Imipenem/cilastatin/relebactam (RECARBRIO)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action[1-3]

- Combination of imipenem (IMI), a carbapenem antibiotic, cilastatin (renal dehydropeptidase inhibitor) and relebactam (REL) a beta-lactamase inhibitor
- Mechanism of action:
    - IMI: Inhibition of penicillin binding proteins (PBPs), leading to the disruption of bacterial cell wall synthesis
        Note: Whenever IMI is referred to, unless otherwise stipulated, it refers to IMI/cilastatin
    - **Relebactam (REL): Beta-lactamase inhibitor that protects imipenem from degradation by certain serine beta-lactamases, including Class A enzymes, such as *Klebsiella pneumoniae* carbapenemases (KPC), and ESBLs such as CTX-M, and class C enzymes (AmpC -including *Pseudomonas*-derived cephalosporinase: PDC)**
        - **MIC_{90} reduced from ≥ 32 mcg/mL to 1 mcg/mL for KPC producing Enterobacteriaceae**
        - **MIC_{90} reduced from 4 mcg/mL to 0.25 mcg/mL for AmpC producing organisms**
        - **MIC**
    - **Relebactam is NOT active against Class B metallo-beta-lactamases (MBL) or most Class D oxacillinases (OXA) and relebactam does not appreciably improve activity of IMI for anaerobic organisms, *Acinetobacter spp, S.maltophilia* or gram-positive organisms**
- The breakpoint for susceptibility of IMI/REL is ≤ 1/4 for *Enterobacteriaceae*, ≤ 2/4 for *P.aeruginosa* and ≤ 4/4 for anaerobes
- Activity against *Klebsiella pneumoniae*
    - IMI/REL shown in vitro to restore IMI susceptibility to 74.1% of IMI non-susceptible isolates (KPC producing organisms)
- Activity against *Pseudomonas aeruginosa*
    - IMI/REL restored susceptibility to 80.5% of the IMI non-susceptible isolates
        - Of the 202/251 IMI non-susceptible isolates were made susceptible by the addition of REL one carried VEB-type ESBL
        - 201 of these isolates carried *Pseudomonas* derived cephalosporinase (PDC)
        - 49 IMI/REL non-susceptible isolates were 2 VIM-type metallo-ß-lactamase, and 47 PDC only
- Activity against *Enterobacter* species
    - IMI/REL shown in vitro to restore IMI susceptibility to 100% of the IMI non-susceptible isolates
    - 1 KPC producer, and 7 with no acquired β-lactamases identified
- Activity against *Acinetobacter baumannii*
    - IMI/REL did not increase susceptibility of IMI non-susceptible isolates. All isolates that were non-susceptible to IMI were also non-susceptible to IMI/REL
- Less active vs. *Proteus spp* or *Morganella spp.* With minimal improvement over IMI alone, especially for *Proteus spp*

Indication(s) Under Review in This Document

- Approved by FDA 7/17/19
- Complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) caused by susceptible gram-negative microorganisms and complicated intra-abdominal infections (cIAI) ***in adults with limited or no alternative treatment options***
- Indicated dose for CrCl ≥ 90 mL/min: 1.25 grams IV every 6 hours

Dosage Form(s) Under Review

- 1.25 grams (IMI 500/cilastatin 500 mg/REL 250 mg) single-dose vial supplied as sterile powder for constitution

Clinical Evidence Summary

Efficacy Considerations[4-6]

- Efficacy data are summarized in Table 1
- FDA approval of IMI/REL based on two Phase II randomized controlled clinical trials, one for cUTI and one for cIAI and a phase 3 pathogen directed trial
- **RESTORE-IMI 1:** phase 3, double-blind, 2:1 randomized trial of IMI/REL vs. IMI+colistin in patients with cUTI, cIAI or hospital/ventilator acquired pneumonia (HAP/VAP) due to IMI non-susceptible pathogens
    - Primary endpoint was defined by infection type
        - HAP/VAP = 28-day mortality
        - cIAI = 28-day clinical response
        - cUTI = composite clinical and microbiologic response at early follow-up
            - **IMI/REL (n=21) compared to colistin + IMI (n=10) adjusted difference was -7.3% (90% CI: -27.5 to 21.4)**

