

1 NAME OF THE MEDICINAL PRODUCT

Recarbrio® 500 mg/500 mg/250 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains imipenem monohydrate equivalent to 500 mg imipenem, cilastatin sodium equivalent to 500 mg cilastatin, and relebactam monohydrate equivalent to 250 mg relebactam.

Excipient(s) with known effect

The total amount of sodium in each vial is 37.5 mg (1.6 mmol).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

A white to light yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Recarbrio is indicated in adult and paediatric patients from birth for:

- Treatment of hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) (see sections 4.4 and 5.1).
- Treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP.
- Treatment of infections due to aerobic Gram-negative organisms with limited treatment options (see sections 4.2, 4.4, and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

It is recommended that Recarbrio should be used to treat infections due to aerobic Gram-negative organisms in patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Posology

Table 1 shows the recommended intravenous dose for adult patients with a creatinine clearance (CrCl) ≥ 90 mL/min and Table 2 shows the recommended intravenous dose for paediatric patients (from birth to < 18 years of age) with normal renal function (see sections 4.4 and 5.1).

Table 1: Recommended doses for adult patients with a CrCl ≥ 90 mL/min*[†]

Type of infection	Dose of Recarbrio (imipenem/cilastatin/relebactam)	Frequency	Infusion time (minutes)	Duration of treatment
Hospital-acquired pneumonia, including ventilator associated pneumonia ^{††}	500 mg/500 mg/250 mg	Every 6 hours	30	7 to 14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options [†]	500 mg/500 mg/250 mg	Every 6 hours	30	Duration in accordance with the site of infection [§]

*As calculated using the Cockcroft-Gault formula.
[†]For HAP or VAP patients with CrCl $\square 250$ mL/min, and for patients with complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI), including pyelonephritis with CrCl $\square 150$ mL/min, the recommended dose may not be sufficient (see section 4.4).
^{††}Includes bacteraemia, in association with, or suspected to be associated with, HAP or VAP.
[§]e.g., for cIAI and cUTI the recommended treatment duration is 5 to 10 days; treatment may continue up to 14 days.

Table 2: Recommended doses for paediatric patients with normal renal function*

Body Weight	Age	Dose of Recarbrio (imipenem/cilastatin/relebactam)	Frequency	Infusion time (minutes)
≥ 30 kg	< 18 years	500 mg/500 mg/250 mg	Every 6 hours	30
2 kg to < 30 kg	≥ 3 months to < 18 years	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg and relebactam 7.5 mg/kg)	Every 6 hours	60
	Birth to < 3 months	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg and relebactam 7.5 mg/kg)	Every 8 hours	60

*As measured by estimated glomerular filtration rate (eGFR) calculated using the bedside Schwartz formula.

The recommended treatment duration for paediatric patients with HAP/VAP is the same as for adults. For treatment of infections due to aerobic Gram-negative organisms in paediatric patients with limited treatment options, duration of treatment should be based on prescriber discretion. See section 5.1.

Special populations

Renal impairment

Adult patients who have a CrCl less than 90 mL/min require dose reduction of imipenem/cilastatin/relebactam as indicated in Table 3. For patients with fluctuating renal function, CrCl should be monitored.

Paediatric patients weighing at least 30 kg with eGFR less than 90 mL/min/1.73 m² require a dose reduction of imipenem/cilastatin/relebactam as indicated in Table 3. Imipenem/cilastatin/relebactam is not recommended in paediatric patients weighing less than 30 kg with renal impairment.

