You follow the clues. Now discover RECARBRIO

A carbapenem/novel BLI combination

When you suspect certain CRE, including KPC-producing Enterobacterales, or CR *P. aeruginosa* but you do not have time to wait for confirmation, consider RECARBRIO.[1]

1 Prior treatment with a carbapenem

2 Admitted from LTC facility

3 Recent antibiogram shows Enterobacteriaceae with KPCs and CR *P. aeruginosa*

4 Patient declining on current antibiotic treatment

Not an actual patient.

BLI, beta-lactamase inhibitor; **CR**, carbapenem-resistant; **CRE**, carbapenem-resistant Enterobacterales; **KPC**, *Klebsiella pneumoniae* carbapenemase; **LTC**, long-term care; *P. aeruginosa, Pseudomonas aeruginosa.*

Reference: 1. Young K, Painter RE, Raghoobar SL, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa.* BMC Microbiol. 2019;19(1):150. doi:10.1186/s12866-019-1522-7

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In case you need any update or you have an inquiry or need to report an adverse reaction, you can contact Tel: +9714 4269100 , Fax: +9714 4269204 , Email:DPOC.GULF@MERCK.COM

RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection 1.25 g

RECARBRIO:
Imipenem/Cilastatin/Relebactam

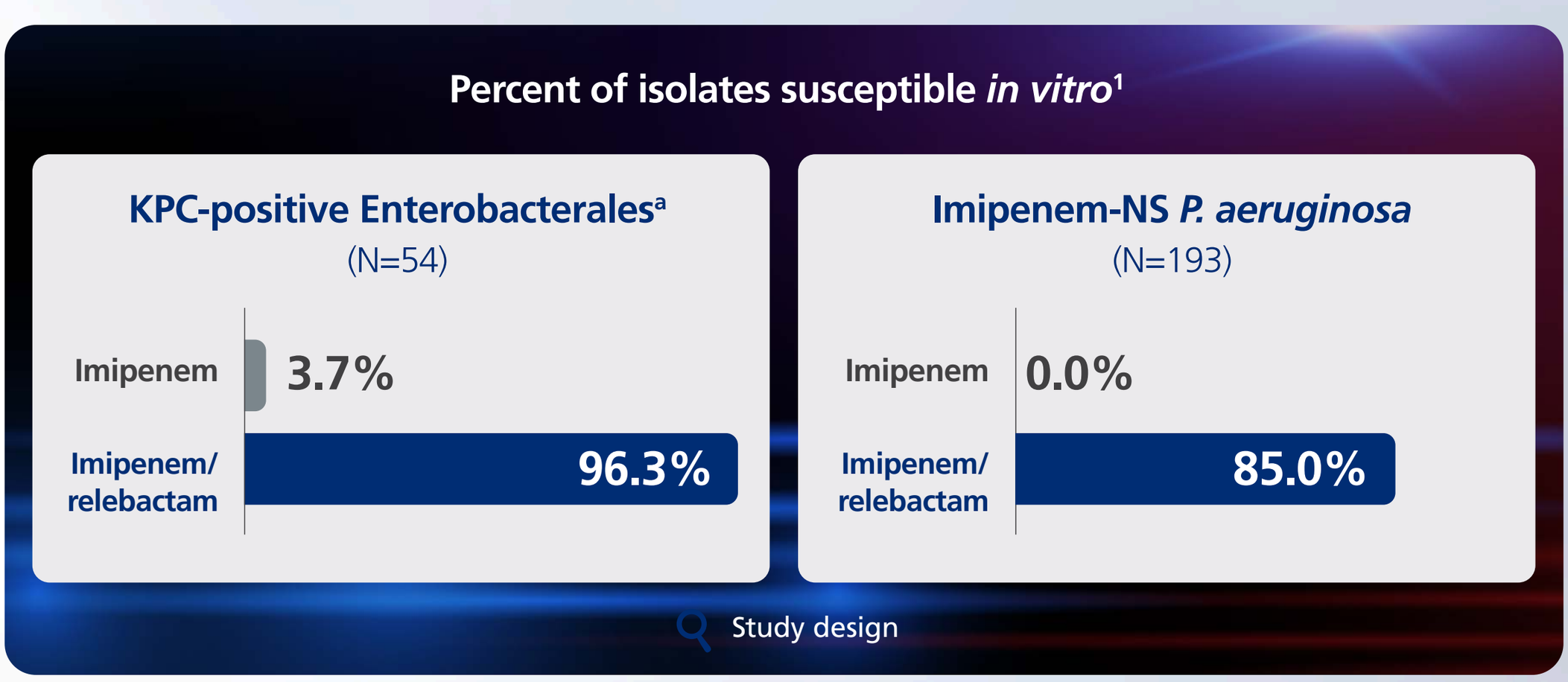
A broad-coverage carbapenem/novel BLI combination[1]

