™
(imipenem, cilastatin, and relebactam) for Injection
1.25 g per vial*



(b) (4)



(b) (4)

Single-dose vial

Rx only

Lot

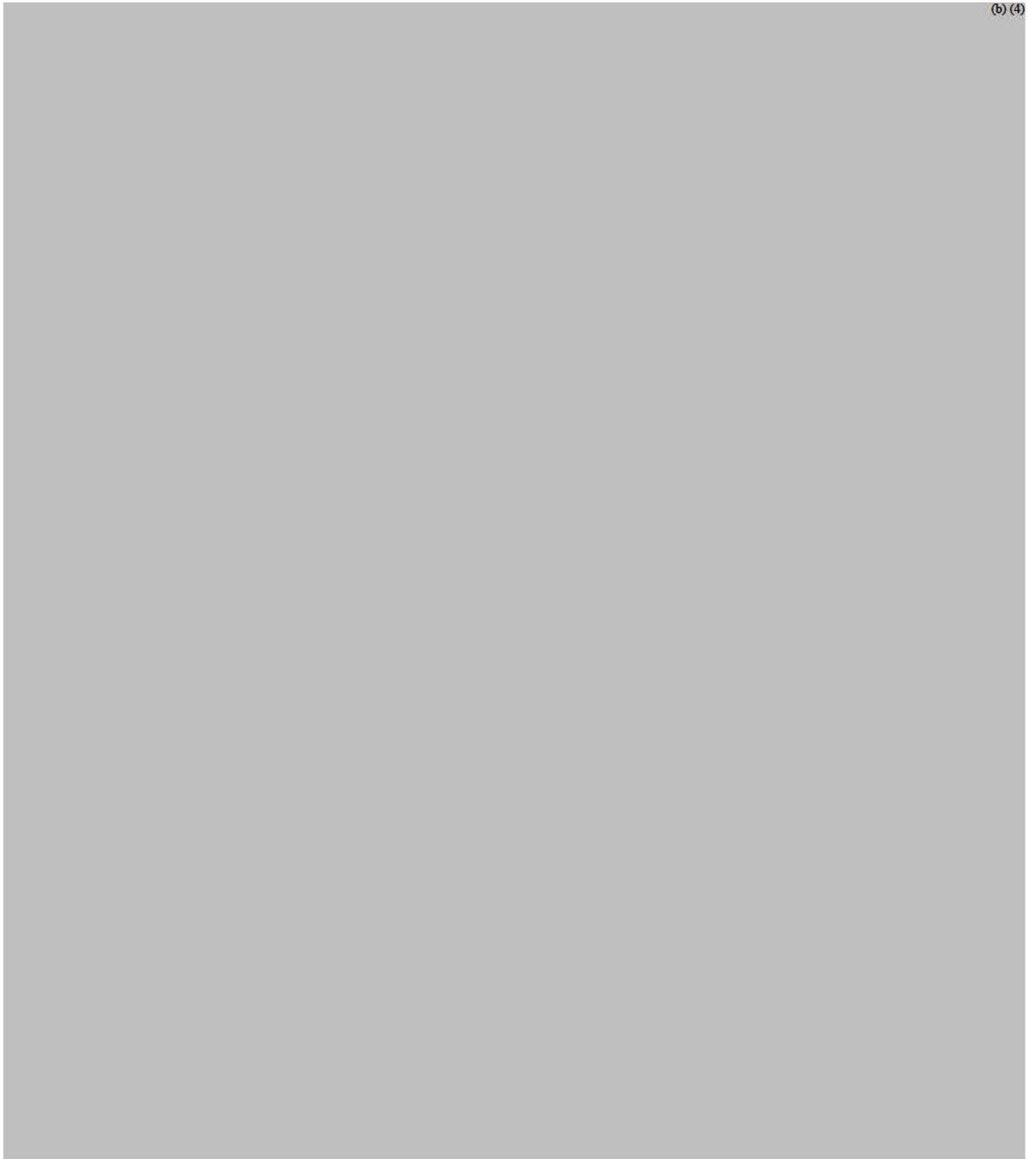
Exp

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Trademark™ (imipenem, cilastatin, and relebactam) for Injection	Adequate.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	*Vial contains (b) (4) (b) (4)	Recommend: Vial contains 500 mg imipenem (equivalent to 530 mg imipenem monohydrate), 500 mg cilastatin (equivalent to 531 mg cilastatin sodium), and 250 mg relebactam (equivalent to 263 mg relebactam monohydrate).
Route of administration (21.CFR 201.100(b)(3))	(b) (4)	Adequate.
Net contents* (21 CFR 201.51(a))	1.25 g per vial*	Adequate.
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) (21CFR 201.100(b)(5)**	Inactive ingredient: 20 mg sodium bicarbonate	Adequate.
Lot number per 21 CFR 201.18	Present	Adequate.
Expiration date per 21 CFR 201.17	Present	Adequate.
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate.
Storage (not required)	Store vial at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 0006-3856-01	Adequate.
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate.
Name of manufacturer/distributor (21 CFR 201.1)	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. , Whitehouse Station, NJ 08889, USA	Adequate.

Others	MUST BE CONSTITUTED (b) (4) FURTHER DILUTED. See enclosed package insert for preparation instructions. USUAL DOSAGE: See package insert.	Adequate. Should indicate that product is sterile
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2) Carton Labeling

In the Amendment of 2/15/19 the applicant states that the vials (b) (4) are placed in a tray that is placed in a carton. The tray label should more correctly be referred to as a tray carton and is as follows.



Text of Trade Tray Label

Note that tray label does not contain the following text (b) (4)

[Redacted] Text shown in green below is found on the tray label but not on the vial label.

[Left hand side of tray label]



(b) (4)

[Right hand side of tray label]



(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Trademark™ (imipenem, cilastatin, and relebactam) for Injection	Adequate.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	*Each vial contains (b) (4)	Recommend: 500 mg imipenem (equivalent to 530 mg imipenem monohydrate), 500 mg cilastatin (equivalent to 531 mg cilastatin sodium), and 250 mg relebactam (equivalent to 263 mg relebactam monohydrate).
Net contents (21 CFR 201.51(a))	25 single-dose vials; 1.25 g per vial*	Adequate.
Lot number per 21 CFR 201.18	Present	Adequate.
Expiration date per 21 CFR 201.17	Present	Adequate.
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(d)(2)]	Inactive ingredient: 20 mg sodium bicarbonate added to each vial as a buffer	Adequate.
Sterility Information (if applicable)	Not present	Should be added
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate.
Storage Conditions	Store vials at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Keep vials in the outer carton.	Adequate.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 0006-3856-02	Adequate.
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate.
Name of	Merck Sharp & Dohme Corp., a subsidiary of	Adequate.

manufacturer/distributor	Merck & Co., Inc. , Whitehouse Station, NJ 08889, USA	
“See package insert for dosage information” (21 CFR 201.55)	See enclosed package insert for preparation instructions.	Adequate.
“Keep out of reach of children” (optional for Rx, required for OTC)	Not present	Adequate.
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Injection	Adequate.

Outstanding Issues which have been communicated to the OND Project Manager:

The vial label and tray label should indicate that the product is sterile.

Note that tray label does not contain the following text (b) (4)

The equivalency statement should be revised as shown.



