

# **Antimicrobial prescribing: imipenem with cilastatin and relebactam**

## **Evidence review**

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This evidence review sets out the best available evidence on imipenem with cilastatin and relebactam for treating infections due to aerobic gram-negative organisms in adults with limited treatment options. It should be read in conjunction with the [evidence summary](#), which gives the likely place in therapy and factors for decision making.

## **Disclaimer**

The content of this evidence review was up to date in October 2020. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [Medicines and Healthcare products Regulatory Agency](#) (MHRA) or [NICE](#) websites for up to date information.

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## Background

This evidence review considers a fixed-dose combination product, imipenem with cilastatin and relebactam (Recarbrio, Merck Sharp & Dohme B.V) for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options. Imipenem is a carbapenem beta-lactam antibiotic, cilastatin prevents renal metabolism of imipenem and relebactam inhibits some types of bacterial beta-lactamases. Cilastatin and relebactam have no antibacterial activity ([Recarbrio: European public assessment report](#) [EPAR]).

Increasing resistance to beta-lactams, including the carbapenems has led to some organisms being untreatable or treatable only with antibiotics of last resort such as colistin, with or without other antibacterials to which they remain at least partially susceptible (Recarbrio EPAR]). Other newer antimicrobials with activity against multi-resistant bacteria include [ceftolozane with tazobactam](#), [ceftazidime with avibactam](#) and [meropenem with vaborbactam](#). One of the mechanisms used by bacteria to be resistant to antimicrobials is by producing bacterial beta-lactamase enzymes. To overcome resistance, carbapenems have been combined with beta-lactamase inhibitors to address the challenge of carbapenemases.

Infections such as complicated urinary tract infection (UTI), complicated intra-abdominal infection and hospital-acquired pneumonia (including ventilator-associated pneumonia), are typically caused by aerobic gram-negative organisms, which may be resistant to carbapenems.

NICE has produced the following antimicrobial prescribing guidelines on complicated UTIs and hospital-acquired pneumonia, which include recommendations on choosing antibiotics:

- [UTI \(catheter-associated\): antimicrobial prescribing](#)
- [pyelonephritis \(acute\): antimicrobial prescribing](#)
- [pneumonia \(hospital-acquired\): antimicrobial prescribing](#).

NICE has not published any guidance on complicated intra-abdominal infections, although there are recommendations on antibiotics for acute diverticulitis in the [NICE guideline on diverticular disease](#).

## Product overview

### Mode of action

Imipenem is a broad-spectrum carbapenem antibacterial, which belongs to the class of beta-lactam antibiotics and has activity against many species of gram-positive and gram-negative bacteria ([Recarbrio summary of product characteristics](#)).

Cilastatin is an inhibitor of dehydropeptidase-I, the renal enzyme which metabolises and inactivates imipenem (Recarbrio EPAR).

Relebactam inhibits:

- Ambler class A beta-lactamases, including class A *Klebsiella pneumoniae* carbapenemase and extended-spectrum beta-lactamases.
- Ambler class C (AmpC-type) beta-lactamases including Pseudomonas-derived cephalosporinase.

Relebactam does not inhibit class B enzymes (metallo-beta-lactamases) or class D carbapenemases.

### Regulatory status

Imipenem and cilastatin with relebactam (Recarbrio, Merck Sharp & Dohme B.V) has a marketing authorisation for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options.

The marketing authorisation was granted in February 2020 and imipenem with cilastatin and relebactam was made available for purchase by hospitals in the UK in August 2020.

### Dosing information

Imipenem with cilastatin and relebactam is given by intravenous infusion. Each vial contains imipenem monohydrate equivalent to 500 mg of imipenem, cilastatin sodium equivalent to 500 mg of cilastatin and relebactam monohydrate equivalent to 250 mg of relebactam.

The person's renal function affects the dosage that is recommended. In adults with a creatinine clearance between 90 ml/minute and 150 ml/minute (calculated using the Cockcroft-Gault formula), the recommended dosage is 500 mg/500 mg/250 mg infused over 30 minutes every 6 hours. For those with a creatinine clearance of 150 ml/min or more, this dosage may not be sufficient and consideration should be given to using alternative treatments. In adults with a creatinine clearance of less than 90 ml/minute, lower doses are recommended (see the summary product of characteristics for details).

No dosage adjustment is needed based on age or hepatic impairment (Recarbrio summary of product characteristics).

According to the summary of product characteristics, the duration of treatment depends on the type of infection, for example for complicated UTI and complicated intra-abdominal infection the recommended duration of treatment is 5 to 10 days (up to 14 days if needed) and for hospital-acquired pneumonia (including ventilator-associated pneumonia) it is 7 to 14 days.

See the [Recarbrio summary of product characteristics](#) for more information.

## **Antimicrobial resistance**

Imipenem with cilastatin and relebactam is a new antimicrobial and therefore data on resistance and impact on clinical practice in the UK are limited. Information on resistance can be found on [Public Health England antimicrobial resistance local indicators](#).

Imipenem does not have activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE) or against *Enterococcus faecium*. A range of mechanisms may affect bacterial resistance to imipenem and relebactam such as gram-negative bacteria producing metallo-beta-lactamases or oxacillinases with carbapenemase activity.

There has been an increase in the total number of carbapenemase-producing Enterobacterales referred to laboratories in 2018. More than 4,000 isolates were confirmed as positive for at least 1 carbapenemase and most isolates represented colonisations with only 3.0% of confirmed carbapenemase-producing

Enterobacterales identified from invasive isolates. OXA-48 carbapenemases (class D, which relebactam does not inhibit) were the most frequently (52.0%) identified carbapenem-resistant Enterobacterales in 2018. In that year, the rates of class B metallo-beta-lactamases, NDM (New Delhi metallo-beta-lactamase), IMP (imipenemase) and VIM (Verona integron-encoded metallo-beta-lactamase) carbapenemases (which relebactam also does not inhibit) were 26.5%, 3.7% and 1.7% respectively. *Klebsiella pneumoniae* carbapenemase (KPC, class A) was the third most frequently identified carbapenemase-producing Enterobacterales (11.2%) ([English Surveillance Programme for Antimicrobial Utilisation and Resistance \[ESPAUR\] Report 2018 to 2019](#)).

The ESPAUR notes that the proportion of isolates of gram-negative pathogens resistant to key antibiotics remained broadly stable between 2014 and 2018. However, year-on-year increases in the incidence of bacteraemia meant that the burden of resistance for gram-negative infections has increased over time. The estimated number of bloodstream infections caused by gram-negative pathogens resistant to 1 or more key antibiotics increased by 32% from 12,972 in 2014 to 17,108 in 2018. The increase was particularly marked for infections caused by Enterobacterales (for example *Escherichia coli*). Antimicrobial resistance remained unchanged for gram-positive infections over the same period.

## Objective

This evidence review considers the best available evidence on the effectiveness and safety of imipenem with cilastatin and relebactam for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options.

## Review questions

The relevant population, intervention, comparison and outcomes ([PICO](#)) for this review were developed by NICE (see [appendix A](#) for more information). The review questions for this evidence review are:

1. What is the clinical effectiveness of imipenem with cilastatin and relebactam for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options?

