MSD

Essential Medicines List Secretariat
Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27, Switzerland

December 20, 2022

Dear Essential Medicines Committee:

MSD submits this application to request the inclusion of imipenem/cilastatin/relebactam (RECARBRIO®) on the World Health Organization (WHO) Model List of Essential Medicines (EML).

Imipenem/cilastatin/relebactam (IMR) is a combination product that contains the active substances imipenem, a carbapenem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor that protects imipenem from degradation by certain serine beta-lactamases such as SHV (sulfhydryl variable), TEM (temoneira), CTX-M (cefotaximase-Munich), P99 (*Enterobacter cloacae* P99), PDC (*Pseudomonas*-derived cephalosporinase), and KPC (*Klebsiella pneumoniae* carbapenemase).

In the US and EU, IMR is indicated for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP); bacteremia that occurs in association with, or is suspected to be associated with HAP or VAP (EU SmPC only); and infections due to aerobic Gram-negative organisms in patients with limited treatment options. We are conducting trials in support of indications in pediatric patients.

Antimicrobial resistance (AMR) is a major global health threat, taking 1.27 million lives in 2019, mostly concentrated in low- and middle-come countries (LMICs). We are seeking inclusion of IMR as an individual drug on the EML as a reserve antibiotic that can support access to effective treatment options and reduce mortality from resistant infections, in particular the WHO priority pathogens *Pseudomonas aeruginosa*, carbapenemase-producing *Klebsiella pneumoniae* (KPC) and carbapenem-resistant Enterobacterales (CRE). We continue to see a proliferation of these multidrug-resistant pathogens and mortality nearly doubles in patients with carbapenem-resistant infections.[1-6] There is a need for additional drug options to ensure effective treatments exist for infections from both CR/KPC-producing Enterobacterales and carbapenem-resistant *P. aeruginosa*.

We propose IMR for inclusion on the EML to provide this additional coverage to these needs for the following reasons:

- Several multi-country *in vitro* and clinical studies have demonstrated that imipenem/cilastatin/relebactam offers coverage of multi-drug-resistant pathogens when

there are limited, or no treatment options available. This is especially important in critically ill patients with hospital-acquired bacterial pneumonia and ventilator-acquired bacterial pneumonia.

- The broad-spectrum *in vitro* activity of IMR coupled with phase 2 and 3 data showing safety and efficacy in patients with complicated urinary tract infections, complicated intra-abdominal infections, and HAP/VAP has led to the recent inclusion of IMR as the preferred treatment option to serious infections, such as CRE and KPC-producing infections outside of the urinary tract, in clinical practice guidelines and guidance.

- We are actively executing on the global launch of IMR, where it is currently registered in 28 countries. In addition, MSD is also working to implement an access pricing framework for IMR.

- Given the rapid rise in antimicrobial resistance where a single agent or limited number of initially effective agents are utilized, having several agents available on the EML can help minimize the risk of pan-resistance while offering continued treatment options should there be interruptions in supply.

Consistent with the AWaRE classification of antibiotics, we support IMR's designation as a Reserve Group antibiotic that should only be deployed for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. With Reserve classification, we recommend that access of IMR is informed with appropriate use and strong stewardship activities.

We strongly recommend the inclusion of IMR on the EML and appreciate your consideration of our application. We are happy to provide the Expert Committee with any additional information if requested.

Sincerely,

Jenelle Krishnamoorthy, PhD, Vice President Global Public Policy and International Affairs, MSD

Elizabeth Rhee, MD, Vice President and Therapeutic Area Head, Infectious Disease Clinical Research, MSD

Application for Inclusion of Imipenem/Cilastatin/Relebactam (IMR) to the WHO Model List of Essential Medicines

Submitted to:
Essential Medicines List Secretariat
Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
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Date of Submission: December 20, 2022

Contents


Recarbio FDA.pdf


Recarbio EMA SPC.pdf

Summary Statement of Proposal for Inclusion

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We propose IMR for inclusion on the EML to provide this additional coverage to these needs for the following reasons:

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minimize the risk of pan-resistance while offering continued treatment options should there be interruptions in supply.

Consistent with the AWaRE classification of antibiotics, we support IMR's designation as a Reserve Group antibiotic that should only be deployed for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. With Reserve classification, we recommend that appropriate access of IMR is informed with appropriate use and strong stewardship activities.

Consultation with WHO Technical Departments

WHO Expert Committee on Selection and Use of Essential Medicines
Essential Medicines Team
Department of Health Products Policy and Standards

Organizations Consulted and/or Supporting the Submission

Merck, Sharp, and Dohme Corp.

Key Information for Proposed Medicine

INN: imipenem/cilastatin/relebactam
ATC: J01DH56

Dose Form and Strengths Proposed for Inclusion, Including Adult and Age-Appropriate Pediatric Dose Forms/Strengths

IMR is available for iv administration. IMR 1.25 g for injection is supplied as sterile powder for constitution in a single-dose vial containing imipenem 500 mg (anhydrate equivalent), cilastatin 500 mg (free acid equivalent), and relebactam 250 mg (anhydrate equivalent).

The recommended dosage of IMR is 1.25 g (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) administered by IV infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CrCl) of 90 mL/min or greater (normal kidney function). A dose reduction is recommended for patients with CrCl less than 90 mL/min (patients with renal impairment) (Table 1). For patients with fluctuating renal function, CrCl should be monitored. Patients with CrCl less than 15 mL/min should not receive IMR unless hemodialysis is instituted within 48 hours.

Table 1: Recommended dosage of IMR for adult patients with renal impairment[7]

Estimated CrCl (mL/min)*	Recommend dosage of IMR (mg)**	Dosing interval
60 to 89	1 g (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 g (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
ESRD†	0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

*CrCl calculated using the Cockcroft-Gault formula; **Administer by IV over 30 minutes every 6 hours; †Administration should be timed to follow hemodialysis.
CrCl = creatinine clearance; ESRD = end-stage renal disease; IMR = imipenem/cilastatin/relebactam; IV = intravenous.
The severity and location of infection, as well as clinical response should guide the duration of therapy. The recommended duration of treatment with IMR is 4 days to 14 days.

Clinical studies are ongoing for indications of IMR in pediatric patients ; data were presented at ID Week 2021.[8]

Indication(s)

FDA Label

IMR is a combination of imipenem, a penem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a β-lactamase inhibitor, indicated in patients 18 years of age and older for the treatment of the following infections caused by susceptible Gram-negative (GN) bacteria:[7]

- Complicated urinary tract infections (cUTI), including pyelonephritis, in patients who have limited or no alternative treatment options, caused by the following susceptible GN microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[7]
- Complicated intra-abdominal infections (cIAI), in patients who have limited or no alternative treatment options, caused by the following susceptible GN microorganisms: *Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides stercoris, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Fusobacterium nucleatum, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Parabacteroides distasonis,* and *Pseudomonas aeruginosa*.[7]
- HABP/VABP caused by the following susceptible GN microorganisms: *Acinetobacter calcoaceticus-baumannii complex, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Serratia marcescens*.[7]
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To reduce the development of drug-resistant pathogens and maintain the effectiveness of IMR and

other antibacterial drugs, IMR should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible pathogens. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.[7]

EMA Label

IMR is indicated for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP), in adults, bacteremia that occurs in association with, or is suspected to be associated with HAP or VAP in adults, and infections due to aerobic GN organisms in adults with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents.[9]

Proposal for Individual Medicine or Representative of a Pharmacological Class/Therapeutic Group

This proposal is for IMR to be included as an individual medicine, classified as a Reserve Group Antibiotic.