Table 1: Efficacy results from clinical trials

Study	Population	Results	Comments
Prospective, double-blind multicenter, Phase II RCT for cUTI/AP **IMI/REL 500/250 mg q6h (n=71) vs. IMI 500mg (n=80) x 4-14 days** **Primary endpoint: favorable microbiologic responses at EOIVT in ME pop***	Median age: 59 Age ≥ 65: 40% cUTI: 52% (119/230) AP: 48% (111/230) Median IV duration 7d (IMI/REL) vs. 8d (IMI) Most common organisms: *E. coli* (65%/59%), followed by *K. pneumoniae* (11%/19%), and *P. aeruginosa* (7%/6%) IMI non-susceptible pathogens 14% and 8% in IMI/REL and IMI groups, respectively	**Response rate ME population** 96% IMI/REL vs. 99% IMI (diff.-3.1% 95% CI -11.2 to 3.2) *- All unfavorable results in patients with IMI-susceptible pathogens* Favorable outcomes for IMI/REL vs IMI by pathogen *- P. aeruginosa* 100% vs 83% *- K. pneumoniae* 100% vs 83% *- E. coli* 96% s 92% Composite clin/micro response at early follow-up: IMI/REL 54%, IMI: 62%	IMI/REL met criteria for noninferiority to IMI for cUTI Microbiological and clinical response rates >95% in ME patients Similar rates of favorable response at other time points between groups Limitations: small sample size, patients mostly with IMI-susceptible organisms
Prospective, multicenter, blinded Phase II RCT for cIAI **IMI/REL 500/250 mg q6h (n=83) vs. IMI 500mg (n=85) x 4-7 days**	Median age: 49 Age ≥ 65: 21% cAPPY: 53% (134/255) cCHOLE: 17% (42/255) Perf. viscus: 11% (29/255) Most common organisms:	**Primary endpoint: favorable response at EOIVT** IMI/REL 96% vs. IMI 95% (diff. 1.1, 95% CI -6.2 to 8.6) By pathogen (IMI/REL vs IMI) *E.coli*: 96% vs. 92% *K.pneumoniae*: 100% vs. 83%	IMI/REL met criteria for noninferiority to IMI for cIAI Source control major contributing factor to clinical success

Primary endpoint: proportion of ME patients with favorable clinical response at EOIVT	*E. coli* (106 isolates), followed by *P. aeruginosa* (23 isolates), and *K. pneumoniae* (22 isolates) Gram-positive organisms also in 40%, anaerobes also in 31% 33 IMI/REL non-susceptible organisms, (17 *P.mirabilis* and 5 *M.morganii*) – 20% of patients	*P.aeruginosa*: 100% vs. 83% Success in evaluable patients: IMI-NS organisms (ME pop) 14/14 IMI/REL (100%) 11/11 IMI (100%)	Study limitations: Small sample size Small number of IMI non-susceptible organisms. Excluded patients with APACHE score >30 and mod/severe renal impairment
RESTORE-IMI: **Phase III, multicenter, blinded RCT of adults with pneumonia, cUTI or cIAI with IMI-nonsusc. organisms** **IMI/REL 500/250 mg q6h (n=21)** **vs IMI 500 mg +colistin (300 mg x 1 then up to 150 mg q12h (n=10) x 5-21 days** **Primary outcome: overall response in mMITT pop.**	Median age: 59 years Age ≥ 65: 36% CrCl < 60 mL/min: 23% HAP/VAP: 35% (11/31) cUTI: 26% (8/31) AP: 26% (8/31) cIAI: 13% (4/31) Median treatment duration IMI/REL: 12.5d vs. IMI +col 9.8d Qualifying causative organisms: *P. aeruginosa* (24/31): 77% *K. pneumoniae* (4/31): 13% Most common ß-lactamases: PDC (24/31): 77% CTX-M (11/31): 36% TEM (10/31): 32% KPC (5/31): 16%	Favorable overall response in m-MITT population in 71% IMI/REL and 70% IMI/colistin groups, respectively Response by pathogen (IMI/REL vs IMI/colistin): *P. aeruginosa*: 81% vs. 63% KPC+ *Enterobacteriaceae*: 25% vs. 100% By infection (REL vs. col) HAP/VAP 7/8 vs. 2/3 cUTI: 8/11 vs. 5/5 cIAI: 0/2 vs. 0/2 Day 28 clinical response was 71% (IMI/REL) vs. 40% (IMI/colistin)	No treatment emergent resistance to IMI/REL 28-day mortality was 10% (IMI/REL) vs. 30% (IMI/colistin) Study limitations: Small sample size, estimation trial, no formal statistical testing Only 19% and 10% KPC in IMI/REL and IMI and colistin, respectively