2. What is the safety of imipenem with cilastatin and relebactam for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options?

## Summary of included studies

A literature search carried out in January 2020 identified 107 references (see [appendix E](#) for full details). These references were screened using their titles and abstracts and a total of 5 full text references were obtained and assessed for relevance. The literature search was re-run in July 2020 and 14 additional references were identified. These references were screened using their titles and abstracts and 1 full text references were obtained and assessed for relevance. An additional study was identified following the re-run searches (September 2020).

Two phase 3, double-blind, [randomised control trials](#) are included in this evidence review. Both studies were carried out in non-UK hospital settings.

[Motsch et al. \(2020\)](#) (RESTORE-IMI-1) evaluated the efficacy and safety of imipenem with cilastatin and relebactam compared with colistin plus imipenem with cilastatin in 47 hospitalised adults with:

- bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia) – 35%
- complicated intra-abdominal infection – 13%
- complicated UTI – 52%.

The authors describe it as a non-inferential, descriptive study; there was no formal statistical testing for efficacy and safety endpoints with the exception of nephrotoxicity. All participants had imipenem non-susceptible gram-negative bacterial infections and were lacking clinical improvement on any prior treatment. The percentage of participants who received 1 or more antimicrobial treatments before study treatment was 86% in the imipenem with cilastatin and relebactam group and 80% in the colistin plus imipenem with cilastatin.

[Titov et al. \(2020\)](#) (RESTORE-IMI 2) was a non-inferiority study that evaluated the efficacy and safety of imipenem with cilastatin and relebactam compared with

piperacillin with tazobactam in 537 hospitalised adults with non-ventilated bacterial hospital-acquired pneumonia (51%), ventilated bacterial hospital-acquired pneumonia (12%) and bacterial ventilator-associated pneumonia (36%). Overall, 45% of participants received 1 or more doses of systemic antimicrobial treatment with gram-negative activity within 72 hours before study treatment.

A summary of the included studies is in [appendix B](#).

Quality assessment of the included studies is in [appendix C](#).

Details of studies identified in the literature search that were then excluded are in [appendix F](#).

## **Effectiveness and safety**

Full details of the study results are in [appendix D](#).

### **Review question 1**

What is the clinical effectiveness of imipenem with cilastatin and relebactam for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options?

#### **Overall response**

[Motsch et al. \(2020\)](#) defined overall response (primary outcome) as follows:

- bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia) – survival up to day 28
- complicated intra-abdominal infection – clinical response at day 28
- complicated UTI – a composite of clinical and microbiological response 5 to 9 days after the end of treatment.

The overall response was 71.4% in the imipenem with cilastatin and relebactam group and 70.0% in the colistin plus imipenem with cilastatin group (n=31, adjusted difference -7.3 [90% CI -27.5 to 21.4], modified microbiologic intention-to-treat [mMITT] population [participants with 1 or more qualifying gram-negative pathogen from the primary infection site [according to central laboratory results] and had 1 or more doses of the study medicines]).

When stratifying according to infection type, participants with:

- bacterial hospital acquired pneumonia (including ventilator associated pneumonia; n=11), the overall response was 87.5% in the imipenem with cilastatin and relebactam group and 66.7% in the colistin plus imipenem with cilastatin group
- complicated UTI (n=16), the overall response was 72.7% in the imipenem with cilastatin and relebactam group and 100.0% in the colistin plus imipenem with cilastatin group (adjusted difference -27.3 [90% CI -52.8 to 12.8])
- complicated intra-abdominal infection (n=4) did not have a favourable overall response in either treatment group and the numbers of participants were low, 2 in each group.

When stratifying according to the baseline pathogen, for infections caused by *Pseudomonas aeruginosa* (n=24), the overall response was 81% in the imipenem with cilastatin and relebactam group and 63% in the colistin plus imipenem with cilastatin group. For infections caused by Enterobacterales (n=7), overall response was 40% in the imipenem with cilastatin and relebactam group and 100% in the colistin plus imipenem with cilastatin group.

### **All-cause mortality**

[Titov et al. \(2020\)](#) found imipenem with cilastatin and relebactam to be non-inferior to piperacillin with tazobactam for all-cause mortality at day 28 (primary outcome) (n=531, 15.9% versus 21.3% respectively, adjusted difference -5.3% [95% CI -11.9 to 1.2], non-inferiority, p<0.001, modified intention-to-treat [MITT] population [all randomised participants who received at least 1 dose of study medicine and whose baseline Gram stain did not show only gram-positive cocci]).

Motsch et al. (2020) found that all-cause mortality at day 28 was 9.5% in the imipenem with cilastatin and relebactam group and 30.0% in the colistin plus imipenem with cilastatin group (n=31, adjusted difference -17.3 [90%CI -46.4 to 6.7], mMITT population).

### **Favourable clinical response**

Titov et al. (2020) defined overall favourable response as resolution of baseline pneumonia signs and symptoms with no non-study antibacterial therapy for hospital

acquired-pneumonia (including ventilator-associated pneumonia). The investigators found imipenem with cilastatin and relebactam to be non-inferior to piperacillin with tazobactam for favourable clinical response at early follow-up (7 to 14 days after end of treatment) (n=531, 61.0% versus 55.8% respectively, adjusted difference 5.0% [95% CI -3.2 to 13.2], non-inferiority,  $p < 0.001$ , MITT population).

Motsch et al. (2020) found that favourable clinical response at day 28 (defined as resolution of baseline signs and symptoms) was 71.4% in the imipenem with cilastatin and relebactam group and 40.0% in the colistin plus imipenem group (n=31, adjusted difference 26.3 ([90% CI 1.3 to 51.5], mMITT population).

### **Favourable microbiologic response**

Titov et al. (2020) defined favourable microbiologic response as eradication (lower respiratory tract culture showing absence of baseline pathogen) or presumed eradication (lower respiratory tract culture unavailable because of clinical cure).

[Favourable microbiologic response](#) at early follow-up was 67.9% in the imipenem with cilastatin and relebactam group and 61.9% in the piperacillin with tazobactam group (n=433, adjusted difference 6.2% [95% CI -2.7 to 15.0], mMITT population [participants in the MITT population with at least 1 baseline pathogen species against which imipenem with cilastatin and relebactam is known to have antibacterial activity]).

## **Review question 2**

What is the safety of imipenem with cilastatin and relebactam for treating infections caused by aerobic gram-negative organisms in adults with limited treatment options?

### **Safety outcomes**

Safety data from Motsch et al. (2020) and Titov et al. (2020) are derived from the safety populations (n=47 and n=535 respectively), which comprised all randomised participants who had 1 or more doses of the study medicines. Adverse events were monitored for 14 days following end of therapy in both studies. In both studies, most of the safety data were analysed descriptively.