Information Supporting Public Health Relevance

Epidemiology

United States

Across the entire US population, the reported incidence of CRE was 0.3 to 2.93 infections per 100,000 person-years, with infection rates being highest in long-term acute-care hospitals.[10]

According to the CDC, 4.6% of acute-care hospitals in the US reported at least 1 HAI caused by CRE in 2012 (short-stay hospitals: 3.9%; long-term acute-care hospitals: 17.8%).[11] While rates of CRE are generally low in the US overall, increasing levels of CRE in the US have been observed; in an analysis of isolates from a variety of healthcare settings (outpatient, inpatient non-ICU, ICU, and nursing home), the proportion of carbapenem-resistant (CR) *K. pneumoniae* isolates increased from 0.1% in 2002 to 4.5% in 2010.[12]

In the Antimicrobial Resistance Patient Safety Atlas, from 2011 to 2014, across tracked HAIs, the national resistance level for CRE was 3.5%, with the rate varying across region (the highest resistance level was reported for Puerto Rico [27.9%]).[13] The national resistance level for CR *E. coli* was 0.7% (Puerto Rico: 4.1%) and for CR *K. pneumoniae* was 8.7% (Puerto Rico: 48.7%).[13] CR *P. aeruginosa* is also a concern, with data indicating that the national prevalence of CR *P. aeruginosa* was 19.3%, with the highest resistance level reported in Delaware (58.3%).[13]

From BD MedMined data, the rate of carbapenem-nonsusceptibility across Enterobacterales, *P. aeruginosa*, and *A. baumannii* together was found to be 3.4% (separately - Enterobacterales: 1.2% [*E.*

coli: 0.3%, *K. pneumoniae* 2.8%], *P. aeruginosa*: 14.6%, *A. baumannii*: 35.6%) and was observed to be significantly higher in ICU vs. non-ICU settings: 5.4% vs. 2.7%, p<0.0001.[14] This difference remained significant after multivariable analysis adjusted for various infection and hospital characteristics (odds ratio [OR]: 1.35, 95% confidence interval [CI]: 1.17 to 1.56, p<0.0001).[14]

The CDC monitor the occurrence of specific carbapenemase types (including KPC, OXA-48, VIM, IMP, and NDM), reporting the number of patients with each resistance mechanism per state; KPC was reported in every US state.[15]

Europe

CRE, especially CR *K. pneumoniae*, have a high potential to cause outbreaks in healthcare settings and outbreaks have already been reported in several EU Member States, eg, Czech Republic, France, Germany, Greece, Italy, Spain, and the UK.[16] The 2019 Antimicrobial Resistance Surveillance in Europe report published by the ECDC showed that countries in the south and east of Europe reporting higher resistance percentages than those in the north of Europe. The ECDC attributes this variation to possible "differences in antimicrobial use, infection control and healthcare utilization practices in the countries". More than a third (36.6%) of the reported *K. pneumoniae* isolates were resistant to at least one of the antimicrobial classes/therapies under regular surveillance. In 2019, the highest EU/EEA population-weighted mean resistance percentage was reported for third-generation cephalosporins (31.3%), fluoroquinolones (31.2%), aminoglycosides (22.3%), and carbapenems (7.9%).[16]

Just under a third (31.8%) of the *P. aeruginosa* isolates were resistant to at least one of the following antimicrobial classes/therapies: piperacillin ± tazobactam, fluoroquinolones, ceftazidime, aminoglycosides, carbapenems.[16] The highest EU/EEA population-weighted mean resistance percentage was for fluoroquinolones (18.9%), followed by piperacillin ± tazobactam (16.9%), carbapenems (16.5%), ceftazidime (14.3%), and aminoglycosides (11.5%). As with *K. pneumoniae*, levels of CR *P. aeruginosa* varied across Europe.[16]

The European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net) and European Survey of Carbapenemase-Producing Enterobacterales (EuSCAPE) report molecular mechanisms of resistance across European countries.[17] For the latter, the presence of KPC, NDM, OXA-48-like, and VIM type genes was confirmed for 71% of *K. pneumoniae* isolates and 40% of *E. coli* samples. In *K. pneumoniae* alone, the most frequently detected carbapenemase was KPC (45%) while in *E. coli*, OXA-48-like enzymes (56%) were the most frequently detected, albeit with substantial country-to-country variation in relative prevalence. At the country level, large proportions of KPC- producing *K. pneumoniae* were found in Italy (187/195 isolates), Israel (31/39), Greece (56/86), and Portugal (36/61). OXA-48-like enzymes were common in Turkey and Romania, and were also detected in Spain, Belgium, France, and Germany.[17]

SMART data

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a Merck-led surveillance initiative which collects data globally on the antibacterial susceptibility and resistance profile of respiratory, urinary, and abdominal isolates. SMART captures data on carbapenemase production.[18] For Enterobacterales, the most common carbapenemase in North and Latin America was KPC. However, the overall level of carbapenemase production was low; only 5.9% of isolates in Latin

America and 0.8% in North America produced a carbapenemase. In Europe, the most common carbapenemases were OXA-48, KPC, and NDM but the overall prevalence was again low (5.0%). In Asia-Pacific, the proportion of isolates expressing carbapenemases was 4.7%, with the most common carbapenemases being NDM, KPC, OXA-48, and KPC. The Middle East and Africa had the highest prevalence of carbapenemase production at 6.2%; OXA-48 was predominant, followed by NDM.[18]

For *P. aeruginosa*, carbapenem resistance is more commonly due to altered porin expression than carbapenemase expression.[18] Consequently, detected levels of carbapenemase were low, at 5.4% in Asia-Pacific, 6.9% in Europe, 11.4% in Latin America, 7.0% in the Middle East/Africa, and just 0.4% in North America. IMP was the only carbapenemase type identified in North America (likely due to the very small numbers of carbapenemases detected overall in North America) and was the most common carbapenemase identified in Asia. The most common carbapenemase detected in Europe, Latin America, and the Middle East/Africa was VIM.[18]

Clinical Impact

Worldwide, an estimated 4.95 million people died with drug-resistant bacterial infections in 2019, with 1.27 million of these deaths directly attributable to resistant infections, most of these concentrated in low- and middle-income countries (LMICs).[19] The report estimates that globally:

- Drug resistant *P. aeruginosa* was responsible for 84,600 deaths, of which 38,100 (45%) were carbapenem-resistant.
- Drug resistant *K. pneumoniae* was responsible for 193,000 deaths, of which 57,000 (29%) were carbapenem-resistant.
- Drug resistant *E. coli* was responsible for 219,000 deaths, of which 29,500 (13.5%) were carbapenem-resistant.

Mortality rates vary between infection sites; one study indicated an overall in-hospital mortality rate of 41.1% (14-day mortality: 34.1%) for KPC-producing *K. pneumoniae* infections, with infection site-specific 14-day mortality ranging from 4.9% (patients with UTI) to 57.0% (patients with septic shock).[20] Resistant infections are associated with a greater clinical burden than susceptible infections; greater in-hospital mortality (57.4% vs. 16.1%) and 30-day mortality (35.1% vs. 17.2%) was detected in CRE vs. CS Enterobacterales infections.[21]

Various risk factors are implicated in worse outcomes and exacerbate the clinical burden of GN infections. These include ICU admission, septic shock, corticosteroid treatment, older age, metastatic cancer, and catheter use in UTI.[22] Patients with underlying comorbid conditions can also be more severely impacted by GN infections, particularly resistant GN infections, eg, patients with neutropenia, hematological malignancies, or transplant recipients.[23-26]

Clinical Management

Patients with GN pathogen infections are often seriously ill and need immediate treatment, meaning an antibacterial agent must be selected before pathogen and susceptibility test results are available.[27] This is known as empiric therapy. When selecting empiric therapy, clinicians need to consider local ecology and resistance patterns and the clinical presentation of the patient, but often broad-spectrum antibacterial agents will be selected to maximize the chance of the chosen antibacterial agent being active against the as yet unknown pathogen/resistance mechanism. Ideally the patient

responds to the empiric therapy, but if not, the empiric antibacterial regimen may need to be altered. This could involve a switch of the initial antibacterial agent for another, or the 'add-on' of additional antibacterial agents to broaden coverage of the pathogens and/or resistance mechanisms.[27]

Once test results are available confirming the pathogen identity and its susceptibility to antibacterial agents, treatment is termed confirmed (or definitive) therapy.[27] If the empiric treatment was appropriate, the patient may remain on that same therapy, or may de-escalate to another antibacterial to which the pathogen is also susceptible, in line with the principles of antimicrobial stewardship. If the empiric therapy was inappropriate (ie, it was inactive against the causative pathogen), its use should be discontinued and the patient should be administered another more suitable therapy.[27] The provision of inappropriate empiric therapy significantly impacts patient outcomes, increasing the risk of mortality, costs, and length of stay.[20,28-31]

Antibacterial agents can either be administered alone (monotherapy) or in combination, most typically combinations of antibacterial agents from different classes.[27] Combination therapy has the advantage of decreasing the ability of the pathogen to survive the antibacterial agents' selection pressure and evolve resistance, ie, if the pathogen is not susceptible to one of the antibacterial agents, the pathogen may still be susceptible to the other agent[s].[27]

Standard of Care

Standard of care for GN pathogen infections includes cephalosporins (eg, cefotaxime, ceftazidime, ceftriaxone, cefepime), carbapenems (doripenem, ertapenem, imipenem/cilastatin, ertapenem), quinolones (ciprofloxacin, levofloxacin, moxifloxacin), aminoglycosides (amikacin, gentamicin, tobramycin), tetracyclines and glycylcyclines (tigecycline), polymyxins (colistin), and β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam).