George
Lunn

Digitally signed by George Lunn
Date: 5/10/2019 11:09:45AM
GUID: 508da72000029f40833369b0a181e8b3
Comments: Revised version



Erika
Englund

Digitally signed by Erika Englund
Date: 5/28/2019 02:32:11PM
GUID: 51389ea30003450414230afb8c3e8114

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 23, 2019

To: Meklit Workneh, M.D.
Division of Anti-Infective Products (DAIP)

Christopher Smith, Regulatory Project Manager, DAIP

Abimbola Adebawale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADEMARK (imipenem, cilastatin, and relebactam) for injection for intravenous use

NDA: 212819

In response to DAIP's consult request dated December 28, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for TRADEMARK.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on May 21, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 14, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

31 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
05/23/2019 05:25:29 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 21, 2019
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 212819
Product Name and Strength: Recarbrio (imipenem, cilastatin, and relebactam) for Injection 1.25 grams per vial
Applicant/Sponsor Name: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck)
FDA Received Date: May 14, 2019 and May 20, 2019
OSE RCM #: 2018-2505-1
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Recarbrio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

Included in the May 14, 2019 submission, Merck also provided their response^b to our container label and carton labeling comments and recommendations sent on April 23, 2019.

2 REGULATORY HISTORY

On May 16, 2019, we sent an information request to Merck asking that they clarify if the “MM” portion of the proposed readable expiration date format is intended to be represented

^a Myers, D. Label and Labeling Review for Recarbrio (NDA 212819). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 16. RCM No.: 2018-2505.

^b Merck Sharp & Dohme Corp. Imipenem/Cilastatin/Relebactam (NDA 212819) Response to FDA Carton and Container Comments dated 23-APR-2019. Whitehouse Station, NJ. Merck. 2019 MAY 14. Available from: <\\cdsesub1\evsprod\nda212819\0035\m1\us\multiple-module-amendment-14may2019.pdf>

numerically (i.e., 01, 02, 03, etc.) or alphabetically (JA, FE, MA, etc). On May 20, 2019, Merck provided their response^c which clarifies that the “MM” portion of the readable expiration date format is intended to be represented numerically (i.e., 01, 02, 03, etc.).

3 CONCLUSION

The Applicant submitted revised container labels and carton labeling received on May 14, 2019 for Recarbrio. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^c Merck Sharp & Dohme Corp. Imipenem/Cilastatin/Relebactam (NDA 212819) Response to FDA Carton and Container Comments dated 16-MAY-2019. Whitehouse Station, NJ. Merck. 2019 MAY 20. Available from: <\\cdsesub1\evsprod\nda212819\0038\m1\us\multiple-module-amendment-20may2019.pdf>

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 14, 2019

Container labels



Carton labeling



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
05/21/2019 04:52:35 PM

OTTO L TOWNSEND
05/22/2019 10:19:34 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA # 212819
Submission Number	# 001
Submission Date	11/16/2018
Date Consult Received	3/11/2019
Clinical Division	OAP/DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review dated 12/06/2013 in DARRTS ([link](#));
- Previous QT-IRT review dated 11/03/2014 in DARRTS ([link](#));
- Previous QT-IRT review dated 01/09/2015 in DARRTS ([link](#));
- Sponsor's clinical study report # P-009 (SN0000 / SDN001; [link](#));
- Investigator's brochure Ed.12 under IND-108754 (SN0150 / SDN151; [link](#));
- Sponsor's propose product label (SN0000 / SDN001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0015/ SDN; [link](#))

1 SUMMARY

No significant QTc prolongation effect of relebactam (MK-7655) was detected in this QT assessment.

The effect of relebactam was evaluated in a dedicated QT study # P-009 (MK-7655-009-00). The highest dose evaluated was 1150 mg (administered as a single intravenous infusion over 30 min), which is the maximum tolerated dose and also, covers the worst-case exposure scenario (renal impairment, section 3.1). The data from Study # P-009 was analyzed using central tendency as the primary analysis, which did not suggest that relebactam is associated with significant QTc prolonging effect (refer to section 0) – see Table 1 for overall results. The largest upper bounds of the 2-sided 90% CI on the mean difference between relebactam and placebo ($\Delta\Delta\text{QTcF}$) was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI on $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 1, indicating that assay sensitivity was established.

The findings of this analysis are further supported by the available exposure-response analysis (section 4.5) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
QTc	Relebactam 1150 mg	0.25	2.9	(0.5, 5.2)

QTc	Moxifloxacin 400 mg	4	14.8	(12.5, 17.2)*
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* Multiplicity adjustment was not applied.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable

2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 ([link](#)) from the QT-IRT. Our changes are highlighted ([addition](#), [deletion](#)). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

<p>12.2 Pharmacodynamics</p> <p><u>Cardiac Electrophysiology</u></p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p><i>prolong the QT interval to</i> (b) (4) <i>clinically relevant extent</i> <i>TRADENAME does not</i> (b) (4)</p> <p><i>We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.</i></p>

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

Merck & Co., Inc., is developing relebactam for use in combination with imipenem and cilastatin for the treatment of 1) complicated urinary tract infections, including pyelonephritis and 2) complicated intra-abdominal infections. Relebactam (MK-7655, MW: 366.39) is a non-β-lactam diazabicyclooctane β-lactamase inhibitor (both class A and C β-lactamases).

A fixed dose combination product consisting of imipenem and cilastatin was previously approved for the treatment of serious infections such as lower respiratory tract infection, urinary tract infection, intra-abdominal infection etc. caused by designated susceptible bacteria (Primaxin®, NDA-050587, 1985, Merck). Imipenem (MW: 317.37) is a

carbapenem (β -lactam) antibacterial agent that inhibits cell wall synthesis and cilastatin (MW: 380.44) is a derivatized heptenoic acid that limits renal metabolism of imipenem by inhibiting renal dehydropeptidase-I. Primaxin is marketed as a sterile powder mixture (500 mg imipenem and 500 mg cilastatin) for reconstitution (a single-dose injection) for intravenous administration. The highest approved dose of Primaxin is 1000 mg every 6 hours (in bacterial species with intermediate susceptibility) in adult patients with normal renal function ($\text{CrCl} \geq 90 \text{ mL/min}$).

The antibacterial combination consisting of 263 mg relebactam monohydrate (eqv. to 250 mg relebactam), 530 mg imipenem monohydrate (eqv. to 500 mg imipenem), and 531 mg cilastatin sodium (eqv. to 500 mg cilastatin) is formulated as injection (single-dose vial with 1.6 mEq Na) for intravenous administration. The proposed dose is single injection (consisting of 500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam) to be administered as intravenous infusion over 30 minutes every 6 hours in adult patients with normal renal function ($\text{CrCl} \geq 90 \text{ mL/min}$). Dose reduction is suggested in patients with renal impairment. The peak concentrations of 48.3 ± 24.9 , 106 ± 26.8 , and $96.4 \pm 21.8 \mu\text{M}$ were observed for relebactam, imipenem, and cilastatin respectively, in healthy subjects at steady-state with the maximum recommended dose (500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam) administered every 6 hours (as 30 min intravenous infusion).