In Motsch et al. (2020), the following safety outcomes were reported for all participants in the imipenem with cilastatin and relebactam group compared with the colistin plus imipenem with cilastatin group:

- deaths (6.5% [2/31] and 18.8% [3/16] respectively)
- treatment-related deaths (0.0% in both groups)
- serious adverse events (9.7% [3/31] and 31.3% [5/16] respectively)
- serious treatment-related adverse events (0.0% in both groups)
- at least 1 adverse event (71.0% [22/31] and 81.3% [13/16] respectively)
- study treatment-related adverse events (16.1% [5/31] and 31.3% [5/16] respectively)
- adverse events leading to study discontinuation (0.0% [0/31] and 18.8% [3/16] respectively)
- adverse events leading to study treatment discontinuation (0.0% [0/31] and 12.5% [2/16] respectively).

Motsch et al. (2020) found that treatment-emergent nephrotoxicity (this was a pre-specified endpoint with statistical analysis) was statistically significantly less frequent with imipenem with cilastatin and relebactam than with colistin plus imipenem with cilastatin (n=45, 10.3% versus 56.3%, adjusted difference -45.9 [90%CI -69.1 to -18.4], p=0.002).

In Titov et al. (2020), the following safety outcomes were reported for all participants in the imipenem with cilastatin and relebactam group compared with piperacillin with tazobactam group :

- deaths (15.0% [40/266] and 21.2% [57/269] respectively)
- treatment-related deaths (0% in both groups)
- serious adverse events (26.7% [71/266] and 32.0% [86/269] respectively)
- serious treatment-related adverse events (1.1% [3/266] and 0.7% [2/269] respectively)
- at least 1 adverse event (85.0% [226/266] and 86.6% [233/269] respectively)
- study treatment-related adverse events (11.7% [31/266] and 9.7% [26/269] respectively)

- adverse events leading to study discontinuation (5.6% [15/266] and 8.2% [22/269] respectively)
- adverse events leading to study treatment discontinuation (2.3% [6/266] and 1.5% [4/269] respectively).

The most commonly reported treatment-related adverse events with imipenem with cilastatin and relebactam in Motsch et al. (2020) were decreased creatinine clearance (2/31, 6.5%) and infusion site erythema, pyrexia and hyperglycaemia (each with an incidence of 1/31, 3.2%). In Titov et al. (2020) they were diarrhoea, increased aspartate aminotransferase and increased alanine aminotransferase (each with an incidence of 6/266, 2.3%).

The [summary of product characteristics for imipenem with cilastatin and relebactam](#) reports common adverse reactions (frequency 1 to 10 per 100) among 431 participants in phase 2 clinical trials as diarrhoea, nausea, vomiting, increased alanine aminotransferase and aspartate aminotransferase. In addition to these, the summary of product characteristics also reports on other commonly (frequency 1 to 10 per 100) reported adverse reactions with imipenem with cilastatin in clinical studies or post-marketing experience include eosinophilia, thrombophlebitis, rash and an increase in serum alkaline phosphatase. *Clostridioides difficile*-associated diarrhoea has also been reported with treatment. This may range in severity from mild diarrhoea to fatal colitis.

## Person-centred factors

Imipenem with cilastatin and relebactam is administered by intravenous infusion over 30 minutes, every 6 hours and is likely to be used in a hospital setting.

## Limitations of the evidence

The efficacy and safety of imipenem with cilastatin and relebactam was assessed in 2 phase 3 randomised controlled trials. Both studies were conducted in non-UK hospital settings. Motsch et al. (2020) was a smaller study (n=47) that included people with bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection and complicated UTI. Titov et al. (2020) was a relatively larger study (n=537) that only included people with

bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia), with a high proportion of participants in critical care. Motsch et al. (2020) evaluated imipenem with cilastatin and relebactam for treating imipenem non-susceptible pathogens (but imipenem and relebactam-susceptible) and Titov et al. (2020) in mostly treatment susceptible pathogens.

Motsch et al. (2020) compared imipenem with cilastatin and relebactam with colistin and imipenem with cilastatin. It was difficult to draw firm conclusions from this study because of the small size (n=47) and non-inferential and descriptive design. Also, the primary outcome combined endpoints that were specific to 3 different infection sites. Most exclusions from the primary efficacy population were due to differences in susceptibility testing between local and central laboratories. Relatively few participants with carbapenem-resistant Enterobacterales infection were enrolled (1 participant each for *Citrobacter freundii*, *Enterobacter cloacae* or *Klebsiella oxytoca* infection, and 4 with *Klebsiella pneumoniae*). The results stratified by pathogen type suggests that imipenem with cilastatin and relebactam may have more of an effect on infections caused by *Pseudomonas aeruginosa* than in infections caused by Enterobacterales. However, these findings are limited to a small study and more data is needed to assess the susceptibility of different microorganisms to imipenem with cilastatin and relebactam.

Titov et al. (2020) compared imipenem with cilastatin and relebactam with piperacillin with tazobactam for treating bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia). This was a relatively large, well-designed and reported non-inferiority study. The results are limited to mostly imipenem-susceptible pathogens. In participants with 1 or more baseline lower respiratory tract pathogens, susceptibility was higher with imipenem with cilastatin and relebactam compared with piperacillin with tazobactam (79.7% and 65.8% respectively) which may have positively influenced the effectiveness of imipenem with a cilastatin and relebactam. The study population mostly included participants at increased risk of adverse treatment outcomes and death. This was reflected in the high proportion of participants in intensive care units, with an [Acute Physiology and Chronic Health Evaluation 2](#) (APACHE 2) score of 15 or more, with either augmented renal clearance or moderate or severe renal impairment, and of older people. The high

rates of adverse events noted in this study may be attributed to the study enrolling a more critically ill patient population. Subgroup analyses were included in the study according to APACHE 2 scores and whether or not participants had ventilated pneumonia for example. However there was no pre-planned inferential statistical testing to draw conclusions from.

Across both studies, efficacy data were limited to bacterial hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated UTI and complicated intra-abdominal infection. In the mixed population study by Motsch et al. (2020), only 4 people with complicated intra-abdominal infection were included and none of them had favourable response to study treatments (2 of the 4 had missing or indeterminate data). Therefore it is difficult to draw a firm conclusion for using imipenem with cilastatin and relebactam for treating complicated intra-abdominal infections. No data were available for treating other gram-negative infections with limited treatment options. Both studies did not enrol participants from the UK and so the results may not be fully generalisable to the UK population. In both studies, participants received 1 or more antimicrobial treatments before study enrolment, however it was unclear whether they received adequate dosing and whether they had combination or sequential treatment.

The comparators used in both studies were suitable options. Piperacillin with tazobactam is a recommended option in the [NICE guideline on hospital-acquired pneumonia: antimicrobial prescribing](#) for people with severe symptoms or signs or at higher risk of resistance. Colistin plus imipenem with cilastatin is reserved for treating multi-drug resistant infections. However, there are no data to show the effectiveness of imipenem with cilastatin and relebactam compared with other best available treatment options, including other newer antibacterial agents with activity against multi-resistant bacteria such as ceftolozane with tazobactam, ceftazidime with avibactam and meropenem with vaborbactam.