EOIVT = end of intravenous therapy, m-ITT = microbiologic intent to treat population, ME = microbiologically evaluable population, cAPPY = complicated appendicitis, cCHOLE = complicated cholecystitis, mMITT – modified microbiologic intent to treat population

Safety Considerations

Safety Results from Clinical Trials:

Safety data for IMI/REL comes from the phase II cUTI and cIAI trials, and the RESTORE-IMI trial

Table 2: Safety results from clinical trials

Study	Results	Comments
Phase II cUTI Study **IMI/REL: n=71** **IMI: n=80**	Drug related AEs: IMI/REL (10%) vs. IMI (9%) Serious treatment emergent AE: 3% in both groups Most commonly reported AE was nausea, headache, and diarrhea with similar incidence between IMI/REL and IMI	Incidence of AEs were similar across all three treatment arms. Discontinuation due to drug-related AE in 2 IMI/REL patients (rash and diarrhea) and 1 IMI patient (diarrhea)
Phase II cIAI Study **IMI/REL: n=83** **IMI: n=85**	Drug related AEs: IMI/REL (14%) vs. IMI (10%) Serious AE: IMI/REL (3%) vs. IMI (7%) Most common AEs were nausea, vomiting, and diarrhea with similar incidence between IMI/REL and IMI	Incidence of drug-related adverse and serious AE similar across study arms. Discontinuation due to drug-related AEs in 3 IMI patients and no IMI/REL recipients One serious drug related AE- thrombocytosis, with IMI and resulted in discontinuation
RESTORE-IMI trial **IMI/REL: n=21** **IMI/COL: n=10**	Drug related AEs: IMI/REL 16% vs 31% with IMI/COL Serious AEs 10% vs 31% IMI/REL vs IMI + colistin, respectively, but none drug-related Discontinuation due to AE was 0% with IMI/REL vs 19% with IMI/COL Treatment emergent nephrotoxicity significantly less frequent with IMI/REL (10%) than with IMI/COL (56%), (p=0.002), diff -46% (95% CI -69% to -18%) Clinically relevant increased AST/ALT less frequent with IMI/REL (0%) vs IMI/COL (13%), (p=0.047)	More AE seen in IMI + colistin study arm Limitations: Small number of patients limits robust evaluation of safety but given phase 2 trials showing no significant addition of adverse effects from REL, safety is likely similar to other beta-lactam/beta-lactamase inhibitor combinations As expected, nephrotoxicity with COL was significant

- **Boxed warnings:** None
- **Contraindications:** history of known hypersensitivity to any component in RECARBRIO
- **Other warnings / precautions: (optional if relevant):**
  - Hypersensitivity reactions
  - **Seizures and other central nervous system adverse reactions – *As with imipenem alone, seizure risk may be greater in patients with pre-existing central-nervous system disorders (seizures, stroke, etc.) or in patients with renal dysfunction***
  - Increased seizure potential due to interaction with valproic acid

Other Considerations

Pharmacokinetics / Pharmacodynamics (REL)

- **Distribution**: protein binding 22%. Steady state volume of distribution 19.0 L, $AUC_{0\text{-}24hr}$ 427 uM-hr, C_{max} 64 uM
- **Metabolism:** REL minimally metabolized
- **Excretion**: > 90% via the kidneys with a half-life of 1.2 $\pm$ 0.7 hours
  - **PK with renal dysfunction**: mean AUC higher in patients with CrCl 60-89 (1.2 fold), 30-59 mL/min (2.2 fold), and 15-29 mL/min (4.7 fold) compared to patients with CrCl $\geq$ 90 mL/min. Accumulation was similar to degree seen with IMI and Cilastatin, suggesting proportional adjustments are appropriate
  - In ERSD patients on HD REL was efficiently removed, therefore patients should receive IMI/REL after the hemodialysis session

Other Therapeutic Options[2,7-8]