Relebactam exhibits a dose proportional pharmacokinetics between studied dose levels of 25 and 1150 mg. It has low accumulation ($< 10\%$) with proposed dosing regimen (q.i.d.) and has short half-life ($< 2\text{h}$). Since no circulating metabolite have been detected for relebactam and it has a low drug interaction potential. Relebactam and imipenem are primarily eliminated by renal excretion as unchanged drugs ($> 90\%$) and dose adjustments are recommended in patients with renal impairment.

Previously, the QT-IRT responded to the Sponsor's question on a thorough QT study design for characterization of QT prolongation risk of relebactam in the combination regimen with imipenem and cilastatin under IND-108754 (12/06/2013). Subsequently, the sponsor submitted thorough QT study protocol (MK-7655-009-00) as per the QT-IRT's request. The sponsor proposed a single-dose, double-blind (with respect to relebactam only), randomized, placebo and positive-controlled, 3-period, 6-sequence, balanced crossover study in 36 healthy adult subjects under fasting conditions to evaluate the effects of relebactam on the QTc interval. In general, the cross-over study design, selected dose and ECG/PK collection were found to be acceptable (11/03/2014). Along with other comments, the QT-IRT indicated that the sample size ($n=30$) is on the lower end and it is necessary study is carefully conducted to keep the variances low. Later, the sponsor submitted revised protocol addressing the QT-IRT's comments on the primary and categorical analyses (01/09/2015).

The sponsor conducted a single-dose, double-blind (with respect to relebactam only), placebo- and positive-controlled, QT study assessing the effect of a suprathreshold dose of relebactam on the QTc in healthy subjects ($N=36$). In this balance crossover study, subjects were randomized to receive a single-dose treatment - A) 1150-mg suprathreshold dose; B) 400-mg oral moxifloxacin (oral, open-label); and C) matched placebo with at least 4 days washout between treatments. Relebactam (1150 mg single dose) or matching placebo were administered as intravenous infusion over 30 min. Peak concentrations of

211 ±36.2 µM were observed (at ~0.5 h) with single dose of relebactam at supra-therapeutic dose level (1150 mg) offering 4-fold margin over the therapeutic exposures.

3.2 SPONSOR'S RESULTS

3.2.1 Central Tendency Analysis

Relebactam excluded the 10 ms threshold at the supratherapeutic dose level. The sponsor used QTcP for the primary analysis and presented QTcF results too. Both results showed that Relebactam 1150 mg excluded the 10 ms threshold. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 0 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. Both FDA's analysis and sponsor's analysis confirm that the assay sensitivity was established. Please see section 0 for additional details.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor. Assay sensitivity was established using central tendency analysis of moxifloxacin arm. Please see section 4.3.1.1 for additional details.

3.2.2 Categorical Analysis

None of the subjects had absolute QTcF > 480 ms or a change from baseline QTcF >60 ms. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

The safety population included all 36 subjects treated with relebactam, matched placebo, and moxifloxacin. There were no deaths, serious adverse events, or subject discontinuation due to an adverse event reported in this study.

Twelve (12, 33%) subjects reported 16 adverse events following relebactam, 6 (17%) subjects reported 13 adverse events following moxifloxacin, and 7 (19%) subjects reported 18 adverse events following placebo.

Overall, 5 (14%) subjects reported a total of 8 drug-related adverse events following relebactam administration such as chest discomfort, headache, catheter site hemorrhage, infusion site pain, pruritus, maculo-papular rash, infusion site erythema. All adverse events were considered mild or moderate intensity, transient in nature, and resolved by study conclusion. No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or safety ECGs as a function of treatment.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

Since no QTc signal was observed by the sponsor in the primary analysis, the sponsor did not perform exposure-response analysis. The sponsor used (non-model-based) descriptive statistics to describe pharmacokinetic parameter by treatment. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcP for the primary analysis and presented QTcF results too. The statistical reviewer used QTcF for the primary analysis, as no significant increases or decreases in heart rate (i.e. mean < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

Overall ECG acquisition and interpretation in this study appears acceptable.

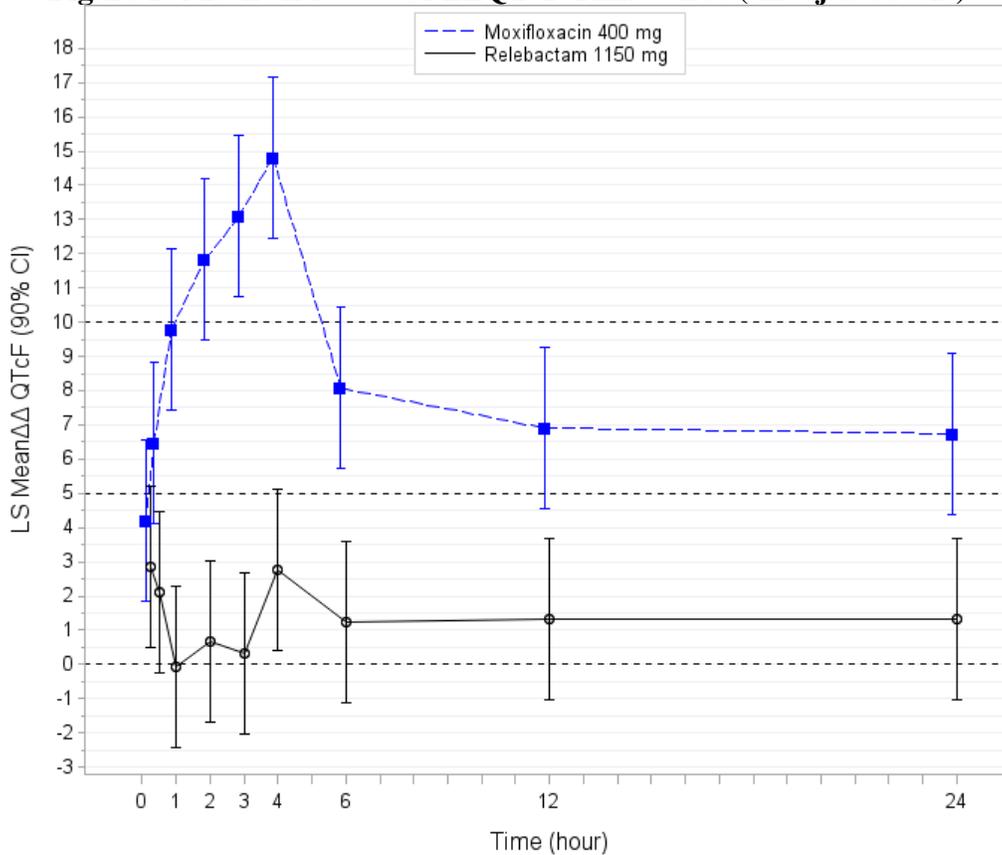
4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used linear mixed model to analyze the Δ QTcF effect. The model includes treatment, time, sequence, period, QTcF baseline, and treatment by time interaction as fixed effects and SUBJECT as a random effect.

Figure 1 displays the time profile of $\Delta\Delta$ QTcF for different treatment groups. The largest upper bounds of the 2-sided 90% CI for the mean difference between Relebactam 1150 mg and placebo is 5.2 ms at 0.25 hour.

Figure 1: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse (unadjusted CIs).