Treatment duration may have varied amongst the participants because of the type of infection, severity and whether or not they had bacteraemia. The mean duration of treatment with imipenem with cilastatin and relebactam in Motsch et al. (2020) was approximately 11 days, and in Titov et al. (2020) it was approximately 9 days. Although this is within the licensed treatment duration, shorter course lengths are

often recommended. For example, the NICE guideline on hospital-acquired pneumonia recommends a 5 day course followed by a review of treatment. The [NICE guideline on antimicrobial stewardship](#) recommends following local (where available) or national guidelines on prescribing the shortest effective course.

## Resource implications

The cost of imipenem with cilastatin and relebactam is £153.55 per vial ([NHS Specialist Pharmacy Service](#)).

The cost of 1 day's treatment at the usual dose (1 vial [500 mg/500 mg/250 mg] every 6 hours) is £614.20.

The costs of other intravenous antibiotics that are used for hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection and complicated UTI are generally lower than that of imipenem with cilastatin and relebactam. For example piperacillin with tazobactam (4 g/0.5 g every 8 hours) costs from £14.40 per day (BNF, October 2020) and colistin and imipenem with cilastatin (9 million units daily and 0.5 g/0.5 g every 6 hours respectively) costs from £64.20 per day (BNF, October 2020).

The manufacturer of imipenem with cilastatin and relebactam (Merck Sharp & Dohme) anticipates that usage will be low in accordance with good antimicrobial stewardship.

## References

[Motsch J, Murta de Oliveira C, Stus V \(2020\) RESTORE-IMI 1: A multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections.](#) *Clinical Infectious Diseases* 70(9): 1799–1808

[Titov I, Wunderink RG, Roquilly A et al \(2020\) a randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia \(RESTORE-IMI 2 study\).](#) *Clinical Infectious Diseases* <https://doi.org/10.1093/cid/ciaa803>

## Development of the evidence review

### Process

The [evidence summary: process guide](#) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

### Expert advisers

#### Details of expert advisers and any declarations of interest

| Name, job title/organisation                                                                                                                                                                                              | DOI                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Daniele Bryden, Consultant in Intensive Care Medicine, Sheffield NHS Foundation Trust; Vice Dean, Faculty of Intensive Care Medicine                                                                                      | Vice Dean Faculty of Intensive Care Medicine (Non-financial interest October 2019 – ongoing)                                                                                                                                                                                                       |
| Professor Ian Pearce, Consultant Urological Surgeon and Andrologist, Manchester University Hospitals NHS Foundation Trust, Honorary, Professor, University of Salford; Honorary Senior Lecturer, University of Manchester | Private practice provider : Partner in Manchester Urology LLP (Financial interest 2012 – ongoing)<br>Partner in Fortify Clinic : Health care provider (Financial interest 2019 – ongoing)<br>Secretary elect: British Association Urological Surgeons (Non-financial interest June 2019 – ongoing) |
| Dr Natasha Ratnaraja, Consultant Microbiologist, University Hospitals Coventry and Warwickshire NHS Trust                                                                                                                 | Microbiologist for BMI Meriden healthcare providing clinical advice (Financial interest October 2018 – ongoing)<br>Council member British Infection Association (Non-financial interest September 2016 – ongoing)<br>Reviewer for NICE (Non-financial interest October 2019 – ongoing)             |
| Dr Rowland Bright-Thomas, Consultant Respiratory Physician, Manchester University Hospitals NHS Foundation Trust                                                                                                          | No relevant interests declared                                                                                                                                                                                                                                                                     |

### Terms used in this evidence review

#### Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) score

This is an illness severity score used to predict mortality when admitted to an intensive care unit. A score of 25 represents a predicted mortality of 50% and a score of over 35 represents a predicted mortality of 80% ([Bouch and Thompson 2008](#)).

## Appendices

### Appendix A: PICO table

#### PICO table

| Criteria                      | Details                                                                                                                                                                                     |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| P – Population and indication | Adults with infections due to aerobic gram-negative organisms                                                                                                                               |
| I – Intervention              | Imipenem with cilastatin and relebactam (Recarbrio) 500mg/500mg/250mg powder for solution for infusion                                                                                      |
| C – Comparator(s)             | Any comparator                                                                                                                                                                              |
| O – Outcomes                  | Any outcomes<br>Outcomes may include:<br>Mortality<br>Clinical response<br>Clinical success<br>Clinical failure<br>Microbiological response<br>Adverse effects                              |
| Inclusion criteria            | -----                                                                                                                                                                                       |
| Study design                  | Systematic reviews, randomised controlled trials, controlled clinical trials.<br>If no higher-level quality evidence is found observational studies including case series can be considered |
| Language                      | English                                                                                                                                                                                     |
| Patients                      | Human studies only                                                                                                                                                                          |
| Age                           | Adults 18 years and over                                                                                                                                                                    |
| Date limits                   | None                                                                                                                                                                                        |
| Exclusion criteria            | -----                                                                                                                                                                                       |
| Publication type              | Pre-prints prior to peer review, conference abstracts or studies that have not been published in full                                                                                       |
| Study design                  | Case reports                                                                                                                                                                                |

## Appendix B: Summary of included studies

### Summary of included studies

| Study                                               | Number of participants                         | Population                                                                                                                                                                                                                                                                                                 | Intervention                                                                                                                                         | Comparison                                                                                                                                                                          | Outcomes                                                                                                                                                                                                                    |
|-----------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Motsch et al. 2020 RCT 16 sites world-wide (not UK) | n=47 randomised (n=31 in the mMITT population) | <p>Hospitalised adults with bacterial HAP/VAP, cIAI or cUTI</p> <p>Detected beta-lactamases included AmpC beta-lactamases (84%), extended-spectrum beta-lactamases (35%), <i>Klebsiella pneumoniae</i> carbapenemase (16%) and OXA-48 (3%).</p> <p>6.5% had known bacteraemia (unknown status, 71.0%).</p> | <p>Imipenem with cilastatin and relebactam, IV 500 mg/ 500 mg/ 250 mg 6 hourly</p> <p>Mean (range) duration of treatment 11.4 (2–18) days (n=21)</p> | <p>imipenem with cilastatin IV 500 mg 6 hourly and colistin, 300 mg loading dose followed by 150 mg 12 hourly</p> <p>Mean (range) duration of treatment 10.8 (2–20) days (n=10)</p> | <p>Primary outcomes:</p> <p>1. Overall response in the mMITT population</p> <p>Key secondary outcomes:</p> <p>1. Favourable clinical response at 28 days</p> <p>2. All-cause mortality at 28 days</p> <p>Adverse events</p> |

| Study                                                     | Number of participants                          | Population                                                                                                                                                                                                                                                                                                     | Intervention                                                                                                               | Comparison                                                                                              | Outcomes                                                                                                                                                                                                    |
|-----------------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Titov et al. 2020<br>RCT<br>113 sites world-wide (not UK) | n=537 randomised (n=531 in the MITT population) | Hospitalised adults with bacterial HAP (ventilated/ non-ventilated) and VAP<br><br>Baseline lower respiratory tract pathogens and susceptibility: 79.7% in imipenem with cilastatin and relebactam, and 65.8% in piperacillin with tazobactam.<br><br>66.1% were in intensive care<br><br>8.1% had bacteraemia | Imipenem with cilastatin and relebactam, IV 500 mg/ 500 mg/ 250 mg 6 hourly<br>Mean duration of treatment 8.7 days (n=264) | Piperacillin with tazobactam IV 4.0 g/0.5 g 6 hourly<br><br>Mean duration of treatment 8.3 days (n=267) | Primary outcome:<br>1. Day 28 all-cause mortality<br>Secondary outcomes:<br>1. Favourable clinical response at EFU<br>2. Day 28 mortality<br>3. Microbiologic response at EOT and EFU<br><br>Adverse events |

Abbreviations: cIAI, complicated intra-abdominal infection; EFU, early follow-up; EOT, end of treatment; HAP, hospital-acquired pneumonia; IV, intravenous; MITT, modified intention-to-treat; mMITT, modified microbiologic intention-to-treat; RCT, randomised controlled trial; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

In Motsch et al. (2020) and Titov et al. (2020), the doses of imipenem with cilastatin and relebactam, and piperacillin with tazobactam were adjusted based on renal function.

