ADMINISTRATION OF IMIPENEM/CILASTATIN/RELEBACTAM (IMI/REL)

March 5, 2019

ICD-10 Coordination and Maintenance Committee Meeting
Centers for Medicare & Medicaid Services
Baltimore, MD

Coding Issue

Merck has applied for New Technology Add-On Payment (NTAP) for IMI/REL

Current ICD-10-PCS codes do not uniquely identify the administration of IMI/REL; adding unique ICD-10-PCS codes would:

- Facilitate NTAP recognition, and
- Allow for tracking of IMI/REL use in the inpatient setting and facilitate research on this use

CDC Identifies carbapenem-resistant infections as an Immediate Health Concern to Monitor and Prevent[1]

CDC designates carbapenem-resistant infections, specifically carbapenem-resistant Enterobacteriaceae, as an “urgent” threat

The “urgent” classification is

- A category that requires more monitoring and infection control activities
- A threat of high consequence because of significant risks identified across several criteria, including

- Clinical impact
- Economic impact
- Incidence
- 10-year projection of incidence

- Transmissibility
- Availability of effective antibiotics
- Barriers to infection control

- Extended-spectrum Beta-lactamase producing Enterobacteriaceae and multi-drug resistant *Pseudomonas aeruginosa* are recognized as ‘serious threats’

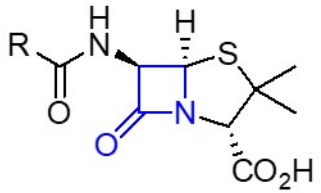
CDC=Centers for Disease Control and Prevention.

1. Centers for Disease Control and Prevention. *Antibiotic resistance threats in the United States, 2013*. Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.

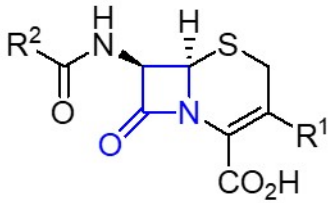
IMI/REL OVERVIEW

Highly Resistant Gram Negative Bacteria: Unmet Medical Need

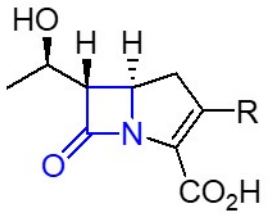
β-lactams (penicillins, cephalosporins, monobactams, carbapenems) are the most commonly prescribed antimicrobials in use today



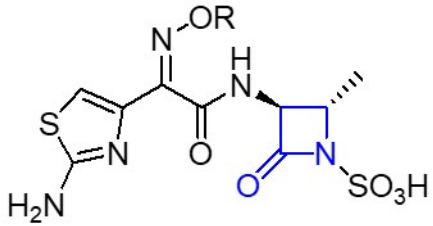
penicillins
1940s



cephalosporins
1960s



carbapenems
1980s



monobactams
1990s

Major cause of bacterial resistance is the production of **β-lactamases**, of which there are 4 main Ambler classes:

A	B	C	D
Serine-based	Metallo-based (Zn)	Serine-based	Serine-based
KPC, CTX-M, TEM	IMP, VIM, NDM	**AmpC**	Oxa
Enterobacteriaceae (*K. pneumoniae, E. coli*)	*Pseudomonas*, Enterobacteriaceae	*Pseudomonas, Acinetobacter*	*Acinetobacter* *Klebsiella*

Administering β-lactamase inhibitors (BLIs) in combination with a β-lactam antibiotic can overcome this resistance

IMIPENEM/RELEBACTAM

Investigational fixed-dose combination of a β-lactam antibiotic, **imipenem** (IMI), with a β-lactamase inhibitor, **relebactam** (REL)

REL is an inhibitor of Class A and C β-lactamases and restores activity to IMI in resistant Gram-negative bacteria

- Active in vitro against enterics producing *Klebsiella pneumoniae* carbapenemases (KPC, Class A) and extended-spectrum β-lactamases (ESBL)
- Active in vitro against Amp-C-producing *Pseudomonas aeruginosa* (Class C)
- Activity confirmed in in vitro and in vivo animal models (thigh and pulmonary)

Seeking indication in patients 18 years of age and older with (a) complicated intra-abdominal infections (cIAI) caused by susceptible gram-negative microorganisms where limited or no alternative therapies are available, and (b) complicated urinary tract infections (cUTI) including pyelonephritis, caused by susceptible gram-negative micoorganisms where limited or no alternative therapies are available.