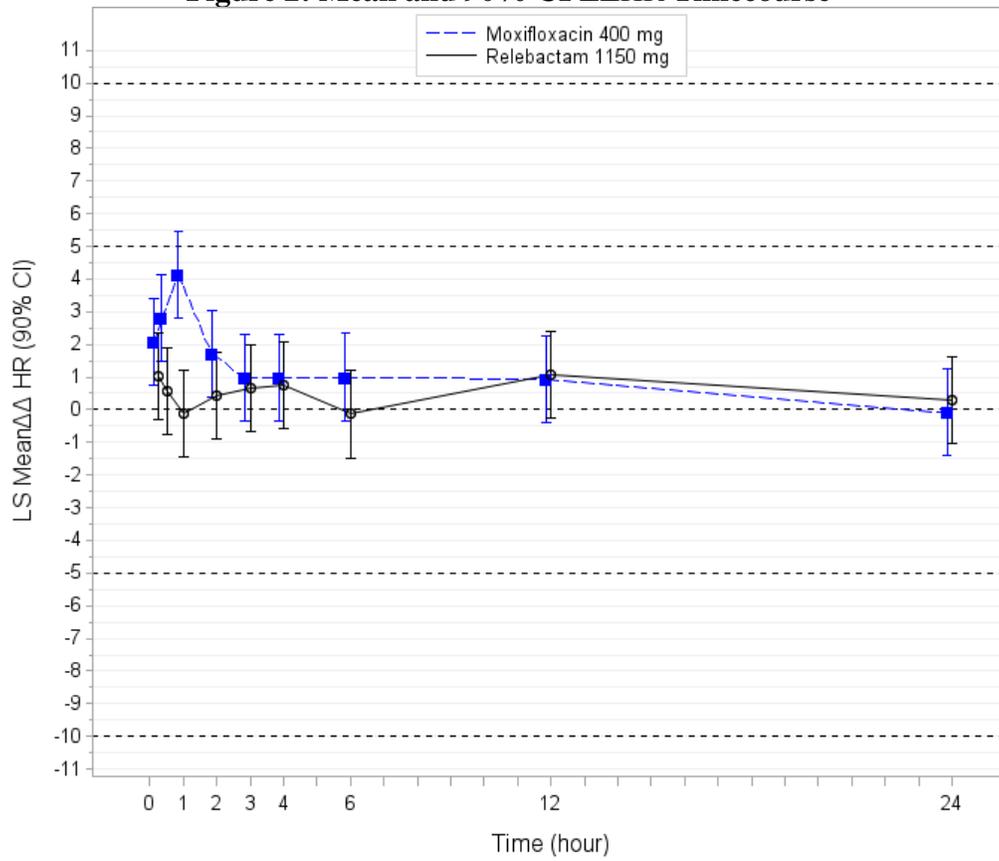
4.3.1.1 Assay Sensitivity

The statistical reviewer used the same statistical model above to analyze the moxifloxacin and placebo data. The results represented in Figure 1. The largest unadjusted 90% lower confidence interval is 12.5 ms. By considering Bonferroni multiplicity adjustment for 4 timepoints, the largest lower confidence interval is 11.6, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

4.3.2 HR

The same statistical analysis was performed on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between Relebactam 1150mg and placebo is 2.4 bpm.

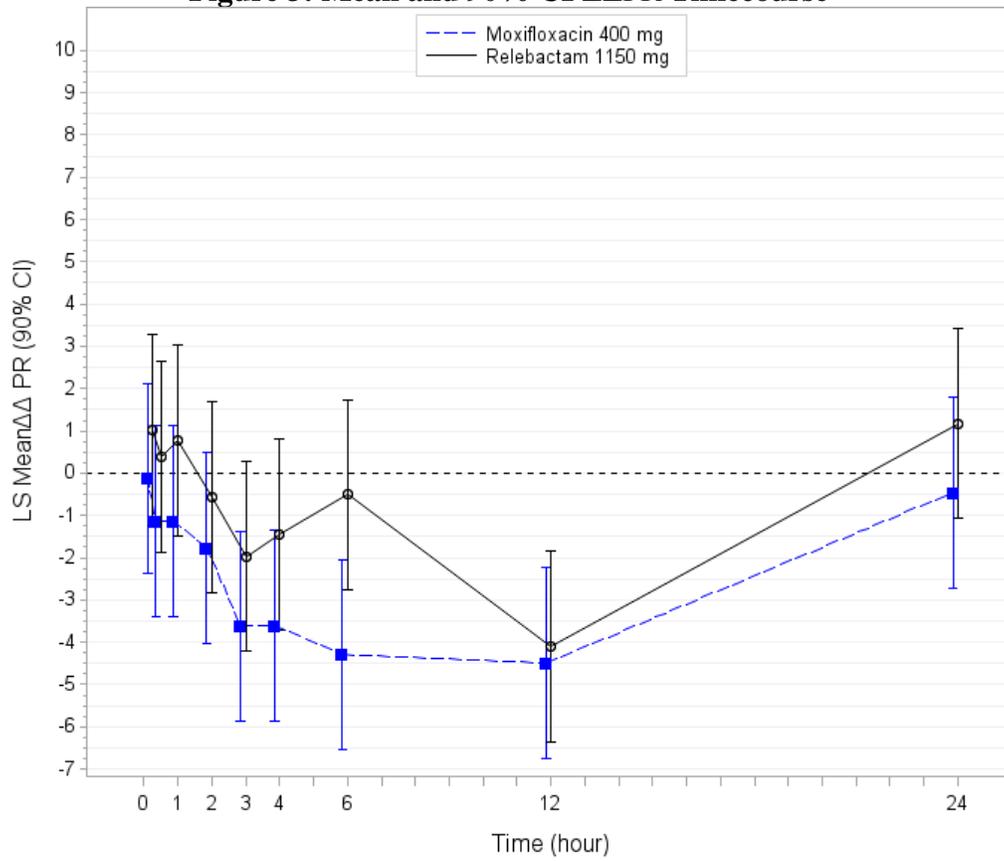
Figure 2: Mean and 90% CI $\Delta\Delta$ HR Timecourse



4.3.3 PR

The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between Relebactam 1150 mg and placebo is 3.4 ms.