Motsch et al. (2020) and Titov et al. (2020), allowed the use of intravenous linezolid (Motsch et al. 2020 also allowed intravenous vancomycin and daptomycin) if methicillin-resistant *Staphylococcus aureus* was present.

## Appendix C: Quality assessment of included studies

### Quality assessment of Motsch et al. 2020

| Question                                                                                 | Motsch et al. 2020                                                                                                                                                                       |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Did the trial address a clearly focused issue?                                           | Yes                                                                                                                                                                                      |
| Was the assignment of patients to treatments randomised?                                 | Yes                                                                                                                                                                                      |
| Were patients, health workers and study personnel blinded?                               | Yes                                                                                                                                                                                      |
| Were the groups similar at the start of the trial?                                       | Probably yes                                                                                                                                                                             |
| Aside from the experimental intervention, were the groups treated equally?               | Probably yes                                                                                                                                                                             |
| Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes                                                                                                                                                                                      |
| How large was the treatment effect?                                                      | See results table                                                                                                                                                                        |
| How precise was the estimate of the treatment effect?                                    | See results table                                                                                                                                                                        |
| Can the results be applied in your context? (or to the local population)                 | Yes<br>Although some participants were European, the trial was not undertaken in the UK and it is unclear whether all participants would have met criteria for hospitalisation in the UK |
| Were all clinically important outcomes considered?                                       | Yes<br>It appears that all relevant outcomes were considered                                                                                                                             |
| Are the benefits worth the harms and costs?                                              | See overview                                                                                                                                                                             |

Checklist used: [CASP RCT checklist](#).

### Quality assessment of Titov et al. 2020

| Question                                                   | Titov et al. 2020 |
|------------------------------------------------------------|-------------------|
| Did the trial address a clearly focused issue?             | Yes               |
| Was the assignment of patients to treatments randomised?   | Yes               |
| Were patients, health workers and study personnel blinded? | Yes               |
| Were the groups similar at the start of the trial?         | Probably yes      |

| Question                                                                                 | Titov et al. 2020                                                                                                                                                                        |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aside from the experimental intervention, were the groups treated equally?               | Probably yes                                                                                                                                                                             |
| Were all of the patients who entered the trial properly accounted for at its conclusion? | Yes                                                                                                                                                                                      |
| How large was the treatment effect?                                                      | See results table                                                                                                                                                                        |
| How precise was the estimate of the treatment effect?                                    | See results table                                                                                                                                                                        |
| Can the results be applied in your context? (or to the local population)                 | Yes<br>Although some participants were European, the trial was not undertaken in the UK and it is unclear whether all participants would have met criteria for hospitalisation in the UK |
| Were all clinically important outcomes considered?                                       | Yes<br>It appears that all relevant outcomes were considered                                                                                                                             |
| Are the benefits worth the harms and costs?                                              | See overview                                                                                                                                                                             |

Checklist used: [CASP RCT checklist](#)

## Appendix D: Results tables

### Results table for Motsch et al. (2020)

| Outcome                                                    | Imipenem with cilastatin and relebactam | Colistin plus imipenem | Analysis                                                 |
|------------------------------------------------------------|-----------------------------------------|------------------------|----------------------------------------------------------|
| <b>Primary outcomes</b>                                    | -----                                   | -----                  | -----                                                    |
| Overall response in the mMITT population                   | 71.4% (15/21)                           | 70.0% (7/10)           | Adjusted difference<br>-7.3% (90% CI -27.5% to 21.4%)    |
| HAP/VAP                                                    | 87.5% (7/8)                             | 66.7% (2/3)            | Adjusted difference 20.8%, (CI not reported)             |
| cIAI                                                       | 0.0% (0/2)                              | 0.0% (0/2)             | 0.0% (CI not reported)                                   |
| cUTI                                                       | 72.7% (8/11)                            | 100% (5/5)             | Adjusted difference<br>-27.3% (90% CI -52.8% to 12.8%)   |
| <b>Secondary outcomes</b>                                  | -----                                   | -----                  | -----                                                    |
| Favourable clinical response at day 28 in mMITT population | 71.4% (15/21)                           | 40.0% (4/10)           | Adjusted difference<br>26.3% (90% CI 1.3% to 51.5%)      |
| 28-day all-cause mortality in mMITT population             | 9.5% (2/21)                             | 30.0% (3/10)           | Adjusted difference<br>-17.3% (90% CI -46.6 to 6.7)      |
| <b>Subgroup analysis by pathogen</b>                       | -----                                   | -----                  | -----                                                    |
| <i>Pseudomonas aeruginosa</i>                              | 81.0% (13/16)                           | 63.0% (5/8)            | -----                                                    |
| Enterobacterales                                           | 40.0% (2/5)                             | 100.0% (2/2)           | -----                                                    |
| <b>Safety outcomes</b>                                     | -----                                   | -----                  | -----                                                    |
| At least 1 adverse event                                   | 71% (22/31)                             | 81.3% (13/16)          | Unadjusted difference<br>-10.3% (95% CI -33.1% to 18.0%) |
| Drug-related adverse events                                | 16.1% (5/31)                            | 31.3% (5/16)           | Unadjusted difference<br>-15.1% (95% CI -42.3% to 9.2%)  |
| Serious adverse events                                     | 9.7% (3/31)                             | 31.3% (5/16)           | Unadjusted difference<br>-26.1% (95% CI -47.8% to 1.3%)  |
| Serious drug-related adverse event                         | 0% (0/31)                               | 0% (0/16)              | Unadjusted difference<br>0.0% (95% CI -19.7% to 11.2%)   |
| Reported deaths                                            | 6.5% (2/31)                             | 18.8% (3/16)           | Unadjusted difference<br>-12.3% (95% CI -37.8% to 6.5%)  |

| <b>Outcome</b>                                     | <b>Imipenem with cilastatin and relebactam</b> | <b>Colistin plus imipenem</b> | <b>Analysis</b>                                       |
|----------------------------------------------------|------------------------------------------------|-------------------------------|-------------------------------------------------------|
| Reported drug-related deaths                       | 0.0% (0/31)                                    | 0.0% (0/16)                   | Unadjusted difference 0.0% (95% CI -19.7% to 11.2%)   |
| Treatment-emergent nephrotoxicity                  | 10.3% (3/29)                                   | 56.3% (9/16)                  | -45.9% (90% CI -69.1% to -18.4%), p=0.002             |
| Discontinuation of treatment due to adverse events | 0.0% (0/31)                                    | 18.8% (3/16)                  | Unadjusted difference -18.8% (95% CI -43.3% to -6.2%) |

Abbreviations: cIAI, complicated intra-abdominal infection; CI, confidence interval; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; IV, intravenous; modified microbiologic intention-to-treat; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

The study was an estimation trial without formal statistical testing for efficacy endpoints.