Carbapenems have been used clinically since the approval of imipenem/cilastatin in 1985.[32] There are two groups of carbapenems, according to their activity against specific pathogens. Ertapenem has no activity against *Pseudomonas* spp. and *Acinetobacter* spp. and is a Group 1 carbapenem; imipenem/cilastatin, doripenem, and meropenem demonstrate activity against non-fermentative pathogens including *Pseudomonas* spp. and *Acinetobacter* spp. and are Group 2 carbapenems.[33] Carbapenems have traditionally been the drug of choice for difficult-to-treat pathogens, eg, ESBL or AmpC-producers, due to their broad-spectrum of activity.[34]

Colistin is a polymyxin-type antibacterial agent which increases the permeability of the outer bacterial cell membrane, causing cytoplasmic leakage and subsequent cell death. Colistin was first discovered in 1949, but use of this drug has diminished over time as a consequence of associated toxicity; rates of nephrotoxicity of up to 53.5% and neurotoxicity have been reported.[35,36] Although nephrotoxicity is typically mild in severity and reversible, damage to the kidney is associated with treatment failure, increased mortality, increased treatment costs, and increased length of stay.[36,37] Additionally, colistin monotherapy is less effective than colistin used in combination and is discouraged due to the potential for resistance development, and is also difficult to dose appropriately.[38-40] However, despite the risk of toxicity and other negative aspects of the drug, the use of colistin for GN infections has increased due to its broad antibacterial spectrum and historically low levels of resistance, coupled with increasing levels of carbapenem resistance and the subsequent reduction in the number of effective antimicrobial treatments.[35] As use of colistin has increased, resistant pathogens have

emerged; a plasmid-encoded colistin resistance gene, *mcr-1*, was found in *E. coli* isolated from livestock and humans in China and found since in multiple geographical regions (South-East Asia, North Africa, North America, and Europe).[41,42]

Novel Agents

Patients with GN infections urgently require new treatment options due to limitations in the standard of care. The emergence and spread of β-lactamase-mediated resistance to β-lactams has driven research into compounds which can inhibit β-lactamase enzymes, preventing them from hydrolyzing the antibacterial agent and removing their antibacterial activity. Examples of β-lactamase inhibitors are tazobactam, vaborbactam, avibactam, and relebactam.[43]

These β-lactamase inhibitors have been combined with existing and novel antibacterial agents to generate a number of significant new β-lactamase/β-lactamase-inhibitor combinations: ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, aztreonam/avibactam.[43] These new treatments have been assessed in clinical trials and are indicated for various infections attributable to GN pathogens (ie, cUTI, cIAI, and HABP/VABP).

Additional antimicrobial treatments which are not β-lactamase/β-lactamase-inhibitor combinations have been developed: plazomicin (next-generation aminoglycoside), eravacycline (fluorocycline), and cefiderocol (siderophore cephalosporin).[44-46]

Treatment Guidelines

The general recommendation for selecting a treatment regimen is that therapy choice must be individualized according to the susceptibility profile, type, and severity of infection, and the characteristics of the patient.[40] Treatment guidelines have also been developed to guide treatment selection, for MDR infections, or for specific infection types (cUTI, cIAI, HABP/VABP). Broadly, these clinical guidelines distinguish by low-risk and high-risk patients, and consider whether the patient is critically ill.

Unmet Need

A World Health Organization (WHO) report on antibacterial medicines in development highlights the unmet need in treatment options for priority resistant pathogens, especially for MDR and XDR GN pathogens.[47] There are numerous antibacterial agents currently in clinical development, but most of these novel antibacterial agents target Gram-positive pathogens.[47] GN pathogens remain the main challenge in addressing the issue of AMR, as outlined by the WHO's global priority list for research and development.[48] The development pipeline could lead to the approval of several new agents for GN infection, most of which are combinations that restore the activity of a trusted antibacterial against specific resistance mechanisms.[47] However, there are a limited number of novel agents which are active against priority pathogens.[47]

The continual evolution of pathogens means that no one therapy will ever be sufficient to combat infections indefinitely; a diverse range of antibacterial agents, active in the presence of a diverse range of resistance mechanisms, are needed. Patients with infections due to CR GN pathogens need novel, effective therapies to reduce the increasing use of last-resort antibacterial agents like colistin; treatments restoring the activity of carbapenems would be ideally suited to address this need.

Treatment Details

IMR is an injectable IV fixed dose combination of imipenem/cilastatin (IMI), a β-lactam antibacterial (specifically, a carbapenem), and relebactam (REL), a novel β-lactamase inhibitor.

IMI was the first marketed carbapenem when approved by the FDA in 1985.[32] It is a sterile formulation of imipenem (a thienamycin antibacterial) and cilastatin sodium (inhibitor of the renal dipeptidase, dehydropeptidase-I). IMI is stable against hydrolysis by many ESBLs and is frequently used for the treatment of severe infections in which GN pathogens and/or anaerobes play a significant role. In the US, IMI (PRIMAXIN™) is indicated for the treatment of the following infections: LRTI, UTI, intra-abdominal infections (IAI), gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections, and endocarditis.

REL is a non-β-lactam, small molecule diazabicyclooctane (DABCO) β-lactamase inhibitor that has no antibacterial activity itself but that does exhibit inhibitory activity against various β-lactamases: Class A carbapenemases (such as KPC), Class C cephalosporinases (including AmpC), and ESBLs. REL has been shown, in *in vitro* susceptibility and hollow fiber time-kill studies, to restore the activity of sub-inhibitory concentrations of IMI in IMI-resistant isolates (*P. aeruginosa* and Enterobacterales expressing the aforementioned β-lactamases). Additional *in vivo* animal efficacy studies further confirm the activity of REL, and integrated *in vivo* and *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) modeling and joint probability of target attainment analyses indicate that the combination of REL and IMI would be efficacious in most IMI-resistant strains at clinically achievable doses and concentrations. REL also enhances the activity of IMI on imipenem-susceptible pathogens by inhibiting resident or acquired β-lactamases. Furthermore, both IMI and REL are not subject to efflux pumps in *P. aeruginosa*.

IMR addresses an area of significant unmet medical need, as identified by regulators (FDA, EMA), public health entities (CDC, WHO), and professional societies (IDSA). IMR has demonstrated clinical safety and efficacy in the target patient population. Many hospitalized patients at risk for MDR infections, and at risk for poor outcomes from these infections, have multiple underlying comorbidities, and the IMR clinical program has included these patients. IMR has also been evaluated in participants with varying degrees of renal insufficiency, and dosing in these patients is well-supported by PK and clinical data. The phase 2 clinical trials for REL (PN003; NCT01505634[49]/PN004; NCT01506271[50]) indicated a comparable safety profile for IMI plus REL and IMI, and indicated the optimal dose of REL (250 mg). The registrational phase 3 clinical trial for IMR (Protocol 013 or RESTORE-IMI 1; NCT02452047[51]) evaluated efficacy and safety of IMR compared with colistin (colistimethate sodium [CMS]) plus IMI. An additional phase 3 clinical trial (Protocol 014 or RESTORE-IMI 2; NCT02493764[52]) evaluated efficacy and safety of IMR compared with piperacillin/tazobactam (PIP/TAZ) in patients with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP).

Place in Therapy

IMR should be considered for use as a 'switch' or 'add-on' therapy for patients in whom a GN infection with CRE (particularly KPC-producing Enterobacterales) or CR *P. aeruginosa* is suspected (prior to receipt of culture and susceptibility results). For these patients, carbapenems are likely no longer an effective treatment option. Such suspicion may be based on local epidemiological data, presence of known risk factors for infection with one of these pathogens, or clinical indicators (ie, the patient is deteriorating on the initial empiric therapy, perhaps due to that empiric therapy being inappropriate).