IMIPENEM/RELEBACTAM (continued)

Clinical pharmacokinetics and safety evaluated in Phase 1 to Phase 3 clinical trials

Clinical efficacy and safety evaluated in 2 completed Phase 2 clinical trials in complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI)

Clinical efficacy and safety evaluated in 1 completed Phase 3 trial in IMI-nonsusceptible (IMI-NS) infections

Ongoing Phase 3 hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP) and pediatric pharmacokinetic studies

Pivotal Phase 3 Trial in Imipenem-Nonsusceptible Infections (RESTORE-IMI 1)

Double-blind design with 2:1 randomization

- Treatment Group 1: IMI/REL (500/250 mg) + placebo to colistin as colistimethate sodium (CMS) (N=31)
- Treatment Group 2: CMS + IMI (N=16)

Patient population

- Patients with 1 of 3 infection types: HABP/VABP (N=16), cIAI (N=8), or cUTI (N=23)
- IMI-NS but colistin- and IMI/REL-susceptible Gram-negative bacterial infection
  - Baseline pathogens: *P aeruginosa* (77%), *Klebsiella* spp (16%), and other Enterobacteriaceae (6%)
  - β-lactamases detected: Amp-C (84% of all isolates), ESBLs (39%), KPC (16%), and OXA-48 (3%)

Treatment duration

- Minimum 5 days (cIAI, cUTI) or 7 days (HABP/VABP), with maximum of 21 days unless approved by Sponsor

Key endpoints

- Overall response

HABP/VABP	cIAI	cUTI
Day 28 all-cause mortality	Clinical response at Day 28	Clinical & micro response at EFU (5-9 days post EOT)

- Treatment-emergent nephrotoxicity

RESTORE-IMI 1: Results in mMITT Population

IMI/REL in the treatment of IMI-non-susceptible infections

Endpoint	Treatment Group 1: IMI/REL + Placebo for CMS (N=21) n	Treatment Group 1: IMI/REL + Placebo for CMS (N=21) % (95% CI)[a]	Treatment Group 2: CMS + IMI (N=10) n	Treatment Group 2: CMS + IMI (N=10) % (95% CI)[a]	Unadjusted Difference %	Adjusted Difference in % vs CMS + IMI % (90% CI)[b]
Favorable Overall Response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	-7.3 (-27.5, 21.4)
Favorable Clinical Response (Day 28)	15	71.4 (49.8, 86.4)	4	40.0 (16.7, 68.8)	31.4	26.3 (1.3, 51.5)
All-Cause Mortality (Through Day 28)	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	-20.5	-17.3 (-46.4, 6.7)