Favourable overall response was defined as resolution of baseline signs and symptoms.

Favourable microbiologic response was defined as eradication of baseline uropathogens.

Modified microbiologic intention-to-treat population included participants with 1 or more qualifying gram-negative pathogens from the primary infection site (according to central laboratory results) and had 1 or more doses of the study medicines.

Overall response in the modified microbiologic intention-to-treat population was assessed centrally and defined differently for each infection type based on regulatory guidance: HAP/VAP survival up to day 28; complicated IAI, clinical response at day 28; complicated UTI, composite clinical and microbiological response 5–9 days after the end of therapy.

## Results table for Titov et al. (2020)

| Outcome                                                                             | Imipenem with cilastatin and relebactam | Piperacillin with tazobactam | Analysis                                                                                                                   |
|-------------------------------------------------------------------------------------|-----------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>Primary outcomes</b>                                                             | -----                                   | -----                        | -----                                                                                                                      |
| Day 28 all-cause mortality in the MITT population                                   | 15.9%<br>(42/264)                       | 21.3%<br>(57/267)            | Adjusted difference<br>-5.3% (95% CI -11.9% to 1.2%) p<0.001<br>Non-inferiority margin of <10% for the upper bound 95%CI   |
| <b>Secondary outcomes</b>                                                           | -----                                   | -----                        | -----                                                                                                                      |
| Favourable clinical response at EFU in the MITT population (key secondary endpoint) | 61.0%<br>(161/264)                      | 55.8%<br>(149/267)           | Adjusted difference<br>5.0% (95% CI -3.2% to 13.2%) p<0.001<br>Non-inferiority margin of >-12.5% for the lower bound 95%CI |
| Day 28 all-cause mortality in mMITT population                                      | 16.7%<br>(36/215)                       | 20.2%<br>(44/218)            | Adjusted difference<br>-3.5% (95% CI -10.9% to 3.6%)                                                                       |
| Favourable microbiologic response at EFU in the mMITT population                    | 67.9%<br>(146/215)                      | 61.9%<br>(135/218)           | Adjusted difference<br>6.2% (95% CI -2.7% to 15.0%)                                                                        |
| Favourable clinical response at EFU in the clinically evaluable population          | 74.3%<br>(101/136)                      | 79.4%<br>(100/126)           | Adjusted difference<br>-3.7% (95% CI -13.6% to 6.4%)                                                                       |
| <b>Safety outcomes</b>                                                              | -----                                   | -----                        | -----                                                                                                                      |
| At least 1 adverse event                                                            | 85.0%<br>(226/266)                      | 86.6%<br>(233/269)           | Unadjusted difference<br>-1.7% (95% CI -7.7% to 4.3%)                                                                      |
| Drug-related adverse events                                                         | 11.7%<br>(31/266)                       | 9.7%<br>(26/269)             | Unadjusted difference<br>2.0% (95% CI -3.3% to 7.4%)                                                                       |
| Serious adverse events                                                              | 26.7%<br>(71/266)                       | 32.0%<br>(86/269)            | Unadjusted difference<br>-5.3% (95% CI -13.0% to 2.5%)                                                                     |
| Serious drug-related adverse event                                                  | 1.1%<br>(3/266)                         | 0.7%<br>(2/269)              | Unadjusted difference<br>0.4% (95% CI -1.7% to 2.6%)                                                                       |
| Deaths                                                                              | 15.0%<br>(40/266)                       | 21.2%<br>(57/269)            | Unadjusted difference<br>-6.2% (95% CI -12.7% to 0.4%)                                                                     |
| Drug-related deaths                                                                 | 0.0%<br>(0/266)                         | 0.0%<br>(0/269)              | Unadjusted difference<br>0.0% (95% CI -1.4% to 1.4%)                                                                       |

| <b>Outcome</b>                                                  | <b>Imipenem with cilastatin and relebactam</b> | <b>Piperacillin with tazobactam</b> | <b>Analysis</b>                                     |
|-----------------------------------------------------------------|------------------------------------------------|-------------------------------------|-----------------------------------------------------|
| Discontinuation of treatment due to adverse events              | 5.6% (15/266)                                  | 8.2% (22/269)                       | Unadjusted difference -2.5% (95% CI -7.1% to -1.8%) |
| Discontinuation of treatment due to drug-related adverse events | 2.3% (6/266)                                   | 1.5% (4/269)                        | Unadjusted difference 0.8% (95% CI -1.8% to 3.5%)   |

Abbreviations: APACHE 2, Acute Physiology and Chronic Health Evaluation 2; EFU, early follow-up; EOT, end of treatment; HAP, hospital-acquired pneumonia; IV, intravenous; MITT, modified intention-to-treat; mMITT, modified microbiologic intention-to-treat; VAP, ventilator-associated pneumonia.

Clinically evaluable population included participants who met diagnostic criteria for bacterial HAP/VAP, had no major protocol violation, received the minimum treatment duration, and had a corresponding efficacy assessment.

Early follow-up was 7 to 14 days after end of treatment.

Favourable clinical response was defined as resolution of baseline bacterial HAP/VAP signs and symptoms and no non-study antibacterial treatment for bacterial HAP/VAP.

Favourable microbiologic response was defined as eradication (lower respiratory tract culture showing absence of baseline pathogen) or presumed eradication (lower respiratory tract culture unavailable because of clinical cure).

Modified intention-to-treat (MITT) population included randomised participants who received 1 or more doses of study treatment and whose baseline Gram stain did not show only gram-positive cocci.

Modified microbiologic intention-to-treat population (mMITT) included the MITT participants with 1 or more baseline lower respiratory tract pathogen species against which imipenem with cilastatin and relebactam is known to have antibacterial activity.

Safety population included all randomised participants who received 1 or more doses of assigned study treatment.