Table 3: Recommended intravenous doses for adult patients with a CrCl < 90 mL/min and paediatric patients (weighing at least 30 kg) with an eGFR of < 90 mL/min/1.73 m²

Estimated renal function (CrCl [mL/min]* or eGFR [mL/min/1.73 m ²] [†])	Recommended dose of Recarbrio (imipenem/cilastatin/relebactam) (mg) [‡]
Less than 90 to greater than or equal to 60	400/400/200
Less than 60 to greater than or equal to 30	300/300/150
Less than 30 to greater than or equal to 15	200/200/100
End stage renal disease (ESRD) on haemodialysis [§]	200/200/100
<p>*CrCl calculated using the Cockcroft-Gault formula for adult patients. [†]eGFR calculated using the bedside Schwartz formula for paediatric patients weighing ≥ 30 kg. [‡]Administer intravenously. See Tables 1 and 2 for infusion duration and dosing frequency. [§]Administration should be timed to follow haemodialysis. Imipenem, cilastatin, and relebactam are cleared from the circulation during haemodialysis. Recarbrio is provided as a single vial in a fixed-dose combination; the dose for each component will be adjusted equally during preparation (see section 6.6).</p>	

Adult patients with CrCl less than 15 mL/min and paediatric patients (weighing at least 30 kg) with an eGFR less than 15 mL/min/1.73 m² should not receive imipenem/cilastatin/relebactam unless haemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of imipenem/cilastatin/relebactam for patients undergoing peritoneal dialysis.

Hepatic impairment

No dose adjustment is required in patients with impaired hepatic function (see section 5.2).

Elderly population

No dose adjustment is required for elderly patients (see section 5.2).

Paediatric population

The safety and efficacy of imipenem/cilastatin/relebactam in children weighing less than 30 kg with renal impairment, children weighing less than 2 kg, or preterm infants (less than 37 weeks post-menstrual age) have not been established. No data are available.

Method of administration

For intravenous infusion.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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) (see section 4.4).

4.4 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 (see sections 4.3 and 4.8).

These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with imipenem/cilastatin/relebactam, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams, and other allergens.

If an allergic reaction to imipenem/cilastatin/relebactam occurs, treatment must be discontinued immediately. Serious anaphylactic reactions require immediate emergency treatment.

Hepatic function

Hepatic function should be closely monitored during treatment with imipenem/cilastatin/relebactam due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure, and fulminant hepatitis) (see section 4.8).

Use in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with imipenem/cilastatin/relebactam. There is no dose adjustment necessary (see section 4.2).

Central nervous system (CNS)

CNS adverse reactions, such as seizures, confusional states, and myoclonic activity have been reported during treatment with imipenem/cilastatin, especially when recommended doses 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.

Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold.

Increased seizure potential due to interaction with valproic acid

The concomitant use of imipenem/cilastatin/relebactam and valproic acid/divalproex sodium is not recommended. Antibacterials 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 this medicine is necessary, supplemental anti-convulsant therapy should be considered (see section 4.5).

Clostridioides difficile-Associated Diarrhoea (CDAD)

Clostridioides difficile-associated diarrhoea (CDAD) has been reported with imipenem/cilastatin/relebactam. 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 imipenem/cilastatin/relebactam (see section 4.8). 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 imipenem/cilastatin/relebactam, and the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with CrCl \geq 150 mL/min

Based on pharmacokinetic-pharmacodynamic analyses, the dose of imipenem/cilastatin/relebactam that is recommended for patients with CrCl of \geq 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 (see section 4.2). There is inadequate information to recommend usage of imipenem/cilastatin/relebactam for patients undergoing peritoneal dialysis.

Limitations of the clinical data

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

Hospital-acquired pneumonia, including ventilator-associated pneumonia

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

Patients with limited treatment options

The use of imipenem/cilastatin/relebactam 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 imipenem/cilastatin/relebactam 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 extended-spectrum beta-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemase (KPC)) and Class C beta-lactamases including Pseudomonas-derived cephalosporinase

(PDC). Relebactam does not inhibit class D carbapenemases such as Oxacillinase-48 (OXA-48) or class B metallo-beta-lactamases such as New Delhi metallo-beta-lactamase (NDM) and Verona integron-encoded metallo-beta-lactamase (VIM) (see section 5.1).

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 (see section 4.8).

Excipients with known effect

Sodium

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.