[a] 95% confidence intervals are based on Agresti & Coull method

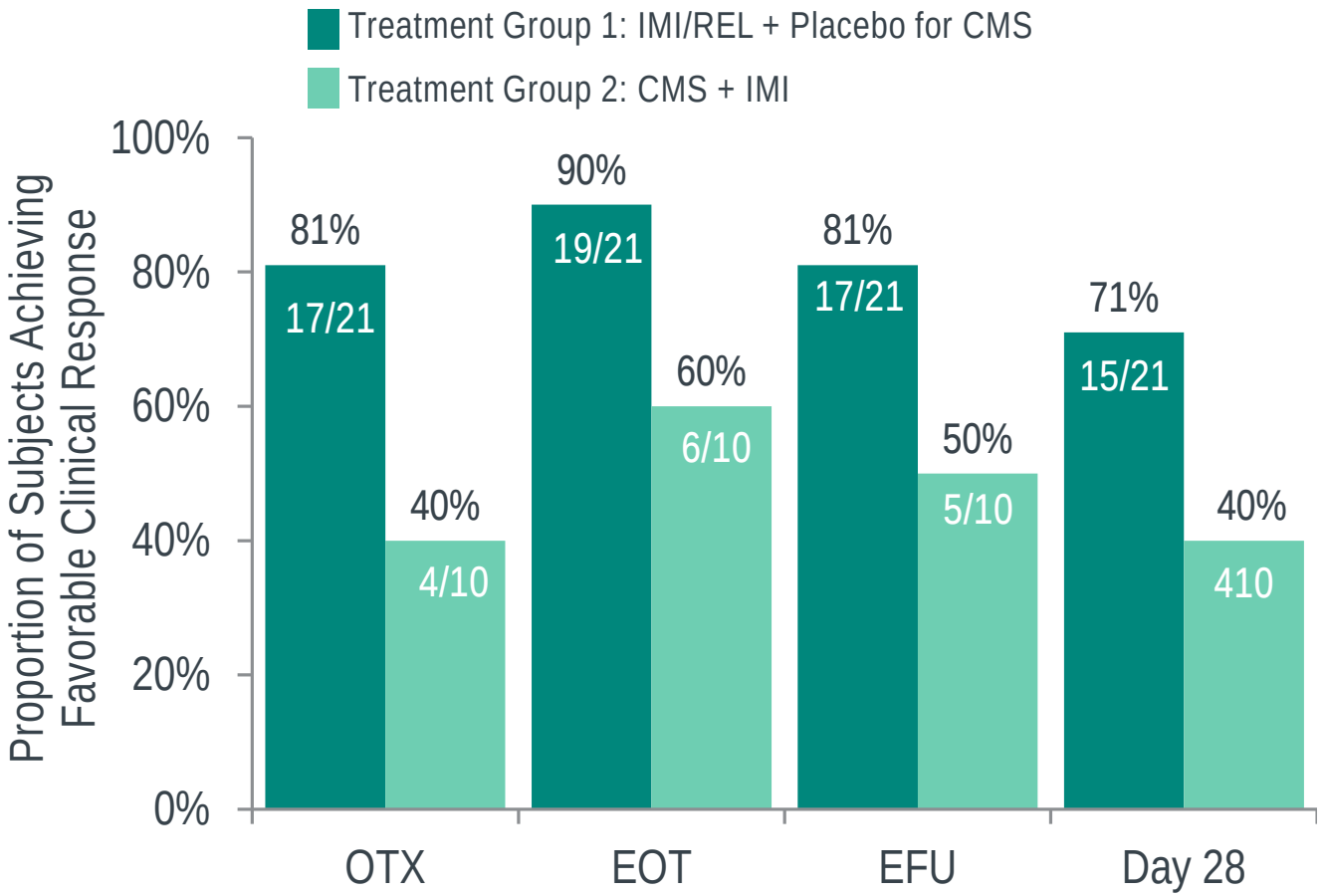
[b] Adjusted differences and 90% CIs based on Miettinen & Nurminen method stratified by infection-site stratum.

[c] Overall response: (a) survival status 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 EFU (5-9 days after EOT) for subjects with cUTI.

[d] 90% CIs not presented due to small sample size.

Abbreviation: mMITT, microbiologically modified intent-to-treat.

RESTORE-IMI 1 Results in mMITT Population (continued)



Visit	Unadjusted Difference vs CMS + IMI %	Adjusted Difference vs CMS + IMI % (90% CI)
OTX	41.0	33.9 (7.4, 61.1)
EOT	30.5	25.4 (3.1, 53.6)
EFU	31.0	24.7 (3.8, 51.4)
Day 28	31.4	26.3 (1.3, 51.5)