## Appendix E: Literature search strategy

### Database search strategies

#### ***Database: Medline***

Platform: Ovid

Version: Ovid MEDLINE(R) 1946 to January 20, 2020

Search date: 21/01/20

Number of results retrieved: 13

Search Strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (9050)  
5 Imipenem/ (4010)  
6 4 or 5 (9700)  
7 cilastatin.ti,ab. (1257)  
8 Cilastatin/ (947)  
9 7 or 8 (1432)  
10 relebactam.ti,ab. (45)  
11 relebactam/ (0)  
12 10 or 11 (45)  
13 6 and 9 and 12 (15)  
14 Cilastatin, Imipenem Drug Combination/ (426)  
15 12 and 14 (4)  
16 3 or 13 or 15 (15)  
17 animals/ not humans/ (4632540)  
18 16 not 17 (14)  
19 limit 18 to english language (13)

Re-run on 03/07/2020:

Database: Ovid MEDLINE(R) 1946 to July 02, 2020

Search Strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (9216)  
5 Imipenem/ (4054)  
6 4 or 5 (9869)  
7 cilastatin.ti,ab. (1273)  
8 Cilastatin/ (952)  
9 7 or 8 (1450)  
10 relebactam.ti,ab. (55)  
11 relebactam/ (0)  
12 10 or 11 (55)

13 6 and 9 and 12 (17)  
14 Cilastatin, Imipenem Drug Combination/ (435)  
15 12 and 14 (4)  
16 3 or 13 or 15 (17)  
17 animals/ not humans/ (4680589)  
18 16 not 17 (16)  
19 limit 18 to english language (15)  
20 limit 19 to ed=20200120-20200703 (3)

**Database: Medline in-process**

Platform: Ovid  
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to January 20, 2020  
Search date: 21/01/20  
Number of results retrieved:  
Search strategy:

---

1 recarbrio.ti,ab. (1)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (1)  
4 imipenem.ti,ab. (1047)  
5 cilastatin.ti,ab. (64)  
6 relebactam.ti,ab. (36)  
7 4 and 5 and 6 (9)  
8 3 or 7 (10)  
9 limit 8 to english language (10)

Re-run on 03/07/2020:  
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to July 02, 2020  
Search Strategy:

---

1 recarbrio.ti,ab. (4)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (4)  
4 imipenem.ti,ab. (1207)  
5 cilastatin.ti,ab. (84)  
6 relebactam.ti,ab. (55)  
7 4 and 5 and 6 (21)  
8 3 or 7 (22)  
9 limit 8 to english language (22)  
10 limit 9 to dt=20200120-20200703 (10)

**Database: Medline epub ahead of print**

Platform: Ovid  
Version: Ovid MEDLINE(R) Epub Ahead of Print January 20, 2020  
Search date: 21/01/20  
Number of results retrieved: 4

Search strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (146)  
5 cilastatin.ti,ab. (16)  
6 relebactam.ti,ab. (8)  
7 4 and 5 and 6 (4)  
8 3 or 7 (4)  
9 limit 8 to english language (4)

Re-run on 03/07/2020

Database: Ovid MEDLINE(R) Epub Ahead of Print July 02, 2020

Search Strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (135)  
5 cilastatin.ti,ab. (12)  
6 relebactam.ti,ab. (9)  
7 4 and 5 and 6 (1)  
8 3 or 7 (1)  
9 limit 8 to english language (1)

**Database: Medline daily update**

Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update January 20, 2020

Search date: 21/01/20

Number of results retrieved: 0

Search strategy

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (5)  
5 cilastatin.ti,ab. (2)  
6 relebactam.ti,ab. (0)  
7 4 and 5 and 6 (0)  
8 3 or 7 (0)  
9 limit 8 to english language (0)

Re-run on 03/07/2020

Database: Ovid MEDLINE(R) Daily Update July 02, 2020

Search Strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)

3 1 or 2 (0)  
4 imipenem.ti,ab. (4)  
5 cilastatin.ti,ab. (1)  
6 relebactam.ti,ab. (1)  
7 4 and 5 and 6 (1)  
8 3 or 7 (1)  
9 limit 8 to english language (1)

**Database: Embase**

Platform: Ovid  
Version: Embase 1974 to 2020 January 20  
Search date: 21/01/20  
Number of results retrieved: 52  
Search strategy:

---

1 recarbrio.ti,ab. (0)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (0)  
4 imipenem.ti,ab. (14899)  
5 imipenem/ (37045)  
6 4 or 5 (39330)  
7 cilastatin.ti,ab. (1986)  
8 cilastatin/ (2668)  
9 7 or 8 (3556)  
10 relebactam.ti,ab. (115)  
11 relebactam/ (191)  
12 10 or 11 (208)  
13 6 and 9 and 12 (45)  
14 cilastatin plus imipenem/ (4782)  
15 12 and 14 (47)  
16 (NCT03293485 or NCT01505634 or NCT01506271 or NCT02452047 or  
NCT03583333 or NCT02493764).cn. (26)  
17 3 or 13 or 15 or 16 (84)  
18 nonhuman/ not (human/ and nonhuman/) (4543484)  
19 17 not 18 (69)  
20 limit 19 to english language (68)

Re-run on 03/07/2020  
Database: Embase 1974 to 2020 July 02  
Search Strategy:

---

1 recarbrio.ti,ab. (3)  
2 mk-7655A.ti,ab. (0)  
3 1 or 2 (3)  
4 imipenem.ti,ab. (15291)  
5 imipenem/ (37964)  
6 4 or 5 (40306)  
7 cilastatin.ti,ab. (2013)  
8 cilastatin/ (2691)

9 7 or 8 (3601)  
 10 relebactam.ti,ab. (145)  
 11 relebactam/ (215)  
 12 10 or 11 (244)  
 13 6 and 9 and 12 (56)  
 14 cilastatin plus imipenem/ (4826)  
 15 12 and 14 (46)  
 16 (NCT03293485 or NCT01505634 or NCT01506271 or NCT02452047 or  
 NCT03583333 or NCT02493764).cn. (31)  
 17 3 or 13 or 15 or 16 (97)  
 18 nonhuman/ not (human/ and nonhuman/) (4634876)  
 19 17 not 18 (80)  
 20 limit 19 to english language (79)  
 21 limit 20 to dc=20200120-20200703 (17)

**Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL**

Platform: Wiley

Version:

CDSR – Issue 1 of 12, January 2020

CENTRAL – Issue 1 of 12, January 2020

Search date: 21/01/20

Number of results retrieved: CDSR 0; CENTRAL 11.

Search strategy:

```

-----
#1  recarbrio:ti,ab      0
#2  MK-7655A:ti,ab     9
#3  #1 or #2            9
#4  imipenem:ti,ab     608
#5  MeSH descriptor: [Imipenem] this term only  295
#6  #4 or #5           635
#7  cilastatin:ti,ab   371
#8  MeSH descriptor: [Cilastatin] this term only  198
#9  #7 or #8           389
#10 relebactam:ti,ab   21
#11 #6 and #9 and #10  18
#12 MeSH descriptor: [Cilastatin, Imipenem Drug Combination] this term only  81
#13 #10 and #12        2
#14 #3 or #11 or #13   18
#15 #14 in Cochrane Reviews  0
#16 "conference":pt or (clinicaltrials or trialsearch):so  446662
#17 #14 and #16 in Trials  11
  
```

Re-run on 03/07/2020

Platform: Wiley

Version:

CDSR – Issue 7 of 12, July 2020

CENTRAL Issue 7 of 12, July 2020, Search date: 03/07/20

Number of results retrieved: CDSR 0; CENTRAL 8.