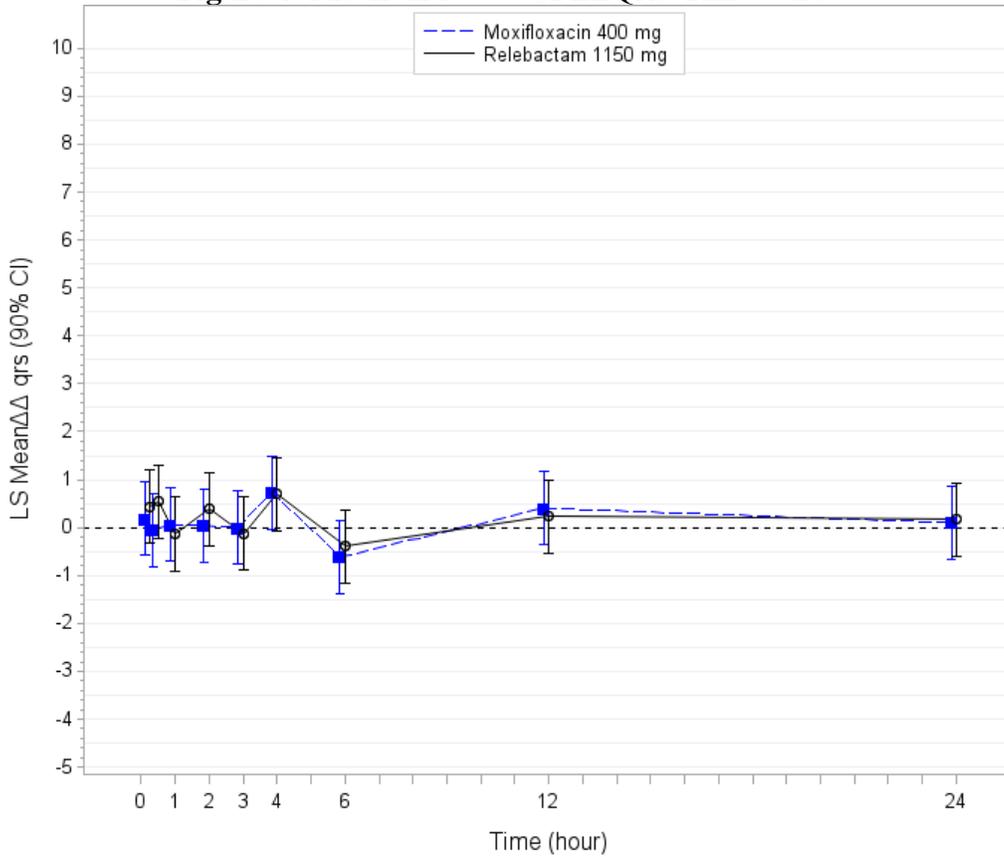
Figure 3: Mean and 90% CI $\Delta\Delta$ PR Timecourse



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between Relebactam 1150 mg and placebo is 1.5 ms.

Figure 4: Mean and 90% CI $\Delta\Delta$ QRS Timecourse



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 2: Categorical Analysis for QTcF

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms	
	#Subj.	#Obs.	#Subj.	#Obs.	#Subj.	#Obs.
Placebo	36	324	36 (100%)	324 (100%)	0 (0.0%)	0 (0.0%)
Relebactam 1150 mg	36	324	35 (97.2%)	323 (99.7%)	1 (2.8%)	1 (0.3%)

Table 3 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 3: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value ≤ 30 ms		30 ms < Value ≤ 60 ms	
	#Subj.	#Obs.	#Subj.	#Obs.	#Subj.	#Obs.
Placebo	36	324	36 (100%)	324 (100%)	0 (0.0%)	0 (0.0%)

Treatment Group	Total N		Value<=30 ms		30 ms<Value<=60 ms	
	#Subj.	#Obs.	#Subj.	#Obs.	#Subj.	#Obs.
Relebactam 1150 mg	36	324	36 (100%)	324 (100%)	0 (0.0%)	0 (0.0%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. Four subjects in Relebactam 1150 mg experienced QRS interval greater than 200 ms. Among those 4 subjects, 2 had averaged baseline PR above 200 ms.

Table 4: Categorical Analysis for PR

Treatment Group	Total N		Value<=200 ms		Value>200 ms	
	#Subj.	#Obs.	#Subj.	#Obs.	#Subj.	#Obs.
Placebo	36	324	32 (88.9%)	293 (90.4%)	4 (11.1%)	31 (9.6%)
Relebactam 1150 mg	36	324	32 (88.9%)	309 (95.4%)	4 (11.1%)	15 (4.6%)

4.4.3 QRS

There are no subjects who experienced QRS interval greater than 110 ms in Relebactam 1150 mg group.

4.4.4 HR

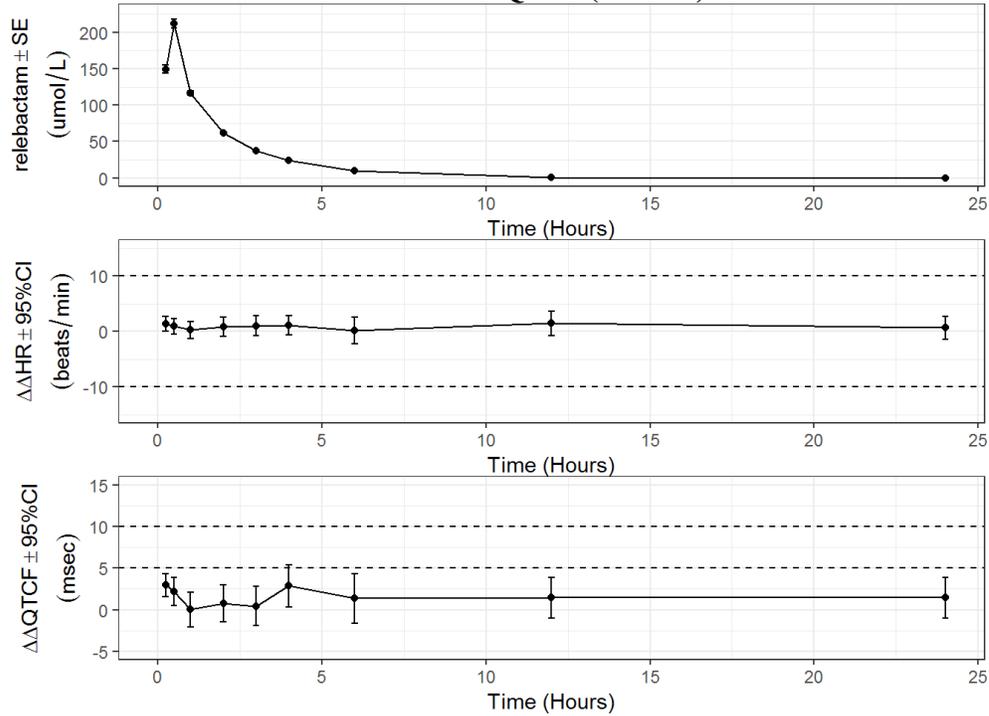
There are no subjects who experienced HR greater than 100 bpm in Relebactam 1150 mg group.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between plasma relebactam concentration and Δ QTcF.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship.

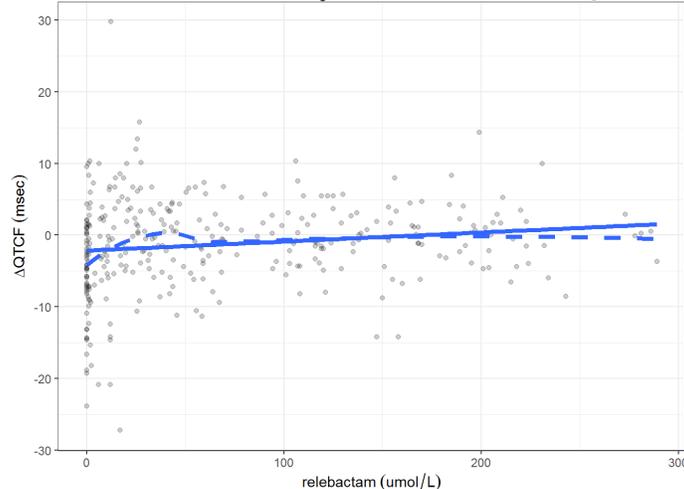
Figure 5: Time course of plasma relebactam concentration (top), heart rate (middle) and QTcF (bottom)