4.5 Interaction with other medicinal products and other forms of interaction

Ganciclovir

Generalised seizures have been reported in patients who received ganciclovir concomitantly with imipenem/cilastatin. Ganciclovir should not be used concomitantly with imipenem/cilastatin/relebactam unless the potential benefits outweigh the risks.

Valproic acid

Case reports in the literature have shown that co-administration of carbapenems, including imipenem/cilastatin, to patients receiving valproic acid or divalproex sodium results in a reduction in valproic acid concentrations. The valproic acid concentrations may drop below the therapeutic range as a result of this interaction, therefore increasing the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from *in vitro* and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. The concomitant use of imipenem/cilastatin/relebactam and valproic acid/divalproex sodium is not recommended (see section 4.4).

Oral anti-coagulants

Simultaneous administration of antibacterial agents with warfarin may augment its anticoagulant effects. It is recommended that the INR should be monitored as appropriate during and shortly after co-administration of antibiotics with oral anti-coagulant medicinal products.

Clinical drug interaction studies

A clinical drug-drug interaction study demonstrated that imipenem and relebactam exposures do not increase by a clinically significant extent when imipenem/cilastatin/relebactam is co-administered with the prototypical OAT-inhibitor probenecid, indicating a lack of clinically meaningful OAT-mediated drug-drug interactions. Concomitant administration of

imipenem/cilastatin and probenecid increased the plasma level and half-life of cilastatin, though not to a clinically meaningful extent. Therefore, this medicine may be administered concomitantly with OAT inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies for the use of imipenem, cilastatin, or relebactam in pregnant women.

Animal studies with imipenem/cilastatin have shown reproductive toxicity in monkeys (see section 5.3). The potential risk for humans is unknown. Animal studies with relebactam do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Recarbrio should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

Imipenem and cilastatin are excreted into the mother's milk in small quantities.

It is unknown whether relebactam is excreted in human milk. Available data in animals have shown excretion of relebactam in the milk of rats (for details see section 5.3).

A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue Recarbrio therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no human data available regarding potential effects of imipenem/cilastatin or relebactam treatment on male or female fertility. Animal studies do not indicate harmful effects of imipenem/cilastatin or relebactam on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Recarbrio has moderate influence on the ability to drive and use machines. CNS adverse reactions, such as seizures, confusional states, and myoclonic activity, have been reported during treatment with imipenem/cilastatin, especially when recommended doses of imipenem were exceeded (see section 4.4). Therefore, caution should be exercised when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reaction ($\geq 2\%$) in adult patients receiving imipenem/cilastatin plus relebactam in pooled Phase 2 studies of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis (N = 431) was diarrhoea. The most frequently occurring adverse reactions ($\geq 2\%$) in patients receiving Recarbrio in a Phase 3 study of HAP or VAP (N = 266) were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during Phase 2 (imipenem/cilastatin plus relebactam including 431 patients) and Phase 3 (Recarbrio including 266 patients) clinical studies and with imipenem/cilastatin in clinical studies or during post-marketing experience with imipenem/cilastatin (see Table 4).

Adverse reactions are classified according to MedDRA System Organ Class and frequency. Frequency categories are derived according to the following conventions: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1\ 000$ to $< 1/100$), Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), Very rare ($< 1/10\ 000$) and not known (cannot be estimated from the available data).

Table 4: Tabulated list of adverse reactions

System Organ Class	Common	Uncommon	Rare	Very rare	Unknown
Infections and infestations			Pseudomembranous colitis* Candidiasis*	Gastro-enteritis*	
Blood and lymphatic system disorders	Eosinophilia*	Pancytopenia* Neutropenia* Leukopenia* Thrombocytopenia* Thrombocytosis*	Agranulocytosis*	Haemolytic anaemia* Bone marrow depression*	
Immune system disorders			Anaphylactic reactions*		
Nervous system disorders		Seizures* Hallucinations* Confusional states* Myoclonic activity* Dizziness* Somnolence*	Encephalopathy* Paraesthesia* Focal tremor* Taste perversion*	Aggravation of myasthenia gravis* Headache*	Agitation* Dyskinesia*
Ear and labyrinth disorders			Hearing loss*	Vertigo* Tinnitus*	