IMR should also be considered for use as a confirmed/definitive treatment once the causative pathogen is established to be susceptible to IMR and non-susceptible to other therapeutic alternatives.

IMR has been compared to colistin in the phase 3 clinical trial RESTORE-IMI 1 and data are supportive of its use in preference to colistin, thus supporting a colistin-avoidance approach. The broad coverage of resistance mechanisms exhibited by IMR, indicate that equal consideration should be given for IMR and other novel agents (eg, ceftazidime/avibactam, meropenem/vaborbactam, cefiderocol [when available]) depending on the local epidemiology, and in some instances, IMR should be preferred (eg, IMR addresses a broader range of resistance mechanisms in *P. aeruginosa* than other agents).

Dose Regimen and Duration of Treatment

The recommended dosage of RECARBRIO is 1.25 g (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) administered by IV infusion over 30 minutes every 6 hours in patients 18 years of age and older with creatinine clearance (CrCl) of 90 mL/min or greater (normal kidney function). A dose reduction is recommended for patients with CrCl less than 90 mL/min (patients with renal impairment) (Table 2). For patients with fluctuating renal function, CrCl should be monitored. Patients with CrCl less than 15 mL/min should not receive RECARBRIO unless hemodialysis is instituted within 48 hours.

Table 2: Recommended dosage of RECARBRIO for adult patients with renal impairment[7]

Estimated CrCl (mL/min)*	Recommend dosage of RECARBRIO (mg)**	Dosing interval
60 to 89	1 g (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 g (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
ESRD†	0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

*CrCl calculated using the Cockcroft-Gault formula; **Administer by IV over 30 minutes every 6 hours; †Administration should be timed to follow hemodialysis.

CrCl = creatinine clearance; ESRD = end-stage renal disease; IV = intravenous.

The severity and location of infection, as well as clinical response should guide the duration of therapy. The recommended duration of treatment with RECARBRIO is 4 days to 14 days.

Requirements to Ensure Appropriate Use

The only diagnostic methods for imipenem/relebactam susceptibility testing are the manual assays; there are plans by Becton Dickinson (Phoenix), BioMerieux (Vitek) and Beckmann Coulter (Microscan) to develop automated testing for imipenem/relebactam susceptibility with MIC but those are not yet commercially available. The diagnostic methods are outlined below:

- **Liofilchem® MIC** test strips for imipenem/relebactam are available from Liofilchem S.R.L. Currently there are interpretive criteria for *Pseudomonas aeruginosa* and Enterobacterales. Additional information can be found online at, https://www.liofilchem.com/company/about-us.html.

- **HardyDisk™ AST's** impregnated paper disks for imipenem/relebactam susceptibility testing (available in single cartridges (Z9441) or in packs of five (Z9445)) are available from Hardy Diagnostics. HardyDisk™ AST's are impregnated paper disks used for Antimicrobial Susceptibility Testing (AST); also known as disk diffusion or Kirby-Bauer testing. Additional information can be found online at, https://hardydiagnostics.com/

- **Thermo Scientific™ Sensititre™ Gram-Negative Standard MIC Plates** for

imipenem/relebactam are available from Thermo Fisher Scientific Microbiology. The Thermo Scientific™ Sensititre™ MDRGN2F and MDRGNX2F plates deliver results directly from broth microdilution (BMD). Additional information can be found online at, www.thermofisher.com/AST.

- **ETEST® MIC** strips for determining imipenem/relebactam MIC for Enterobacterales and *Pseudomonas aeruginosa* are available for order by BioMérieux.
    - BioMérieux, in a letter to their customers, has acknowledged there is a performance issue involving an MIC overestimation issue on different lot numbers of ETEST® imipenem/relebactam (IPR) strips specific to some *Pseudomonas aeruginosa*. This is not an issue for the Enterobacterales.

Recommendations in Clinical Guidelines

IMR has broad-spectrum *in vitro* activity against Gram-negative pathogens, including resistant pathogens such a CRE and difficult-to-treat resistance *P. aeruginosa*, in which few available therapeutic options are available. Inclusion of newly developed agents into prominent disease-focused guidelines (eg, HAP/VAP) is hampered by the long delay in updating the guidelines. For example, the latest IDSA or ESCMID guidelines for the treatment of HAP/VAP were published in 2016 and 2017 respectively, and none of the newer beta-lactam agents (eg, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam or cefiderocol) are included as the phase 3 trials were completed and/or regulatory approvals of these agents were not granted until after this cut-off date for these publications.[53,54]

To accommodate the long delay in publication of formal guidelines, authorities such as the IDSA have published pathogen-specific guidance documents to provide guidance on the treatment of certain commonly encountered problematic resistant Gram-negative pathogens.[55]

The broad-spectrum *in vitro* activity of IMR coupled with phase 2 and 3 data showing safety and efficacy in patients with complicated UTI, complicated IAI, and HAP/VAP has led to the inclusion of IMR as monotherapy for the treatment of serious infections. More specifically, IMR is a preferred treatment option for pyelonephritis and complicated urinary tract infections caused by CRE resistant to both ertapenem and meropenem. In addition, IMR is a preferred treatment option for infections outside of the urinary tract caused by CRE resistant to both ertapenem and meropenem when carbapenemase testing results are not available or negative. For KPC-producing organisms that are outside of the urinary tract, IMR is a preferred agent. For uncomplicated cystitis, complicated urinary tract infections, pyelonephritis, and infections outside of the urinary tract caused by DTR *P. aeruginosa*, IMR is a preferred treatment option as well.

Consistent with recommendations in this guidance document, IMR is listed as a treatment option for resistant pathogens such as CRE/KPC or DTR *P. aeruginosa* in prominent clinical bedside references including the Sanford Guide[56] and UpToDate[57] as well.

Review of Benefits: Summary of Evidence of Comparative Effectiveness and Safety

RESTORE-IMI 1 (NCT02452047; Motsch 2020)[51]

The efficacy and safety of IMR for the treatment of cIAI, cUTI, and HABP/VABP was assessed in a phase 3, randomized, double-blind, active comparator-controlled, parallel-group, multicenter trial of IMR (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) plus placebo vs. colistin (300 mg colistin base activity; 720 mg colistimethate sodium) plus IMI (imipenem 500 mg/cilastatin 500 mg) in adult patients with IMI-non-susceptible GN pathogen infections.[51] The primary efficacy endpoint was favorable overall response.

RESTORE-IMI 1 was an estimation trial, not powered to infer statistically significant differences in efficacy between the treatment arms. Because IMR is a QIDP, this design was permitted by the Food and Drug Administration (FDA).[51] RESTORE-IMI 1 met its primary efficacy endpoint, showing that IMR was at least as efficacious as colistin plus IMI for the treatment of IMI-non-susceptible, colistin-susceptible GN pathogen infections (Table 3).

Table 3: Summary of efficacy endpoints for RESTORE-IMI 1[51]

Group 1: IMR (N=31)		Group 2: Colistin plus IMI (N=16)	Group 1 vs. Group 2 unadjusted difference, %	Group 1 vs. Group 2 adjusted difference*, % (90% CI)**
mMITT population, n (%)	(n=21)	(n=10)		
Favorable overall response	15 (71.4)	7 (70.0)	1.4	-7.3 (-27.5, 21.4)
Favorable clinical response at Day 28	15 (71.4)	4 (40.0)	31.4	26.3† (1.3, 51.5)
All-cause mortality at Day 28	2 (9.5)	3 (30.0)	-20.5	-17.3 (-46.4, 6.7)
SmMITT population, n (%)	(n=28)	(n=13)		
Favorable overall response	21 (75.0)	10 (76.9)	-1.9	-4.5 (-24.2, 20.7)
Favorable clinical response at Day 28	21 (75.0)	7 (53.8)	21.2	17.6 (-5.9, 42.5)
All-cause mortality at Day 28	3 (10.7)	3 (23.1)	-12.4	-10.5 (-35.2, 9.6)
PP population, n (%)	(n=15)	(n=5)		
Favorable overall response	13 (86.7)	4 (80.0)	6.7	14.6 (-7.0, 54.2)

*Adjusted differences account for the different infection types in each treatment arm; **90% CI calculated using the Miettinen & Nurminen method; †Clinically significant as the 90% CI does not include zero.
CI = confidence interval; IMI = imipenem/cilastatin; IMR = imipenem/cilastatin/relebactam; mMITT = modified microbiological intent-to-treat; PP = per protocol; SmMITT = supplemental modified microbiological intent-to-treat.