Imipenem / Cilastatin

+

Relebactam

A novel BLI that restores the activity of imipenem



[a]Non-Proteeae Enterobacteriaceae species.

The clinical significance of *in vitro* data is unknown.

RECARBRIO is not active against metallo-beta-lactamases, oxacillinases with carbapenemase activity, or certain alleles of GES.

Study Design :
The SMART program was initiated by Merck in 2002 to monitor the in vitro susceptibility of clinical aerobic and facultative Gram-negative bacterial isolates, enabling longitudinal analyses to determine if susceptibility patterns change over time.[1]
The activity of imipenem/relebactam, as assessed against Gram-negative bacilli from intra-abdominal infections and urinary tract infections submitted to the SMART global surveillance program in 26 participating hospital laboratories in 18 states in the United States from 2015 to 2017.[1]
The limitations of this study included a lack of identifiable patient-specific information regarding clinical presentation or antimicrobial therapy, which would have allowed differentiation between complicated and uncomplicated intra-abdominal infections and urinary tract infections and more detailed stratified analyses. Generalizability is limited since the described resistance patterns are based on data from 26 hospitals in 18 states in the United States. Since the majority of hospitals participating in the SMART surveillance program are tertiary care centers, resistance rates seen here are likely higher than would be found in smaller hospitals and in the community.[1]

BLI, beta-lactamase inhibitor; **KPC**, *Klebsiella pneumoniae* carbapenemase; **NS**, nonsusceptible; **GES**, Guiana-extended-spectrum beta-lactamase.

References: 1. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem-relebactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance United States 2015-2017. *J Glob Antimicrob Resist*. 2020;21:223-228. https://doi.org/10.1016/j.jgar.2019.10.028 **2.** SMART Data on File, 2018.

RECARBRIO™
(imipenem, cilastatin, and relebactam) for injection 1.25 g

Dosing and Administration

RECARBRIO 1.25 g is a fixed-dose combination of imipenem, cilastatin, and relebactam (500/500/250 mg) in a single vial, infused over 30 minutes every 6 hours[1]

500 mg imipenem
500 mg cilastatin
250 mg relebactam

30 min intravenous (IV) infusion

Q6H

Dosage in patients 18 years of age and older with creatinine clearance (CrCl) greater than or equal to 90 mL/min