Cardiac disorders				Cyanosis* Tachycardia* Palpitations*	
Vascular disorders	Thrombophlebitis*	Hypotension*		Flushing*	
Respiratory, thoracic and mediastinal disorders				Dyspnoea* Hyperventilation* Pharyngeal pain*	
Gastrointestinal disorders	Diarrhoea [†] * Nausea [†] * Vomiting [†] *		Staining of teeth and/or tongue*	Haemorrhagic colitis* Abdominal pain* Heartburn* Glossitis* Tongue papilla hypertrophy* Increased salivation*	
Hepatobiliary disorders	Alanine aminotransferase increased [†] * Aspartate aminotransferase increased [†] *		Hepatic failure* Hepatitis*	Fulminant hepatitis*	Jaundice*
Skin and subcutaneous tissue disorders	Rash (e.g., exanthematous)*	Urticaria* Pruritus*	Toxic epidermal necrolysis* Angioedema* Stevens-Johnson syndrome* Erythema multiforme* Exfoliative dermatitis*	Hyperhidrosis* Skin texture changes*	
Musculoskeletal and connective tissue disorders				Polyarthralgia* Thoracic spine pain*	

Renal and urinary disorders		Elevations in serum creatinine*	Acute renal failure* Oliguria/anuria* Polyuria* Urine discolouration (harmless and should not be confused with haematuria)*		
Reproductive system and breast disorders				Pruritus vulvae*	
General disorders and administration site conditions		Fever* Local pain and induration at the injection site*		Chest discomfort* Asthenia/weakness*	
Investigations	Increases in serum alkaline phosphatase*	Coombs test positive* Prolonged prothrombin time* Decreased haemoglobin* Increases in serum bilirubin* Elevations in blood urea nitrogen*			Blood lactate dehydrogenase increased*
*reported with imipenem/cilastatin in clinical studies or during post-marketing experience with imipenem/cilastatin †reported with imipenem/cilastatin plus relebactam in Phase 2 (N = 431) and in Phase 3 (N = 266) studies					

Paediatric population

The safety of imipenem/cilastatin/relebactam was evaluated in one phase 2/3 clinical study in paediatric participants from birth to less than 18 years of age (see section 5.1). Eighty-five participants were enrolled and treated in the imipenem/cilastatin/relebactam arm out of whom there were 10 adolescents, 31 children aged 6 to less than 12 years, 21 from 2 years to less than 6 years, 15 from 3 months to less than 2 years, and 8 from birth (full-term) to less than 3 months. Based on this data, adverse reactions were generally comparable to those observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, discontinue Recarbrio, treat based on symptoms, and institute general supportive treatment. Imipenem, cilastatin, and relebactam can be removed by haemodialysis. No clinical information is available on the use of haemodialysis to treat overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, carbapenems, ATC code: J01DH56

Mechanism of action

The bactericidal activity of imipenem results from the inhibition of penicillin binding proteins (PBPs) leading to inhibition of peptidoglycan cell wall synthesis.

Cilastatin limits the renal metabolism of imipenem and does not have antibacterial activity.

Relebactam is a non-beta lactam inhibitor of Ambler class A and class C beta-lactamases, including class A *Klebsiella pneumoniae* carbapenemase (KPC) and extended-spectrum beta-lactamases (ESBLs), and class C (AmpC-type) beta-lactamases including Pseudomonas-Derived Cephalosporinase (PDC). Relebactam does not inhibit class B enzymes (metallo-beta-lactamases) or class D carbapenemases. Relebactam has no antibacterial activity.

Resistance

Mechanisms of resistance in Gram-negative bacteria that are known to affect imipenem/relebactam include the production of metallo-beta-lactamases or oxacillinases with carbapenemase activity.