RESTORE-IMI 1 Additional Analysis

A secondary analysis of RESTORE-IMI 1 data compared outcomes between the mMITT population and the supplemental mMITT (SmMITT) population, in which eligibility was based on local site testing (n=41). The analysis found that the outcomes in the SmMITT population were consistent with those in the mMITT population.[58]

An additional secondary analysis was conducted to evaluate nephrotoxicity retrospectively using two AKI assessment criteria (kidney disease improving global outcomes [KDIGO] and risk, injury, failure, loss, and end-stage kidney disease [RIFLE]). The analysis found that, based on KDIGO and RIFLE criteria, imipenem/cilastatin/relebactam had a more favorable renal safety profile than colistin-based therapy in patients with serious, IMI-non-susceptible GN bacterial infections.[59]

RESTORE-IMI 2 (NCT02493764; Titov 2020)[52]

The efficacy of IMR for the treatment of HABP/VABP was assessed in a phase 3, randomized, double-blind, active comparator-controlled, parallel-group, multicenter trial of IMR (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg) vs. PIP/TAZ (piperacillin 4 g/tazobactam 500 mg). The primary efficacy endpoint was all-cause mortality through Day 28, while the key secondary endpoint was favorable clinical response at early follow-up (EFU).[52]

RESTORE-IMI-2 met the primary and key secondary efficacy endpoints, showing that IMR was at least as efficacious as PIP/TAZ for the treatment of patients with HABP/VABP (Table 4).

Table 4: Summary of efficacy endpoints for RESTORE-IMI 2[52]

	Group 1: IMR (N=268)	Group 2: PIP/TAZ (N=269)	Group 1 vs. Group 2 unadjusted difference, %	Group 1 vs. Group 2 adjusted difference, % (95% CI)***
MITT population, n (%)	(n=264)	(n=267)		
All-cause mortality at Day 28*	42 (15.9)	57 (21.3)	-5.4	-5.3 (-11.9, 1.2)†
Favorable clinical response at EFU**	161 (61.0)	149 (55.8)	5.2	5.0 (-3.2, 13.2)†
Favorable clinical response at Day 28	137 (51.9)	135 (50.6)	1.3	1.1 (-7.2, 9.4)

*Denotes primary efficacy outcome; **denotes key secondary efficacy outcome; ***adjusted differences are calculated to account for the stratification factors in the trial randomization including ventilation status and APACHE (Acute Physiology and Chronic Health Evaluation) II score (<15 vs. >15); point estimates and the corresponding CIs based on the stratified Miettinen & Nurminen method; †p<0.001 (p=0.025 indicates non-inferiority).
CI = confidence interval; EFU = early follow-up; IMR = imipenem/cilastatin/relebactam; MITT = modified intent-to-treat; PIP/TAZ = piperacillin/tazobactam.

RESTORE IMI-2 Additional Analysis

A *post-hoc* analysis of RESTORE-IMI 2 evaluated outcomes among participants infected with imipenem-resistant pathogens. Among the microbiological modified intent-to-treat participants who received IMR, 18 had imipenem-nonsusceptible pathogens and 112 had imipenem-susceptible pathogens. Relebactam restored the *in vitro* susceptibility to imipenem and IMR was an efficacious treatment option for HABP/VABP caused by these imipenem-nonsusceptible pathogens. Among IMR treated participants, efficacy measures including microbiologic response, clinical response, and Day 28 all-cause mortality were not affected by baseline pathogen susceptibility to imipenem.[60]

Emergence of resistance on treatment not only jeopardizes the individual patient's outcome, but also poses considerable collateral damage on infection control. A secondary analysis of RESTORE-IMI 2 observed that emergence of nonsusceptibility to IMR occurred rarely. Emergence of nonsusceptibility

to IMR was identified by isolates that were susceptible at baseline but subsequently were identified during treatment and tested nonsusceptible. Of all randomized participants who received IMR, 5/268 (1.9%) participants and 2/268 (0.7%) had nonsusceptible post-baseline isolates by CLSI criteria and EUCAST criteria, respectively.[61]

A secondary analysis of RESTORE-IMI 2 compared the efficacy of IMR and PIP/TAZ stratified by different characteristics that define patients as critically ill, including APACHE II score ≥15 at baseline, ICU at baseline, moderate/severe renal impairment (creatinine clearance <60 mL/min) at baseline, and patients who received vasopressors within 72 hours of the first study dose or during the study. The Day 28 ACM rate was lower in the IMR treatment arm compared with the PIP/TAZ arm in participants with an APACHE II score ≥15 and in participants who received vasopressors with 95% confidence intervals that excluded zero, suggesting a potential advantage for IMR. In participants with moderate/severe renal impairment and in those in the ICU at baseline, Day 28 ACM rates were similar between treatment arms.[62]

In critically ill patients, such as those with HABP/VABP, there is a high frequency of augmented renal clearance (ARC), commonly defined as a body surface adjusted creatinine clearance of >130 mL/min, which may lead to reduced exposure for renally eliminated antibacterial agents, such as β-lactams. This potentially results in inadequate dosing leading to treatment failure. Conversely, renal impairment (RI) is also common in critically ill patients and is associated with high mortality. To better understand the relationship between baseline renal function (including ARC and RI) and outcomes upon treatment with IMR or PIP/TAZ, a *post hoc* efficacy assessment of RESTORE-IMI 2 participants was conducted along with the probability of PK/PD target attainment for imipenem and relebactam. Clinical efficacy results from this analysis supported the current IMR dosage regimen for HABP/VABP, with full 1.25 g every 6-hour dosing in ARC and reduced dosing with patients with renal insufficiency. Adequate exposures of both imipenem and relebactam were achieved, even among patients with ARC, which further reinforced the adequacy of the regulatory approved dosage of IMR.[63]

There is a need for broad-spectrum agents to treat nosocomial infections, such as HABP/VABP, that are active against MDR pathogens and have the potential to be given as a monotherapy for both empiric and/or definitive treatment. IMR has broad-spectrum activity against Gram-negative pathogens, including carbapenem resistant Enterobacterales (CRE) and MDR *P. aeruginosa*, as well as Gram-positive pathogens. A *post hoc* analysis was performed to evaluate treatment outcomes with IMR in the subgroup of RESTORE-IMI 2 participants with polymicrobial HABP/VABP. Approximately 28.8% of IMR treated participants were infected with more than one pathogen. No differences in outcomes including microbiologic response, clinical response, and Day 28 all-cause mortality were observed among IMR treated participants infected with monomicrobial vs. polymicrobial infection.[64]

IMR for Complicated Intra-Abdominal Infections (NCT01506271; Lucasti 2016)[50]

The efficacy and safety of IMR for the treatment of cIAI was assessed in a phase 2 multicenter, double-blind, randomized, active comparator-controlled trial comparing the safety and efficacy of IMI (imipenem 500 mg/cilastatin 500 mg) plus REL (250 mg or 125 mg) vs. IMI (imipenem 500 mg/cilastatin 500 mg) monotherapy in patients with cIAI, irrespective of the type or susceptibility profile of the causative pathogen.[50] The primary efficacy objective was to demonstrate non-inferiority of IMR vs. IMI, assessed by the proportion of patients in each arm that achieved a favorable

clinical response. Non-inferiority would be concluded if the lower bound of the 95% CI was greater than -15%.[50]

This trial met its primary endpoint, IMR, with either 250 mg or 125 mg of REL, given once every 6 hours for 4 to 14 days was as efficacious as IMI alone in the treatment of cIAI (Table 5).