An evaluation of the time-course of drug concentration and changes in $\Delta\Delta\text{HR}$ and $\Delta\Delta\text{QTcF}$ is shown in Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

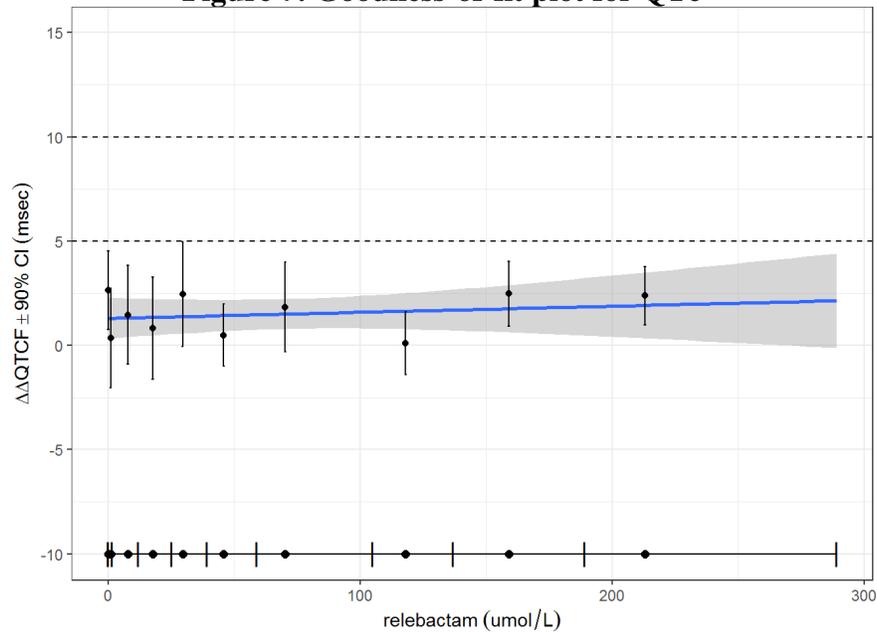
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7.

Figure 7: Goodness-of-fit plot for QTc



4.5.1 Assay Sensitivity

Moxifloxacin concentrations were not determined in this study (# P009). Assay sensitivity was established using central tendency analysis. Please see section 4.3.1.1 for additional details.

4.6 SAFETY ASSESSMENTS

No additional safety assessments were conducted. See section 3.2.3.

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed following a single-dose (1150 mg) of relebactam administered as intravenous infusion over 30 min.

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/s/

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LARS JOHANNESSEN
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CHRISTINE E GARNETT
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 16, 2019
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: NDA 212819
Product Name and Strength: Recarbrio (imipenem, cilastatin, and relebactam) for Injection
1.25 grams per vial
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.,
Inc. (Merck)
FDA Received Date: November 16, 2018
OSE RCM #: 2018-2505
DMEPA Safety Evaluator: Deborah Myers, RPh, MBA
DMEPA Team Leader: Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Recarbrio (imipenem, cilastatin, and relebactam) for Injection 1.25 grams per vial, the Division of Anti-Infective Products (DAIP) requested that we review the proposed container label, carton labeling, and prescribing information (PI) for areas that may lead to medication errors.

2 REGULATORY HISTORY

On March 11, 2019, we sent an Information Request (IR) to Merck asking, “Does each vial have an individual carton or does the tray function as a carton for all 25 vials.” In a response, to our IR dated March 11, 2019, received on March 15, 2019^a, Merck confirmed that “Each individual vial is not in an individual carton. The 25 vials are placed into a tray that is inserted into a carton.”

On March 28, 2019, we sent an IR request to Merck seeking their reasoning for their proposed preparation directions for renal insufficient patients included in Section 2.4 of their proposed prescribing information (PI). These proposed preparation instructions, for patients that have renal insufficiency, are unique in that the practitioner is directed to remove and discard volume from the final infusion solution.^b

On April 2, 2019, Merck responded to our March 28, 2019 IR. Their response provides clarity (b) (4) to use the proposed unique methodology to prepare Recarbrio for renal insufficient patients.^c

On April 9, 2019, during an internal meeting with DAIP, DMEPA presented our concerns that as currently presented that the proposed preparation of doses of less than 1.25 grams for patients with renal impairment may be prone to medication errors such as; wrong dose (overdose) in which practitioners fail to remove the ‘excess’ to reach the reduced dose. We also discussed the clinical implications if a renal impaired patient receives a full dose due to incorrect preparation.

^a Merck Sharp & Dohme Corp. Imipenem/Cilastatin/Relebactam (NDA 212819) Response to FDA Request for Information. Whitehouse Station, NJ. Merck. 2019 MAR 15. Available from: <\\cdsesub1\evsprod\nda212819\0011\m1\us\quality-information-amendment-15mar2019.pdf>.

^b Smith, C. FDA Communication: NDA 212819 DMEPA IR. Silver Spring (MD): FDA, CDER, OND, DAIP (US); 2019 MAR 28. NDA 212819. Available from: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804e7e3d>

^c Merck Sharp & Dohme Corp. Imipenem/Cilastatin/Relebactam (NDA 212819) Response to FDA Request for Information – DMEPA Review. Whitehouse Station, NJ. Merck. 2019 APR 02. Available from: <\\cdsesub1\evsprod\nda212819\0025\m1\us\multiple-module-amendment-02-apr-2019.pdf>

Based on our April 9, 2019 internal meeting discussion, DAIP recommended that we draft a response to Merck’s April 2, 2019, response to our March 28, 2019 IR. On April 16, 2019, an IR was sent in which we recommend that Merck^d:

1. Develop and submit an instructions for use (IFU) for the intended user (practitioner preparing Recarbrio for patients with renal impairment).
2. Incorporate information into your proposed PI (i.e., Dosage and Administration Section) (b) (4) to inform providers why the proposed preparation methods for doses in patients with renal impairment are necessary.
3. Develop training materials regarding correct preparation of Recarbrio for patients with renal impairment. We see this effort as being aligned with your involvement in promoting health literacy.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E –N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We note the product strength is presented as the total of each active ingredient (i.e., 1.25 grams) on the container labels and carton labeling, (b) (4)
 From a medication error perspective and based on our postmarketing experience with similar β -Lactam/ β -Lactamase Inhibitor