Search strategy:

---

|     |                                                                                               |        |
|-----|-----------------------------------------------------------------------------------------------|--------|
| #1  | recarbrio:ti,ab                                                                               | 0      |
| #2  | MK-7655A:ti,ab                                                                                | 11     |
| #3  | #1 or #2                                                                                      | 11     |
| #4  | imipenem:ti,ab                                                                                | 609    |
| #5  | MeSH descriptor: [Imipenem] this term only                                                    | 312    |
| #6  | #4 or #5                                                                                      | 638    |
| #7  | cilastatin:ti,ab                                                                              | 384    |
| #8  | MeSH descriptor: [Cilastatin] this term only                                                  | 210    |
| #9  | #7 or #8                                                                                      | 404    |
| #10 | relebactam:ti,ab                                                                              | 26     |
| #11 | #6 and #9 and #10                                                                             | 23     |
| #12 | MeSH descriptor: [Cilastatin, Imipenem Drug Combination] this term only                       | 82     |
| #13 | #10 and #12                                                                                   | 2      |
| #14 | #3 or #11 or #13                                                                              | 23     |
| #15 | #14 with Cochrane Library publication date Between Jan 2020 and Jul 2020, in Cochrane Reviews | 0      |
| #16 | #14                                                                                           | 23     |
| #17 | "conference":pt or (clinicaltrials or trialsearch):so                                         | 492465 |
| #18 | #16 not #17 in Trials                                                                         | 8      |

**Database: HTA**

Platform: CRD

Version: 21st Jan

Search date: 21/01/20

Number of results retrieved: 1

Search strategy:

---

1 (recarbrio) OR (MK-7655a) 0  
2 MeSH DESCRIPTOR Imipenem EXPLODE ALL TREES 25  
3 (imipenem) 68  
4 #2 OR #3 68  
5 (cilastatin) 43  
6 MeSH DESCRIPTOR Cilastatin EXPLODE ALL TREES 19  
7 #5 OR #6 43  
8 (relebactam) 1  
9 #4 AND #7 AND #8 1  
10 (#9) IN HTA 1

Re-run on 03/07/2020

Platform: CRD

Version: 3rd July

Search date: 03/07/2020

Number of results retrieved: 0

Search strategy:

---

1 (recarbrio) OR (MK-7655a) 0  
2 MeSH DESCRIPTOR Imipenem EXPLODE ALL TREES 25

3 (imipenem) 68  
4 #2 OR #3 68  
5 (cilastatin) 43  
6 MeSH DESCRIPTOR Cilastatin EXPLODE ALL TREES 19  
7 #5 OR #6 43  
8 (relebactam) 1  
9 #4 AND #7 AND #8 1  
10 (#9) IN HTA 1\*  
\*Result was from 2016

## **Trials registry search strategies**

### ***Clinicaltrials.gov***

Search date: 15/1/2020  
Number of results retrieved: 0  
Search strategy: recarbrio

Search date: 15/1/2020  
Number of results retrieved: 9  
Search strategy: imipenem AND cilastatin AND relebactam

Search date: 15/1/2020  
Number of results retrieved: 6  
Search strategy: MK-7655A

Searches re-run on 02/07/2020, no new results identified.

### ***Clinicaltrialsregister.eu***

Search date: 15/1/2020  
Number of results retrieved: 0  
Search strategy: recarbrio

Search date: 15/1/2020  
Number of results retrieved: 5  
Search strategy: imipenem AND cilastatin AND relebactam

Search date: 15/1/2020  
Number of results retrieved: 5  
Search strategy: MK-7655A

Searches re-run on 02/07/2020, no new results identified.

## Appendix F: Excluded studies

### Excluded studies

| Study reference                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Reason for exclusion                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Excludes from January 2020 searches</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | -----                                                           |
| Brown, M.; Motsch, J.; Kaye, K.; File, T.; Boucher, H.W.; Vendetti, N.; Aggrey, A.; Joeng, H.-K.; Tipping, R.; Du, J.; Depestel, D.D.; Butterson, J.; Kartsonis, N.A.; Paschke, A. Nephrotoxicity associated with imipenem/cilastatin/relebactam (IMI/REL) vs. imipenem/cilastatin plus colistin (IMI+CST) in patients with imipenem-nonsusceptible (NS) bacterial infections Open Forum Infectious Diseases, 5, supplement1, 563, 2018                                                                      | Conference abstract only                                        |
| Kaye, K.; File, T.; Boucher, H.W.; Brown, M.; Aggrey, A.; Khan, I.; Joeng, H.-K.; Tipping, R.; Du, J.; Young, K.; Butterson, J.; Kartsonis, N.A.; Paschke, A. Results for the supplemental microbiological modified intent-to-treat (smmitt) population of the RESTORE-IMI 1 Trial of Imipenem/Cilastatin/ Relebactam (IMI/REL) vs. Imipenem/Cilastatin Plus Colistin (IMI+CST) in patients with imipenem-nonsusceptible (NS) bacterial infections Open Forum Infectious Diseases, 5, supplement1, 409, 2018 | Conference abstract only                                        |
| Lucasti, C.; Vasile, L.; Sandesc, D.; Venskutonis, D.; McLeroth, P.; Lala, M.; Rizk, M.L.; Brown, M.L.; Losada, M.C.; Pedley, A.; Kartsonis, N.A.; Paschke, A. Phase 2, dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection Antimicrobial Agents and Chemotherapy, 60, 10, 6234-6243, 2016                                                                                                                                                      | Phase 2 study, better evidence available                        |
| Sims, M.; Mariyanovski, V.; McLeroth, P.; Akers, W.; Lee, Y.-C.; Brown, M.L.; Du, J.; Pedley, A.; Kartsonis, N.A.; Paschke, A. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections Journal of Antimicrobial Chemotherapy, 72, 9, 2616-2626, 2017                                                                                     | Phase 2 study, better evidence available                        |
| <b>Excludes from July 2020 searches</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | -----                                                           |
| Brown, Michelle L; Motsch, Johann; Kaye, Keith S; File, Thomas M; Boucher, Helen W; Vendetti, Neika; Aggrey, Angela; Joeng, Hee-Koung; Tipping, Robert W; Du, Jiejun; DePestel, Daryl D; Butterson, Joan R; Paschke, Amanda Evaluation of Renal Safety Between Imipenem/Relebactam and Colistin Plus Imipenem in Patients With Imipenem-Nonsusceptible Bacterial Infections in the Randomized, Phase 3 RESTORE-IMI 1 Study. Open forum infectious diseases, 7, 3, ofaa054, 2020                              | Secondary publication of an included study (Motsch et al. 2020) |

| <b>Study reference</b>                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>Reason for exclusion</b>                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <p>Kaye, K.S.; Boucher, H.W.; Brown, M.L.; Aggrey, A.; Khan, I.; Joeng, H.-K.; Tipping, R.W.; Du, J.; Young, K.; Butterson, J.R.; Paschke, A. Comparison of treatment outcomes between analysis populations in the RESTORE-IMI 1 phase 3 trial of imipenem-cilastatin-relebactam versus colistin plus imipenem-cilastatin in patients with imipenem-nonsusceptible bacterial infections <i>Antimicrobial Agents and Chemotherapy</i>, 64, 5, e02203-19, 2020</p> | <p>Secondary publication of an included study (Motsch et al. 2020)</p> |