Table 5: Summary of efficacy endpoints in ME patients in NCT01506271[50]

	Group 1: IMI + REL (REL 250 mg)	Group 2: IMI + REL (REL 125 mg)	Group 3: IMI (plus placebo)	Group 1 vs. Group 3 difference, % (95% CI)	Group 2 vs. Group 3 difference, % (95% CI)
Favorable clinical response, n/N (%)					
At DCIV*	78/81 (96.3)	85/86 (98.8)	79/83 (95.2)	1.1 (-6.2, 8.6)**	3.7 (-2.0, 10.8)**
At EFU	75/79 (94.9)	81/86 (94.2)	78/81 (96.3)	-1.4 (-9.1, 6.0)	-2.1 (-9.7, 5.3)
At LFU	74/79 (93.7)	81/85 (95.3)	75/79 (94.9)	-1.3 (-9.6, 6.9)	-0.4 (-7.2, 8.2)
Favorable microbiological response, n/N (%)					
At DCIV	81/83 (97.6)	86/86 (100)	82/84 (97.6)	-0.0 (-6.3, 6.2)	2.4 (-2.0, 8.3)
At EFU	76/78 (97.4)	80/82 (97.6)	78/80 (97.5)	-0.1 (-6.7, 6.4)	-0.1 (-6.3, 6.5)
At LFU	75/78 (96.2)	80/82 (97.6)	75/78 (96.2)	0.0 (-7.4, 7.4)	-1.4 (-5.1, 8.6)

*Denotes primary efficacy outcome; **$P<0.001$ ($P<0.025$ indicates non-inferiority).
CI = confidence interval; DCIV = discontinuation of intravenous therapy; EFU = early follow-up; IMI = imipenem/cilastatin; LFU = late follow-up; ME = microbiologically evaluable; REL = relebactam.

Furthermore, IMI plus REL had a comparable safety profile to IMI monotherapy; rates of AEs, SAEs, and drug-related AEs were similar between each group and between different doses of REL (Table 10).

IMR for Complicated Urinary Tract Infections (NCT01505634; Sims 2017)[49]

The efficacy and safety of IMR for the treatment of cUTI was assessed in a phase 2 multicenter, double-blind, randomized, active comparator-controlled trial comparing the safety and efficacy of IMI (imipenem 500 mg/cilastatin 500 mg) plus REL (250 mg or 125 mg) vs. IMI (imipenem 500 mg/cilastatin 250 mg) monotherapy in patients with cUTI, irrespective of the type or susceptibility profile of the causative pathogen.[49] The primary efficacy objective was to demonstrate non-inferiority of IMR vs. IMI, assessed by the proportion of patients in each arm that achieved a favorable microbiological response. Non-inferiority would be concluded if the lower bound of the 95% CI was greater than -15%.[49]

This trial met its primary endpoint; IMR, with either 250 mg or 125 mg of REL, given once every 6 hours for 4 to 14 days was as efficacious as IMI alone in the treatment of cUTI (Table 6).

Table 6: Summary of efficacy endpoints in ME population in NCT01505634[49]

	Group 1: IMI + REL (REL 250 mg)	Group 2: IMI + REL (REL 125 mg)	Group 3: IMI (plus placebo)	Group 1 vs. Group 3 difference, % (95% CI)	Group 2 vs. Group 3 difference, % (95% CI)
Favorable microbiological response, n/N (%)					
At DCIV*	64/67 (95.5)	70/71 (98.6)	74/75 (98.7)	-3.1 (-11.2, 3.2)	-0.1 (-6.4, 5.9)
At EFU	40/65 (61.5)	49/72 (68.1)	50/71 (70.4)	-8.9 (-24.6, 7.1)	-2.4 (-17.4, 12.8)
At LFU	43/63 (68.3)	45/69 (65.2)	45/72 (62.5)	5.8 (-10.4, 21.5)	2.7 (-13.1, 18.4)
Favorable clinical response, n/N (%)					
At DCIV	67/69 (97.1)	77/78 (98.7)	79/80 (98.8)	-1.6 (-8.9, 4.2)	-0.0 (-5.8, 5.6)
At EFU	57/64 (89.1)	67/73 (91.8)	71/76 (93.4)	-4.4 (-15.2, 5.3)	-1.6 (-11.2, 7.5)
At LFU	55/62 (88.7)	62/71 (87.3)	67/76 (88.2)	0.6 (-11.2, 11.6)	-0.8 (-12.1, 10.2)

*Denotes primary efficacy outcome.
CI = confidence interval; DCIV = discontinuation of intravenous therapy; EFU = early follow-up; IMI = imipenem/cilastatin; LFU = late follow-up; ME = microbiologically evaluable; REL = relebactam.

Real World Evidence from Observational Studies IMR

IMR is guideline-recommended as a preferred treatment option for XDR and DTR *P. aeruginosa* infections but there is limited real world data published to date.

Real-life experience of IMR for the treatment of extensively drug-resistant and difficult-to-treat Pseudomonas infections showed IMR was effective in a cohort of critically ill patients with pneumonia. In this retrospective, observational study of patients >18 years with a respiratory culture positive for MDR *P. Aeruginosa* that was susceptible to IMR, patients received IMR ≥72 hours. IMR had a 70% rate of clinical success. The medium age was 63, medium APACHE II score was 26, and 70% of the patients had VAP. Isolates demonstrated XDR (n=2), DTR (n=8), and VIM+ (n=1).[65]

In a 2021 study of early multicenter experience with IMR for MDR GN infections, case series provided preliminary real-world evidence regarding the safety and efficacy of IMR in patients with MDR GNI. There were mixed infection sources, with pulmonary infections (11/21, 52%) composing the majority. The primary pathogen was *P. aeruginosa* (16/21, 76%), and 15/16 (94%) isolates were multidrug-resistant.[66]

Review of Comparative Safety: Summary of Evidence of Harms and Toxicity

RESTORE-IMI 1 (NCT02452047; Motsch 2020)[51]

In RESTORE-IMI 1, treatment with IMR was well-tolerated and exhibited a more favorable renal safety profile than treatment with colistin plus IMI: there was a statistically significant lower incidence of treatment-emergent nephrotoxicity in patients who received IMR than in patients who received colistin plus IMI (3/29 [10.3%] vs. 9/16 [56.3%], p=0.002).[51] The incidence of adverse events (AEs), deaths, serious adverse events (SAE), drug-related AEs, and discontinuations due to AEs, and drug-related AEs was lower in patients who received IMR than in patients who received colistin plus

IMI, though the trial was not powered to detect statistical significance in these outcomes (Table 7).

Table 7: Summary of AEs in RESTORE-IMI 1[51]

	Group 1: IMR (N=31)	Group 2: Colistin plus IMI (N=16)	Group 3: IMR (open-label) (N=3)	Group 1 vs. Group 2 difference, % (95% CI)*
Patients in treatment group, n (%)				
With ≥1 AE	22 (71.0)	13 (81.3)	3 (100.0)	-10.3 (-33.1, 18.0)
With drug-related AE**	9 (29.0)	3 (18.8)	0 (0.0)	10.2 (-18.0, 33.1)
With SAE	5 (16.1)	5 (31.3)	1 (33.3)	-15.2 (-42.3, 9.2)
With serious drug-related AE**	3 (9.7)	5 (31.3)	3 (100.0)	-21.6 (-47.8, 1.3)
Who died	0 (0.0)	0 (0.0)	1 (33.3)	0.0 (-19.7, 11.2)
Discontinued therapy due to AE	2 (6.5)	3 (18.8)	1 (33.3)	-12.3 (-37.8, 6.5)
Discontinued therapy due to a drug-related AE**	0 (0.0)	3 (18.8)	1 (33.3)	-18.8 (-43.3, -6.2)
Discontinued therapy due to SAE	0 (0.0)	2 (12.5)	1 (33.3)	-12.5 (-36.3, -0.3)
Discontinued therapy due to a drug-related SAE**	0 (0.0)	0 (0.0)	1 (33.3)	0.0 (-19.7, 11.2)
With ≥1 AE	0 (0.0)	0 (0.0)	1 (33.3)	0.0 (-19.7, 11.2)

*Based on the Miettinen & Nurminen method; **As determined by the investigator.
AE = adverse events; CI = confidence interval; IMI = imipenem/cilastatin; IMR = imipenem/cilastatin/relebactam; SAE = serious adverse event.

RESTORE-IMI 2 (NCT02493764; Titov 2020)[52]

In RESTORE-IMI 2, treatment with IMR resulted in no notable or unexpected safety signals that would preclude its use in adults with HABP/VABP.[52] The incidence of AEs, deaths, serious AEs, drug-related AEs, and discontinuations due to AEs were comparable between patients who received IMR and those who received PIP/TAZ (Table 8).