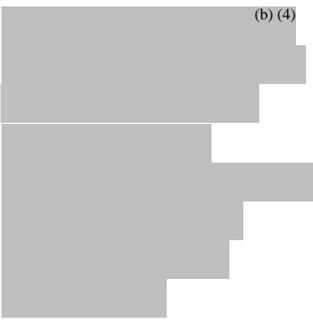
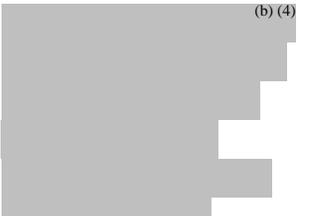
^d Smith, C. FDA Communication: NDA 212819 DMEPA IR. Silver Spring (MD): FDA, CDER, OND, DAIP (US); 2019 APR 16. NDA 212819. Available from: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804ecf8e>

products such as, Avycaz 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) and Zerbaxa 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g), we agree with the proposed strength presentation of 1.25 grams per vial for the proposed product and the use of the strength 1.25 grams throughout the PI. See Tables 2 and 3 below for recommendations to address this discrepancy and for other identified medication error issues with the submitted container label, carton labeling, and PI, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anti-Infective Products (DAIP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The proprietary name is currently denoted by the placeholder “Trademark™.”	The proposed proprietary name “Recarbrio” was found conditionally acceptable on April 11, 2019.	Remove the placeholders “ Trademark™” and replace with the conditionally acceptable name “Recarbrio.”
2.	We note the use of the abbreviation “g” throughout the PI.	Abbreviations can be misinterpreted and result in confusion, as well as medication errors.	To provide clarity and minimize the potential for misinterpretation, we recommend replacing the abbreviation “g” with its intended meaning “gram” or “grams”, as appropriate.
Highlights of Prescribing Information – Dosage and Administration			
1.	As currently presented the recommended dosage, “1.25 grams” is not included following the placeholder “Trademark.”	As currently presented, the recommended dosage (b) (4) is inconsistent with the overall product strength (i.e., 1.25 grams) as presented on the container label and carton labeling (b) (4)	Add the recommended dosage “1.25 grams” following the placeholder “Trademark™.”

		(b) (4) Inconsistencies in strength and dosage can result in wrong strength, as well as wrong dose medication errors.	
2.	(b) (4)	For consistency and readability, each individual dosage should follow each individual active ingredient.	Change each individual dosage to follow each individual active ingredient. Additionally, add the word “and” prior to “relebactam.” For example, “...(imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg)...”
3.	<p>As currently presented, the dosages included in the renal dosage adjustment table are inconsistent with the overall strength, 1.25 grams, presented on the container label and carton labeling (b) (4)</p> <p>(b) (4) Inconsistencies in dosages can result in wrong dose medication errors. For each recommended dosage included in the renal dosage adjustment table, add the recommended dosage that represents the total dosage for each active ingredient. This dosage should precede the strengths of the individual active ingredients enclosed in parentheses. For example:</p> <p>(b) (4)</p>		
Highlights of Prescribing Information – Dosage Forms and Strengths			

1.	As currently presented the product strength “1.25 grams” and individual active ingredients are not included following the placeholder “Trademark.”	A lack of the product strength may cause could potentially result in a wrong dose medication error (overdose or underdose).	Add the product strength, “1.25 grams” followed by the individual active ingredients “imipenem, cilastatin, and relebactam” enclosed in parentheses. For example, “TRADEMARK 1.25 grams (imipenem, cilastatin, and relebactam) for injection, is...”
2.	 (b) (4)	For consistency and readability, each individual strength should follow each individual active ingredient. Customarily, the product strength follows the product name.  (b) (4)	Change each individual strength to follow each individual active ingredient. For example, “...containing imipenem 500 mg (anhydrate equivalent), cilastatin 500 mg (free acid equivalent), and relebactam 250 mg (anhydrate equivalent).”
Full Prescribing Information (FPI), Section 2.1 Recommended Dosage in Adults			
1.	As currently presented the recommended dosage “1.25 grams” is not included following the placeholder “Trademark.”	A lack of the product strength may cause could potentially result in a wrong dose medication error (overdose or underdose).	Add the recommended dosage, “1.25 grams.” For example, “The recommended dose of TRADEMARK is 1.25 grams...”
2.	 (b) (4)	For consistency and readability, each individual dosage should follow each individual active ingredient.	Change dosage associated with each individual active ingredient to follow each individual active ingredient, enclosed in parentheses.

	(b) (4)		For example, "...is 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered..."
3.	As currently presented the error-prone abbreviation, "(IV)" is included	Error-prone abbreviations can be misinterpreted and have been involved in harmful medication errors, including wrong route of administration, such as misinterpreting the abbreviation I.V., for intravascular, as I.M., for intramuscular.	Eliminate the error-prone abbreviation "(IV)" by replacing with its intended meaning "intravenous." For example, "...administered by intravenous infusion over 30 minutes..."
FPI, Section 2.2, Dosage Adjustments in Patients with Renal Impairment			
1.	(b) (4)	Inconsistencies in recommended dosage can result in wrong dose medication errors.	Add the appropriate recommended dosage to Table 1, in the second column "Recommended Dosage of TRADEMARK (imipenem/cilastatin/relebactam (mg))", preceding the dosage of the individual active ingredients enclosed in parentheses. For example, see recommendation #2.
2.	(b) (4) We are concerned that the dosing interval information may be missed (b) (4) (b) (4) Therefore, we recommend adding a column that includes the dosing interval, "every 6 hours." For example:		

<p style="text-align: center;">Table 1: Dosage of TRADEMARK for Adult Patients with Renal Impairment (b) (4)</p> <div style="background-color: #cccccc; height: 200px; width: 100%;"></div> <p>Subsequently, (b) (4) can be deleted.</p>			
<p>FPI, Section Preparation of TRADEMARK Solution for IV Administration</p>			
1.	<p>As currently presented the error-prone abbreviation, “IV” is included in the header “Preparation of TRADEMARK Solution for IV Administration”, as well as in the first sentence “...technique prior to IV infusion...”</p>	<p>Error-prone abbreviations can be misinterpreted and have been involved in harmful medication errors, including wrong route of administration, such as misinterpreting the abbreviation I.V., for intravascular, as I.M., for intramuscular.</p>	<p>Eliminate the error-prone abbreviation “IV” by replacing with its intended meaning “intravenous.”</p> <p>For example, change the header to read “Preparation of TRADEMARK Solution for Intravenous Administration” and the first sentence to read “...technique prior to intravenous infusion...”</p>
2.	<div style="background-color: #cccccc; height: 100px; width: 100%;"></div>	<p>Negative statements such as (b) (4) have the potential to result in the opposite of its intended effect, (b) (4)</p>	<p>To provide clarity we recommend revising the negative statement (b) (4)</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div>

		(b) (4)	
3.	To prepare reduced doses of less than 1.25 grams, for patients with renal impairment, practitioners are instructed to remove and discard specific volumes of the prepared intravenous infusion to reach the appropriate reduced dose (see Table 2 in recommendation #4, below).	We are concerned about wrong dose (overdose) medication errors that may occur if practitioners fail to remove the 'excess' to reach the reduced dose. This proposed unique preparation technique for patients with renal impairment is not consistent with other intravenous infusion products (i.e., practitioner would withdraw the appropriate volume from the vial containing the constituted solution and add this volume to an infusion bag of the appropriate volume).	We acknowledge Merck's 04/02/2019 response, to our 03/28/2019 IR, in which they cite (b) (4) the need for their proposed unique methodology to prepare Recarbrio for patients with renal impairment. However, we think more can be done to mitigate the risk of administering the entire contents of the bag in patients with renal impairment. Therefore, on April 16, 2019 we sent an IR to Merck ^d recommending they: <ul style="list-style-type: none"> • Develop an IFU. • Incorporate information (b) (4) into their proposed PI. • Develop training materials.
4.	(b) (4)		
	Inconsistencies in dosage presentation can result in wrong dose medication errors. Add the appropriate dosages to Table 2, in the second column "Dosage of TRADEMARK (imipenem/cilastatin/relebactam (mg))", preceding the dosages of the individual active ingredients enclosed in parentheses. For example:		