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
IMI/REL	TBD	FDA approved for cUTI and cIAI Phase 3 trial vs. pip/tazo for HAP/VAP completed but data not yet available Activity against KPC carbapenemases and class C β-lactamases (PDC) No activity vs. class B / D β-lactamases Improves activity against many CRE strains and carbapenem resistant strains of *P. aeruginosa* Does not improve activity against *A. baumannii* or *S. maltophilia*	Higher seizure risk than most other beta-lactams due to IMI, especially in elderly, those with pre-existing seizure disorder or reduced renal function Stipulation in FDA indication that IMI/REL only used if limited or no treatment alternatives due to limited data Interaction with valproate/divalproex
Ceftazidime/ avibactam	F	FDA approved for cUTI, cIAI, HAP/VAP Activity against KPC-producing CRE and OXA-48 producing organisms Improves activity against ceftazidime resistant *P.aeruginosa*	Reduced clinical cure rates seen in patients with CrCl 30-50 mL/min in cIAI than those with CrCl > 50mL/min Emergence of resistance on therapy seen in up to 10% of patients with KPC producing CRE Limited activity vs. gram-negative anaerobes requires addition of metronidazole for cIAI
Ceftolozane/ tazobactam	NF	FDA approved for cUTI, cIAI, HAP/VAP Very active against many multi-drug resistant strains of *P.aeruginosa* Variable activity against extended spectrum β lactamases (ESBL), especially in *K.pneumoniae*	Reduced clinical cure rates seen in patients with CrCl 30-50 mL/min than those with CrCl > 50mL/min No activity vs. CRE but excellent for carbapenem resistant *P.aeruginosa* supported by many case series showing efficacy
Meropenem/ vaborbactam	NF	FDA approved for cUTI only Vaborbactam inhibits class A β-lactamases, KPC carbapenemases Does not inhibit class B MBLs such as or class D β-lactamases Active against 67%-89% of carbapenem non-susceptible *P. aeruginosa*	Less clinical data for treatment of CRE than with ceftazidime/avibactam and no data about emergence of resistance on therapy Meropenem backbone provides strong activity against gram-negatives producing ESBL, AmpC and anaerobes

Colistin	NF	Activity against *Enterobacteriaceae* (except for *Serratia marcescens* and *Proteus, Providencia, Morganella,* and *Hafnia* species), *P. aeruginosa, A. baumannii* and some *S. maltophilia* strains Activity against carbapenem-resistant pathogens	IV and inhaled formulation Higher incidence of acute kidney injury vs. most other agents with activity vs. CRE (33%-60% in comparative trials) Risk of neurotoxicity Typically administered in combination with other agent due to concerns about efficacy or resistance
Eravacycline	NF	FDA indicated for cIAI Activity against CRE, carbapenem-resistant strains of *A. baumannii* and *S. maltophilia* Not active against *P. aeruginosa*	Increased dose needed with strong CYP3A4 inducers Only indicated for cIAI – cUTI trials failed to meet non-inferiority Data for treatment of serious infections due to carbapenem resistant pathogens extremely limited
Plazomicin	NF	FDA indicated for cUTI only in patients with limited to no treatment alternatives Active against Enterobacteriaceae, including strains resistant to other existing aminoglycosides, and CRE producing carbapenemases (including KPC and some class B MBLs	Black box warning for nephrotoxicity, neuromuscular blockade, and ototoxicity Requires therapeutic drug monitoring in patients with CrCl < 90 mL/min to target trough goal <3 mcg/mL but used AUC based dosing in trial for CRE
Cefiderocol	TBD	FDA indicated for cUTI only in patients with limited or no treatment alternatives Active against class A, class B and class D carbapenemases Activity against *P. aeruginosa, A. baumannii, S. maltophilia* Expected indications: cUTI/AP, HAP/VAP	Increased all-cause mortality seen in pathogen-directed trial in carbapenem-resistant organisms versus best available therapy (25% vs. 18%) Data very limited on safety and efficacy

Projected Place in Therapy

- RECARBRIO is an option for MDROs such as β-lactamase producing Enterobacteriaceae and *P. aeruginosa*, to help restore activity to previously IMI resistant organisms
- No data on how compares with other agents with activity against KPC producing CRE or carbapenem-resistant pneumonia
- Imipenem backbone may result in higher risk of seizures, particularly in those with prior history of seizure disorders, reduced renal function or the elderly, and the interaction with valproic acid may also lead to breakthrough seizures
- Prior authorization restricted to infectious diseases specialist or other facility authorized providers is appropriate

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