Table 8: Summary of AEs in RESTORE-IMI 2[52]

	Group 1: IMR (N=268)	Group 2: PIP-TAZ (N=269)	Group 1 vs. Group 2 difference, % (95% CI)*
Patients in treatment group, n (%)	(n=266)	(n=269)	
With ≥1 AE	226 (85.0)	233 (86.6)	-1.7 (-7.7, 4.3)
With drug-related AE**	31 (11.7)	26 (9.7)	2.0 (-3.3, 7.4)
With serious AE	71 (26.7)	86 (32.0)	-5.3 (-13.0, 2.5)
With serious and drug-related AE**	3 (1.1)	2 (0.7)	0.4 (-1.7, 2.6)
Who died	40 (15.0)	57 (21.2)	-6.2 (-12.7, 0.4)
Who discontinued therapy due to an AE	15 (5.6)	22 (8.2)	-2.5 (-7.1, 1.8)

Who discontinued therapy due to a drug-related AE**	6 (2.3)	4 (1.5)	0.8 (-1.8, 3.5)
Who discontinued therapy due to a serious AE	9 (3.4)	18 (6.7)	-3.3 (-7.3, 0.4)
Who discontinued therapy due to a drug-related serious AE**	2 (0.8)	1 (0.4)	0.4 (-1.4, 2.4)

*Based on the Miettinen & Nurminen method; **As determined by the investigator.
AE = adverse events; CI = confidence interval; IMR = imipenem/cilastatin/relebactam; PIP/TAZ = piperacillin/tazobactam.

IMR for Complicated Intra-Abdominal Infections (NCT01506271; Lucasti 2016)[50]

The efficacy and safety of IMR for the treatment of cIAI was assessed in a phase 2 multicenter, double-blind, randomized, active comparator-controlled trial comparing the safety and efficacy of IMI (imipenem 500 mg/cilastatin 500 mg) plus REL (250 mg or 125 mg) vs. IMI (imipenem 500 mg/cilastatin 500 mg) monotherapy in patients with cIAI, irrespective of the type or susceptibility profile of the causative pathogen.[50] The primary efficacy objective was to demonstrate non-inferiority of IMI plus REL vs. IMI, assessed by the proportion of patients in each arm that achieved a favorable clinical response. Non-inferiority would be concluded if the lower bound of the 95% CI was greater than -15%.[50]

This trial met its primary endpoint, IMR, with either 250 mg or 125 mg of REL, given once every 6 hours for 4 to 14 days was as efficacious as IMI alone in the treatment of cIAI (Table 9).

Table 9: Summary of efficacy endpoints in ME patients in NCT01506271[50]

	Group 1: IMI + REL (REL 250 mg)	Group 2: IMI + REL (REL 125 mg)	Group 3: IMI (plus placebo)	Group 1 vs. Group 3 difference, % (95% CI)	Group 2 vs. Group 3 difference, % (95% CI)
Favorable clinical response, n/N (%)					
At DCIV*	78/81 (96.3)	85/86 (98.8)	79/83 (95.2)	1.1 (-6.2, 8.6)**	3.7 (-2.0, 10.8)**
At EFU	75/79 (94.9)	81/86 (94.2)	78/81 (96.3)	-1.4 (-9.1, 6.0)	-2.1 (-9.7, 5.3)
At LFU	74/79 (93.7)	81/85 (95.3)	75/79 (94.9)	-1.3 (-9.6, 6.9)	-0.4 (-7.2, 8.2)
Favorable microbiological response, n/N (%)					
At DCIV	81/83 (97.6)	86/86 (100)	82/84 (97.6)	-0.0 (-6.3, 6.2)	2.4 (-2.0, 8.3)
At EFU	76/78 (97.4)	80/82 (97.6)	78/80 (97.5)	-0.1 (-6.7, 6.4)	-0.1 (-6.3, 6.5)
At LFU	75/78 (96.2)	80/82 (97.6)	75/78 (96.2)	0.0 (-7.4, 7.4)	-1.4 (-5.1, 8.6)

*Denotes primary efficacy outcome; **$P<0.001$ ($P<0.025$ indicates non-inferiority).
CI = confidence interval; DCIV = discontinuation of intravenous therapy; EFU = early follow-up; IMI = imipenem/cilastatin; LFU = late follow-up; ME = microbiologically evaluable; REL = relebactam.

Furthermore, IMI plus REL had a comparable safety profile to IMI monotherapy; rates of AEs, SAEs, and drug-related AEs were similar between each group and between different doses of REL (Table 10).

Table 10: Summary of AEs in NCT01506271[50]

	Group 1: IMI + REL (REL 250mg) (N=117)	Group 2: IMI + REL (REL 125mg) (N=116)	Group 3: IMI (plus placebo) (N=114)	Group 1 difference vs. Group 3, % (95% CI)	Group 2 difference vs. Group 3, % (95% CI)
Patients in treatment group, n (%)					
With ≥1 AE	57 (48.7)	55 (47.4)	47 (41.2)	7.5 (-5.4, 20.1)	6.2 (-6.7, 18.8)
With drug-related* AE	16 (13.7)	16 (13.8)	11 (9.6)	4.0 (-4.5, 12.7)	4.1 (-4.4, 12.8)
With SAE	4 (3.4)	11 (9.5)	8 (7.0)	-3.6 (-10.3, 2.4)	2.5 (-5.0, 10.1)
With serious and drug-related* AE	0 (0.0)	0 (0.0)	1 (0.9)	-0.0 (-4.0, 3.9)	-0.9 (-4.8, 2.4)
Who died	0 (0.0)	3 (2.6)	0 (0.0)	0.0 (-3.3, 3.2)	2.6 (-0.7, 7.3)
Who discontinued therapy due to AE	1 (0.9)	5 (4.3)	3 (2.6)	-1.8 (-6.7, 2.3)	1.7 (-3.7, 7.4)
Who discontinued therapy due to drug-related* AE	0 (0.0)	1 (0.9)	3 (2.6)	-2.6 (-7.5, 0.6)	-1.8 (-6.7, 2.4)
Who discontinued therapy due to SAE	0 (0.0)	3 (2.6)	1 (0.9)	-0.9 (-4.8, 2.3)	1.7 (-2.5, 6.6)
Who discontinued therapy due to drug-related* SAE	0 (0.0)	0 (0.0)	1 (0.9)	-0.9 (-4.8, 2.3)	-0.9 (-4.8, 2.4)

*As determined by the investigator.
AE = adverse events; CI = confidence interval; IMI = imipenem/cilastatin; REL = relebactam; SAE = serious adverse event.

IMI + REL for Complicated Urinary Tract Infections (NCT01505634; Sims 2017)[49]

Similarly, in the cUTI Phase 2 trial, IMI plus REL had a comparable safety profile to IMI monotherapy; rates of AEs, SAEs, and drug-related AEs were similar between each group and between different doses of REL (Table 11).

Table 11: Summary of AEs in NCT01505634[49]

	Group 1: IMI + REL (REL 250 mg) (N=99)	Group 2: IMI + REL (REL 125 mg) (N=99)	Group 3: IMI (plus placebo) (N=100)	Group 1 difference vs. Group 3, % (95% CI)	Group 2 difference vs. Group 3, % (95% CI)
Patients in treatment group, n (%)					
With ≥1 AE	28 (28.3)	29 (29.3)	30 (30.0)	-1.7 (-14.3, 10.9)	-0.7 (-13.4, 12.0)
With drug-related AE	10 (10.1)	9 (9.1)	9 (9.0)	1.1 (-7.5, 9.8)	0.1 (-8.4, 8.6)
With SAE	3 (3.0)	1 (1.0)	3 (3.0)	0.0 (-5.8, 5.9)	-2.0 (-7.6, 2.8)
With serious and drug-related AE	1 (1.0)	0 (0.0)	1 (1.0)	0.0 (-3.7, 3.8)	0.0 (-3.7, 3.8)
Who died	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (-4.5, 4.6)	-1.0 (-5.5, 2.8)
Who discontinued therapy due to AE	3 (3.0)	1 (1.0)	2 (2.0)	1.0 (-4.4, 6.8)	1.0 (-6.1, 3.7)
Who discontinued therapy due to drug-related* AE	2 (2.0)	1 (1.0)	1 (1.0)	1.0 (-3.6, 6.2)	0.0 (-4.5, 4.6)

*As determined by the investigator.
AE = adverse events; CI = confidence interval; IMI = imipenem/cilastatin; REL = relebactam; SAE = serious adverse event.

Summary of Available Data on Comparative Cost and Cost-Effectiveness

RESTORE-IMI 1

To demonstrate the economic value and support the reimbursement of IMR across multiple markets, a global cost-effectiveness (CE) and budgetary impact (BI) model were developed.