Expression of certain alleles of the class A beta-lactamase Guiana extended-spectrum beta-lactamase (GES) and overexpression of PDC coupled with loss of imipenem entry porin OprD may confer resistance to imipenem/relebactam in *P. aeruginosa*. The expression of efflux pumps in *P. aeruginosa* does not affect activity of either imipenem or relebactam. Mechanisms of bacterial resistance that could decrease the antibacterial activity of imipenem/relebactam in Enterobacterales include porin mutations affecting outer membrane permeability.

Antibacterial activity in combination with other antibacterial agents

In vitro studies have demonstrated no antagonism between imipenem/relebactam and amikacin, azithromycin, aztreonam, colistin, gentamicin, levofloxacin, linezolid, tigecycline, tobramycin, or vancomycin.

Susceptibility testing breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Organism group	Minimum Inhibitory Concentrations (mg/L)	
	Susceptible ≤	Resistant >
Enterobacterales (except Morganellaceae)	2	2

<i>Pseudomonas aeruginosa</i>	2	2
<i>Acinetobacter</i> spp.	2	2
Viridans group streptococci	2	2
Anaerobes, Gram-positive	2	2
Anaerobes, Gram-negative	2	2

Pharmacokinetic/pharmacodynamic relationship

Time that unbound plasma concentrations of imipenem exceed the imipenem/relebactam minimum inhibitory concentration (% $fT > MIC$) has been shown to best correlate with efficacy. The ratio of the 24 - hour unbound plasma relebactam AUC to imipenem/relebactam MIC ($fAUC / MIC$) has been determined to be the index that best predicts activity of relebactam.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to imipenem and relebactam *in vitro*:

Hospital-acquired pneumonia, including ventilator-associated pneumonia

Gram-negative micro-organisms

- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

In vitro studies suggest that the following pathogens would be susceptible to imipenem and relebactam in the absence of acquired mechanisms of resistance:

Gram-negative aerobic micro-organisms

- *Acinetobacter calcoaceticus-baumannii* complex
- *Citrobacter* spp. (including *C. freundii* and *C. koseri*)
- *Enterobacter* spp. (including *E. asburiae* and *E. cloacae*)
- *Escherichia coli*
- *Klebsiella* spp. (including *K. aerogenes*, *K. oxytoca* and *K. pneumoniae*)
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Gram-negative anaerobic micro-organisms

- *Bacteroides* spp. (including *B. fragilis*)
- *Fusobacterium* spp. (including *F. nucleatum* and *F. necrophorum*)
- *Prevotella* spp. (including *P. melaninogenica*, *P. bivia*, and *P. buccae*)

Gram-positive aerobic micro-organisms

- *Enterococcus faecalis*
- *Staphylococcus aureus* (methicillin susceptible isolates only)
- Viridans group streptococci (including *S. anginosus* and *S. constellatus*)

In vitro studies indicate that the following species are not susceptible to imipenem and relebactam:

Gram-negative aerobic micro-organisms

- *Legionella* spp.
- *Stenotrophomonas maltophilia*

Paediatric population

Recarbrio was evaluated in an open-label, randomised, active-controlled, phase 2/3 clinical study in 115 paediatric participants from birth (full-term) to less than 18 years of age with HAP/VAP (n=6), cUTI (n=55) or cIAI (n=54), which included a total of 85 patients treated with imipenem/cilastatin/relebactam and 28 patients treated with active control. The minimum antibiotic treatment duration was 5 days for cIAI and cUTI or 7 days for HAP/VAP, up to a maximum of 14 days. For participants with cUTI or cIAI in the imipenem/cilastatin/relebactam arm, a switch to optional oral step-down therapy was allowed after receiving at least 3 days of intravenous imipenem/cilastatin/relebactam therapy. The primary objective was safety and tolerability, and all statistical analyses were descriptive. Efficacy in the paediatric population is established on the basis of achieving similar systemic exposures as in adults.