Dosage adjustment is recommended in adult patients with renal impairment

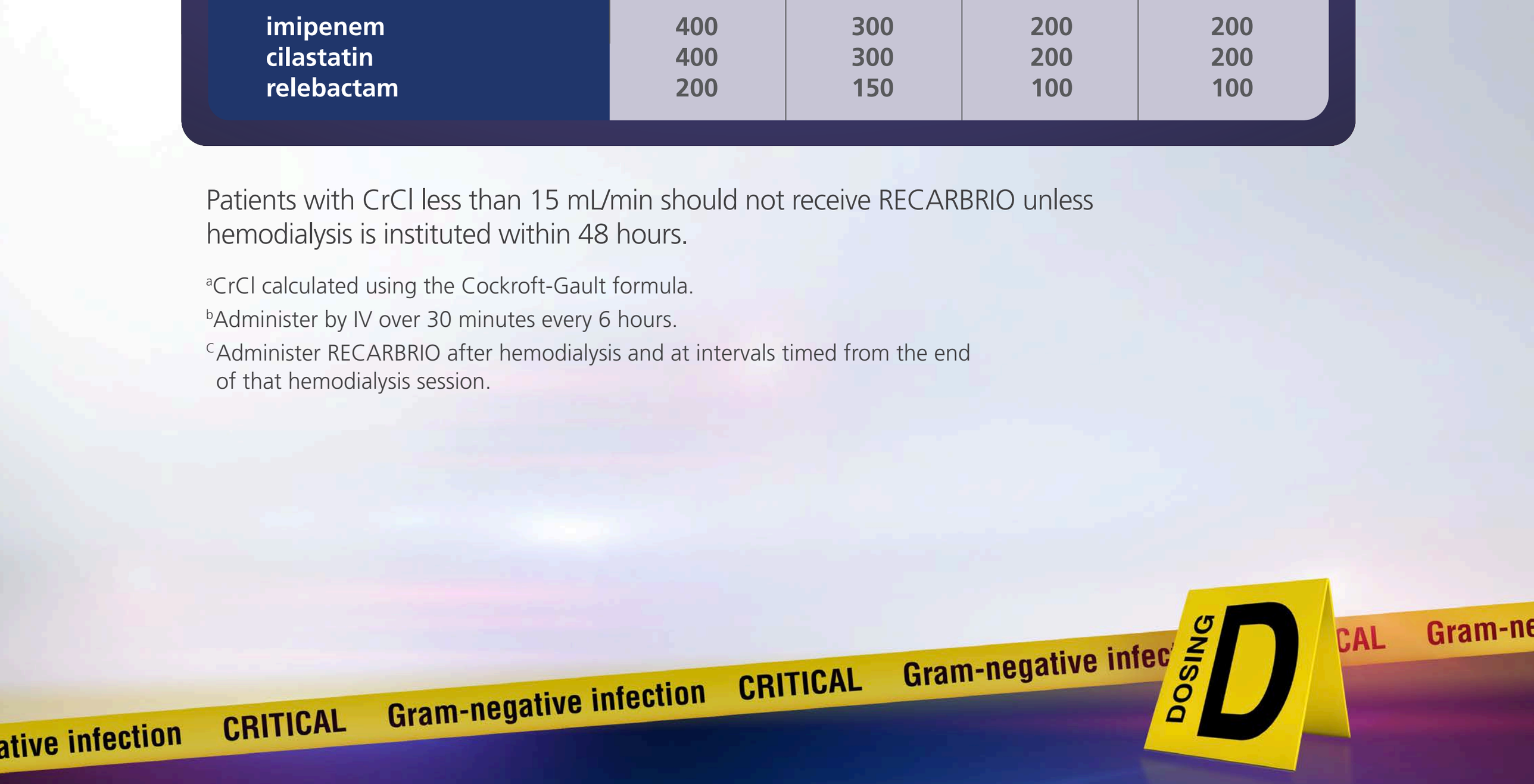
Estimated Creatinine Clearance (mL/min)[a]	<90 to ≥60	<60 to ≥30	<30 to ≥15	End-Stage Renal Disease on Hemodialysis[c]
Recommended Dosage of RECARBRIO (mg)[b]				
imipenem	**400**	**300**	**200**	**200**
cilastatin	**400**	**300**	**200**	**200**
relebactam	**200**	**150**	**100**	**100**

Patients with CrCl less than 15 mL/min should not receive RECARBRIO unless hemodialysis is instituted within 48 hours.

[a]CrCl calculated using the Cockroft-Gault formula.

[b]Administer by IV over 30 minutes every 6 hours.

[C]Administer RECARBRIO after hemodialysis and at intervals timed from the end of that hemodialysis session.



1. RECARBRIO™ summary of product characteristics FEB-2021

RECARBRIO™
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Selected Saftey Information

INDICATIONS AND CLINICAL USE RECARBRIO™ 500 mg/500 mg/250 mg is indicated for:

• Treatment of hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), in adults

• Treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adults.

• Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options Consideration should be given to official guidance on the appropriate use of antibacterial agents.

CONTRAINDICATIONS

RECARBRIO™ is contraindicated in: Hypersensitivity to the active substances or to any of the excipients

Hypersensitivity to any other carbapenem antibacterial agent. Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins, cephalosporins or monobactams)

Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams . These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with Recarbrio, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to Recarbrio occurs, treatment with Recarbrio must be discontinued immediately. Serious anaphylactic reactions require immediate emergency treatment.

Hepatic function

Hepatic function should be closely monitored during treatment with Recarbrio due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure, and fulminant hepatitis)

use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with Recarbrio.