Imipenem/cilastatin/relebactam (IMR), a combination β-lactam antibiotic (imipenem) with a novel β-lactamase inhibitor (relebactam), is an efficacious and well-tolerated option for the treatment of hospitalized patients with gram-negative (GN) bacterial infections caused by carbapenem-non-susceptible (CNS) pathogens. This study examines cost-effectiveness of IMR vs. colistin plus imipenem (CMS + IMI) for the treatment of infection(s) caused by confirmed CNS pathogens.

An economic model comprised of a decision-tree depicting initial hospitalization, and a Markov model projecting long-term health and economic impacts following discharge were developed. The decision tree, informed by clinical data from RESTORE-IMI 1 trial, modelled clinical outcomes (mortality, cure rate, and adverse events including nephrotoxicity) in the two comparison scenarios of IMR vs. CMS + IMI for patients with CNS GN infection. Subsequently, a Markov model translated these hospitalization stage outcomes (ie, death or uncured infection) to long-term consequences such as quality-adjusted life years (QALYs). Sensitivity analyses were conducted to test the model robustness.

IMR compared to CMS + IMI demonstrated a higher cure rate (79.0% vs. 52.0%), lower mortality (15.2% vs. 39.0%), and reduced nephrotoxicity (14.6% vs. 56.4%). On average a patient treated with IMR vs. CMS + IMI gained additional 3.7 QALYs over a lifetime. Higher drug acquisition costs for IMR

were offset by shorter hospital length of stay and lower AE-related costs, which result in net savings of $11,015 per patient. Sensitivity analyses suggested that IMR has a high likelihood (greater than 95%) of being cost-effective at a US willingness-to-pay threshold of $100,000–150,000 per QALY.

For patients with confirmed CNS GN infection, IMR could yield favorable clinical outcomes and may be cost-saving—as the higher IMR drug acquisition cost is offset by reduced nephrotoxicity-related cost—for the US payer compared to CMS + IMI.

RESTORE-IMI 2

To demonstrate the economic value and support the reimbursement of IMR for treatment of HABP/VABP across multiple markets, a global CE and BI model were developed. IMR is an efficacious and well-tolerated option for the treatment of hospitalized patients with Gram-negative (GN) bacterial infections caused by carbapenem-resistant (CR) pathogens (RESTORE-IMI 2 trial).

Given IMR's efficacy and susceptibility, among patients with HABP/VABP, it could be a candidate for use in the early adjustment prescribing scenario following first line use with PIP/TAZ among patients with worsening disease and/or with suspected resistant infection.

An economic model comprised of a decision-tree depicting initial hospitalization, and a Markov model projecting long-term health and economic impacts following discharge were developed. Efficacy data to determine clinical outcomes in the short-term decision tree, were taken from the modified intent-to-treat (MITT) population of RESTORE-IMI2. Treatment acquisition costs for IMR and PIP/TAZ were sourced from REDBOOK online[67] and combined with RESTORE-IMI 2[52] observed average treatment duration for IMR and PIP/TAZ. Hospitalization costs were modelled using the average observed length of stay as reported in RESTORE-IMI 2[52] for IMR and PIP/TAZ, and unit costs for ICU ward ($5,743 per day)[68] and general ward ($2,694 per day)[69] sourced from the literature.

Total costs in both arms are primarily driven by hospitalization (resource use) costs in the short term. Resource use costs, AE costs, and monitoring costs are comparable across treatment arms, with the incremental IMR costs primarily being driven by increased treatment acquisition costs. The resulting incremental cost-effectiveness ratio (ICER) of $14,053 per QALY gained falls below the typical US WTP threshold of $100,000 per QALY gained, indicating that IMR may be considered a cost-effective treatment option in a US setting when compared against continued empiric PIP/TAZ in the early adjustment prescribing scenario.

The results of this analysis suggest that IMR, used as an early adjustment option, could be considered cost effective for patients with worsening or suspected resistant HABP/VABP infection in a US healthcare setting, when compared against PIP/TAZ.

Summary of regulatory status and market availability

Country	Regulatory Approval Date	Market Availability
Argentina	6/13/2022	Pending
Austria	8/31/2019	Yes
Belgium	2/13/2020	Pending
Croatia	2/13/2020	Yes
Czech Republic	2/13/2020	Yes
Denmark	2/13/2020	Pending
Finland	2/13/2020	Yes
France	2/13/2020	Yes
Germany	2/13/2020	Yes
Greece	2/13/2020	Yes
Hungary	2/13/2020	Yes
Ireland	2/13/2020	Pending
Italy	2/13/2020	Yes
Japan	6/23/2021	Yes
Netherlands	2/13/2020	Yes
Norway	2/13/2020	Yes
Palau	2/1/2022	Pending
Poland	2/13/2020	Yes
Portugal	2/13/2020	Yes
Puerto Rico	7/17/2019	Yes
Romania	2/13/2020	Yes
Serbia	3/9/2021	Yes
Slovakia	2/13/2020	Yes
Slovenia	2/13/2020	Yes
Spain	2/13/2020	Pending
Sweden	2/13/2020	Yes
UK	2/13/2020	Yes
USA	7/17/2019	Yes

Availability of Pharmacopoeia Standards

IMR is not currently available in any pharmacopoeia standards.

Appendix A – Acronyms

Abbreviation	Definition
AE	Adverse event
AKI	Acute kidney injury
AMR	Antimicrobial resistance
APACHE	Acute Physiology and Chronic Health Evaluation
APaT	All patients as treated
AST	Antimicrobial susceptibility test
BD	Becton, Dickinson & Company
BI	Budgetary impact
BMD	Broth microdilution
CDC	Centers for Disease Control and Prevention
CE	Cost-effectiveness
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CrCl	Creatinine clearance
CLSI	Clinical and Laboratory Standards Institute
CMS	Colistimethate sodium
CNS	Carbapenem-non-susceptible
CR	Carbapenem-resistant
CRE	Carbapenem-resistant Enterobacterales
CS	Carbapenem-susceptible
CTX-M	Cefotaximase-Munich
cUTI	Complicated urinary tract infection
DABCO	Diazabicyclooctane
DCIV	Discontinuation of intravenous therapy
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFU	Early follow-up
EMA	European Medicines Agency
EML	Model List of Essential Medicines
ESBL	Extended-spectrum β-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESRD	End-stage renal disease
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EURGen-Net	European Antimicrobial Resistance Genes Surveillance Network
EuSCAPE	European Survey of Carbapenemase-Producing Enterobacterales
FDA	Food and Drug Administration
GN	Gram-negative
HAP	Hospital-acquired pneumonia
HABP	Hospital-acquired bacterial pneumonia
HAI	Healthcare-associated infection
IAI	Intra-abdominal infection
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IMI	Imipenem/cilastatin
IMR	Imipenem/cilastatin/relebactam
IMP	Active on imipenem metallo-β-lactamase
IV	Intravenous
KPC	Klebsiella pneumoniae carbapenemase
LFU	Late follow-up

LIMIC	Low-and-middle-come countries
LRTI	Lower respiratory tract infection
MDR	Multidrug-resistant
ME	Microbiologically evaluable
MIC	Minimal inhibitory concentration
MITT	Modified intent-to-treat
mMITT	Microbiological modified intent-to-treat
NDM	New Delhi metallo-β-lactamase
OR	Odds ratio
OXA	Oxacillinase
PDC	*Pseudomonas*-derived cephalosporinase
PD	Pharmacodynamic
PIP/TAZ	Piperacillin/tazobactam
PK	Pharmacokinetic
PP	Per protocol
QALY	Quality-adjusted life-year
REL	Relebactam
RI	Renal impairment
RIFLE	Risk, Injury, Failure, Loss, End-stage kidney disease
SAE	Serious adverse event
SD	Standard deviation
SHV	Sulfhydryl variable
SMART	Study for Monitoring Antimicrobial Resistance Trends
SmMITT	Supplemental microbiological modified intent-to-treat
TEM	Temoniera
UK	United Kingdom
US	United States
UTI	Urinary tract infection
VABP	Ventilator-associated bacterial pneumonia
VAP	Ventilator-associated pneumonia
VIM	Verona integron-encoded metallo-β-lactamase
WHO	World Health Organization
WTP	Willingness-to-pay
XDR	Extensively drug-resistant

Appendix B: regulatory documents

Recarbio FDA.pdf

Recarbio EMA SPC.pdf

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