RESTORE-IMI 1: Adverse Event Summary

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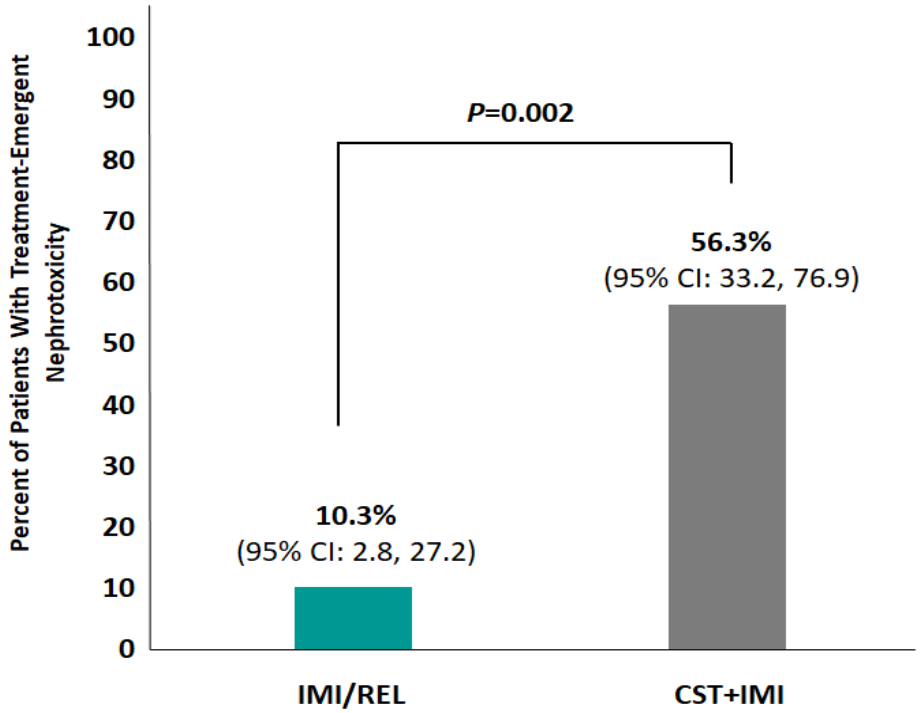
	Treatment Group 1: IMI/REL + Placebo for CMS n	Treatment Group 1: IMI/REL + Placebo for CMS (%)	Treatment Group 2: CMS + IMI n	Treatment Group 2: CMS + IMI (%)	Difference in % vs Treatment Group 2: CMS + IMI Estimate (95% CI) [a]
Subjects in population	31		16		
With one or more adverse events (AEs)	22	(71.0)	13	(81.3)	-10.3 (-33.1, 18.0)
With drug-related[b] AEs	5	(16.1)	5	(31.3)	-15.1 (-42.3, 9.2)
With serious AEs	3	(9.7)	5	(31.3)	-21.6 (-47.8, 1.3)
With serious drug-related AEs	0	(0.0)	0	(0.0)	0.0 (-19.7, 11.2)
Who died	2	(6.5)	3	(18.8)	-12.3 (-37.8, 6.5)
Discontinued drug due to an AE	0	(0.0)	3	(18.8)	-18.8 (-43.3, -6.2)
Discontinued drug due to a drug-related AE	0	(0.0)	2	(12.5)	-12.5 (-36.3, -0.3)
Number of subjects with treatment-emergent nephrotoxicity[c]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)	-45.9 (-69.1, -18.4); *p* = .002*

**P*-value is based on Fisher Exact Test.
No drug discontinuations due to serious AE or to serious drug-related AE occurred in either group.
[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.
[c]Number of subjects with treatment-emergent nephrotoxicity/number of subjects with a baseline creatinine measurement and at least one creatinine measurement following at least one dose of IV study therapy.

RESTORE-IMI 1: Nephrotoxicity



Criteria for AKI

- Treatment-emergent nephrotoxicity was assessed by protocol-defined criteria:
  - In participants **with normal baseline renal function** (serum creatinine [Cr] <1.2 mg/dL), treatment-emergent nephrotoxicity was defined as doubling of serum Cr up to >1.2 mg/dL or a ≥50% reduction in creatinine clearance (CrCL)
  - In participants **with pre-existing renal dysfunction** (serum Cr ≥1.2 mg/dL), treatment-emergent nephrotoxicity was defined as an increase in serum Cr by ≥1 mg/dL, a ≥20% reduction in CrCL, or a need for renal replacement therapy

RESTORE-IMI 1: Nephrotoxicity (continued)

Nephrotoxicity was also assessed by guideline-based definitions of AKI

	KDIGO Criteria
Stage[a]	**Serum Cr**
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 μmol/L) increase
2	2.0–2.9 times baseline
3	3.0 times baseline OR Increase ≥4.0 mg/dL (≥353.6 μmol/L) OR Initiation of renal replacement therapy

	RIFLE Criteria
Classification[a,b]	**GFR Criteria**
Risk	Increased serum Cr x1.5 OR GFR decrease >25%
Injury	Increased serum Cr x2 OR GFR decrease >50%
Failure	Increase serum Cr x3 GFR decrease 75% OR serum Cr ≥4mg/dL (acute rise ≥0.5 mg/dL)

	IMI/REL n/m	IMI/REL % (95% CI)	CST+IMI n/m	CST+IMI % (95% CI)
Protocol-defined nephrotoxicity	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)
AKI (KDIGO)	**n/m**	**%**	**n/m**	**%**
Stage 1	5/29	17.2	6/16	37.5
Stage 2	1/29	3.4	2/16	12.5
Stage 3	0/29	0	5/16	31.3
AKI (RIFLE)	**n/m**	**%**	**n/m**	**%**
Risk	3/29	10.3	6/16	37.5
Injury	2/29	6.9	2/16	12.5
Failure	0/29	0	4/16	25.0

KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease.

[a]If a participant met criteria for more than one AKI stage/classification, the participant was only included once, in the "worst case" stage/classification; [b]Loss of kidney function (>4 weeks) and end-stage kidney disease (>3 months) classifications were not included due to the study duration being less than the defined timelines.

THANK YOU