There is no dose adjustment necessary

Central nervous system (CNS)

CNS adverse reactions, such as seizures, confusional states, and myoclonic activity have been reported during treatment with imipenem/cilastatin, components of Recarbrio, especially when recommended dosages of imipenem were exceeded. These reactions have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Increased seizure potential : due to interaction with valproic acid The concomitant use of Recarbrio and valproic acid/divalproex sodium is not recommended. Antibacterial other than carbapenems should be considered to treat infections in patients whose seizures are well-controlled on valproic acid or divalproex sodium. If administration of Recarbrio is necessary, supplemental anti-convulsant therapy should be considered

Clostridioides difficile-Associated Diarrhoea (CDAD)

Clostridioides difficile-associated diarrhoea (CDAD) has been reported with Recarbrio. CDAD may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea during or following the administration of Recarbrio . Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, discontinuation of therapy with Recarbrio, and the administration of specific treatment for C. difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with CrCl ≥ 150 mL/min

Based on pharmacokinetic-pharmacodynamic analyses, the dose of Recarbrio that is recommended for patients with CrCl of ≥ 90 mL/min may not be sufficient to treat patients with HAP or VAP and CrCl > 250 mL/min, or patients with cIAI or cUTI and CrCl > 150 mL/min. Consideration should be given to using alternative therapies for these patients.

Renal impairment

Dose adjustment is recommended in patients with renal impairment. There is inadequate information to recommend usage of Recarbrio for patients undergoing peritoneal dialysis.

Limitations of the clinical data

Patients who were immunocompromised, including those with neutropenia, were excluded from clinical trials.

Hospital-acquired pneumonia, including ventilator-associated pneumonia

In a single study of hospital-acquired pneumonia, including ventilator-associated pneumonia, 535/33) % 6.2) of patients had bacteraemia at baseline.

Patients with limited treatment options

The use of Recarbrio to treat patients with infections due to aerobic Gram-negative organisms who have limited treatment options is based on experience with imipenem/ cilastatin, pharmacokinetic-pharmacodynamic analysis for imipenem/cilastatin/relebactam, and on limited data from a randomised clinical study in which 21 evaluable patients were treated with Recarbrio and 10 evaluable patients were treated with colistin and imipenem/cilastatin for infections caused by imipenem-non-susceptible organisms.

Limitations of the spectrum of antibacterial activity

Imipenem does not have activity against methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE) or against Enterococcus faecium.

Alternative or additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of relebactam includes class A beta-lactamases (such as ESBLs and KPC) and Class C beta-lactamases including PDC. Relebactam does not inhibit class D carbapenemases such as OXA48- or class B metallo-beta-lactamases such as NDM and VIM .

Non-susceptible organisms

The use of imipenem/cilastatin/relebactam may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.

Antiglobulin test (Coombs test) seroconversion

A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin/relebactam .

Controlled sodium diet

Each vial contains a total of 37.5 mg of sodium (1.6 mmol), equivalent to 1.9 % of the WHO (World Health Organization) recommended maximum daily intake of 2 g sodium for an adult. This should be considered when administering Recarbrio to patients who are on a controlled sodium diet

ADVERSE REACTIONS

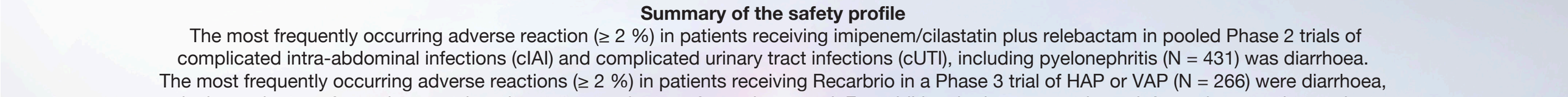
Summary of the safety profile

The most frequently occurring adverse reaction (≥ 2 %) in patients receiving imipenem/cilastatin plus relebactam in pooled Phase 2 trials of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis (N = 431) was diarrhoea. The most frequently occurring adverse reactions (≥ 2 %) in patients receiving Recarbrio in a Phase 3 trial of HAP or VAP (N = 266) were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased. For additional adverse experience information, see the product circular.

Before initiating therapy, please consult the full prescribing information.

For additional safety information, please consult the Summary of Product Characteristics.

Before prescribing RECARBRIO, please read the Summary of Product Characteristics.



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