	Table 2: (b) (4) (b) (4)
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FPI, Section 2.5, *Storage of Constituted Solution*

1.	<p>As currently presented the storage statement includes, "...under refrigeration at 2 to 8°C (36 to 46°F)."</p>	<p>The degree symbol (°) and units of temperature measurement (Centigrade and Fahrenheit) following the first numbers in the temperature ranges (e.g., the degree and Centigrade symbols (°C) following the 2 and the degree and Fahrenheit symbols (°F) following the 36) are missing.</p>	<p>Add the degree and Centigrade symbols (°C) following the 2 and degree and Fahrenheit symbols (°F) following the 36 within the storage information to provide clarity.</p> <p>For example, "...under refrigeration at 2°C to 8°C (36°F to 46°F)."</p>
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FPI, Section 2.6, *Injectable Drug Products* (b) (4)

1.	<p>As currently presented (b) (4)</p> <p>" (b) (4) Injectable Drug Products (b) (4) ", as well throughout this section.</p>	<p>(b) (4)</p>	<p>Eliminate (b) (4) as well as throughout this section.</p> <p>For example, change the header to read " (b) (4) Injectable Drug Products (b) (4) "</p>
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FPI, Section 3, Dosage Forms and Strengths			
1.	As currently presented the product strength “1.25 grams” is not included following the placeholder “Trademark.”	A lack of the product strength may cause could potentially result in a wrong dose medication error (overdose or underdose).	Add the product strength, “1.25 grams.” For example, “TRADEMARK 1.25 grams (imipenem, cilastatin, and relebactam)...”
2.	(b) (4)	For consistency and readability, each individual strength should follow each individual active ingredient. Customarily, the product strength follows the product name. (b) (4)	Change each individual strength to follow each individual active ingredient, as well as add parentheses to improve readability . For example, “...imipenem monohydrate 530 mg (equivalent to imipenem 500 mg), cilastatin sodium salt 531 mg (equivalent to cilastatin 500 mg), and relebactam monohydrate 263 mg (equivalent to relebactam 250 mg).”
FPI, Section 16, How Supplied/Storage and Handling			
1.	As currently presented the product strength “1.25 grams” is not included following the placeholder “Trademark.”	A lack of the product strength may cause could potentially result in a wrong dose medication error (overdose or underdose).	Add the product strength, “1.25 grams.” For example, “TRADEMARK 1.25 grams (imipenem, cilastatin, and relebactam)...”
2.	(b) (4)	For consistency and readability, each individual strength should follow each individual active ingredient. Customarily, the product strength follows the product name. (b) (4)	Change each individual strength to follow each individual active ingredient, as well as add parentheses to improve readability . For example, “...imipenem monohydrate 530 mg (equivalent

	(b) (4)	(b) (4)	to imipenem 500 mg), cilastatin sodium salt 531 mg (equivalent to cilastatin 500 mg), and relebactam monohydrate 263 mg (equivalent to relebactam 250 mg)."
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Table 3: Identified Issues and Recommendations for Merck (entire table to be conveyed to Applicant)

Container Label and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proprietary name is currently denoted by the placeholder "Trademark™."	The proposed proprietary name "Recarbrio" was found conditionally acceptable on April 11, 2019.	Remove the placeholder "Trademark™" and replace with the conditionally acceptable name "Recarbrio."
2.	As currently presented the strength statement reads "1.25 g per vial*"	Abbreviations, such as "g" can be misinterpreted and result in confusion, as well as medication errors.	To minimize the potential for misinterpretation, we recommend replacing the abbreviation "g" with the intended meaning "grams." For example. The strength statement should read "1.25 grams per vial*."
3.	As currently presented, the format for the expiration date is not defined.	The (b) (4) can result in confusion regarding the actual expiration date leading to deteriorated drug medication errors.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

			numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	As currently presented (b) (4) appears on the principal display panel (PDP) of the container label and carton labeling.	Medication errors could occur involving incorrectly administering the drug as an intravenous bolus.	Revise the statement (b) (4) to read "For Intravenous Infusion Only."
5.	As currently presented, the text (b) (4) appears on the side panel of the container label.	Risk of wrong technique medication errors in the preparation of the product.	If space permits consider adding the statement, "Must be reconstituted and further diluted.", to appear before the revised route of administration statement, "For Intravenous Infusion Only" on the PDP. For example, "Must be reconstituted and further diluted. For Intravenous Infusion Only." For the container label, if additional space is needed, consider relocating the contents list to the side panel.

6.	We note that the statement “Discard Unused Portion” has not been included following the package type on the container label and carton labeling.	Any remaining contents of the vial could be “saved” for future use resulting in use of deteriorated drug product medication errors.	Revise the statement “Single-Dose Vial” on the PDP to read “Single-Dose Vial – Discard Unused Portion.” Additionally, we recommend that you bold the font of the statement “Discard unused portion” to increase the prominence of this important information. For example, “Single-Dose Vial – Discard Unused Portion. ”
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5 CONCLUSION

Our evaluation of the proposed container label, carton labeling, and PI identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Merck so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Recarbrio (imipenem, cilastatin, and relebactam) for Injection that Merck submitted on November 16, 2018.

Table 4. Relevant Product Information for Recarbrio for Injection	
Initial Approval Date	N/A
Active Ingredient	imipenem, cilastatin, and relebactam
Indication	Treatment of patients 18 years of age and older (limited or no alternative therapies are available) with the following infections caused by susceptible gram-negative bacteria: <ul style="list-style-type: none">• Complicated urinary tract infections, including pyelonephritis• Complicated intra-abdominal infections
Route of Administration	Intravenous infusion
Dosage Form	Powder for injection
Strength	1.25 grams per vial (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) ^e
Dose and Frequency	Administer 1.25 grams (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) by intravenous (IV) infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CrCl) greater than or equal to 90 mL/min. Dosage adjustment in patients with renal impairment.  (b) (4)

^e Vial contains 

(b) (4)

	Patients with CrCl less than 15 mL/min should not receive Recarbrio unless hemodialysis is instituted within 48 hours.
How Supplied	A single dose glass vial containing (b) (4)
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to 86°F) [See USP Controlled Room Temperature]. Keep vials in the outer carton.
Container Closure	Consists of a 20 mL (b) (4) clear glass tubing vial, a 20 mm (b) (4) stopper, and a 20 mm flip-off seal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 19, 2019, we searched the L:drive and AIMS using the term, Recarbrio to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review^f that we reviewed and determined was not applicable to this review.

^f Myers, D. Proprietary Name Review for Recarbrio (IND 108754). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); Insert Date As 2018 MAY 11. RCM No.: 2017-19173629.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁶ along with postmarket medication error data, we reviewed the following Recarbrio (imipenem, cilastatin, and relebactam) for Injection labels and labeling submitted by Merck on November 16, 2018.

- Container label
- Carton labeling
- Prescribing Information available at the following link:
<\\cdsesub1\evsprod\nda212819\0000\m1\us\01-crt-uspi-mk7655a-iv-original.doc>

F.2 Label and Labeling Images

Container label (not to scale)



⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton labeling (trade tray label) (not to scale)



(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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