At the early follow-up visit (EFU), 7 to 14 days after the end of therapy, 70.6 % (60/85) of paediatric participants in the imipenem/cilastatin/relebactam arm achieved a favourable clinical response (cure or sustained cure), compared to 75 % (21/28) in the comparator arm (modified Intention-To-Treat (ITT) population). A favourable clinical response at the late follow-up visit (LFU), 7 to 14 days after the EFU visit was achieved by 69.4 % (59/85) and 75.0 % (21/28) of participants, respectively.

5.2 Pharmacokinetic properties

The steady-state pharmacokinetic parameters of imipenem, cilastatin, and relebactam in healthy adults with normal renal function (CrCl 90 mL/min or greater), after multiple 30-minute intravenous infusions of 500 mg imipenem/500 mg cilastatin + 250 mg relebactam administered every 6 hours are summarised in Table 5. The steady-state pharmacokinetic parameters of imipenem and relebactam in patients with cIAI or cUTI and HAP or VAP with normal renal function ($90 \text{ mL/min} \leq \text{CrCl} < 150 \text{ mL/min}$) after multiple 30-minute intravenous infusions of 500 mg imipenem/500 mg cilastatin + 250 mg relebactam administered every 6 hours are summarised in Tables 6 and 7, respectively. Pharmacokinetic parameters were similar for single- and multiple-dose administration due to minimal accumulation.

The C_{max} and AUC of imipenem, cilastatin, and relebactam increase in proportion to dose. The elimination half-lives ($t_{1/2}$) of imipenem, cilastatin, and relebactam are independent of dose.

Table 5: Steady-state geometric mean (% geometric co-efficient of variation) plasma pharmacokinetic parameters of imipenem, cilastatin, and relebactam after multiple intravenous 30-minute infusions of 500 mg imipenem/500 mg cilastatin/250 mg relebactam every 6 hours in healthy adults

	Imipenem (n=6)	Cilastatin (n=6)	Relebactam (n=6)
AUC _{0-6 hr} (µM-hr)	138.0 (17.8)	98.0 (17.0)	81.6 (17.8)
C _{max} (µM)	106.0 (26.8)	96.4 (21.8)	48.3 (24.9)
CL (L/hr)	12.0 (17.8)	14.2 (17.0)	8.8 (17.8)
t _{1/2} (hr)*	1.1 (±0.1)	1.0 (±0.1)	1.7 (±0.2)
*Arithmetic mean (standard deviation) reported for t _{1/2} AUC _{0-6 hr} = area under the concentration time curve from 0 to 6 hours; C _{max} = maximum concentration; CL = plasma clearance; t _{1/2} = elimination half-life			

Table 6: Population pharmacokinetic model based steady-state geometric mean (% geometric co-efficient of variation) plasma pharmacokinetic parameters of imipenem and relebactam after multiple intravenous 30-minute infusions of Recarbrio (500 mg imipenem/500 mg cilastatin/250 mg relebactam) every 6 hours in cIAI or cUTI adult patients with CrCl 90 mL/min or greater

	Imipenem	Relebactam
AUC _{0-24 hr} (μM-hr)	500.0 (56.3)	390.5 (44.5)
C _{max} (μM)	88.9 (62.1)	58.5 (44.9)
CL (L/hr)	13.4 (56.3)	7.4 (44.5)
t _{1/2} (hr)*	1.0 (±0.5)	1.2 (±0.7)
*Arithmetic mean (standard deviation) reported for t _{1/2} AUC _{0-24 hr} = area under the concentration time curve from 0 to 24 hours; C _{max} = maximum concentration; CL = plasma clearance; t _{1/2} = elimination half-life		

Table 7: Population pharmacokinetic model based steady-state geometric mean (% geometric co-efficient of variation) plasma pharmacokinetic parameters of imipenem and relebactam after multiple intravenous 30-minute infusions of Recarbrio (500 mg imipenem/500 mg cilastatin/250 mg relebactam) every 6 hours in HAP or VAP adult patients with CrCl 90 mL/min or greater

	Imipenem	Relebactam
AUC _{0-24hr} (μM-hr)	812.2 (59.4)	655.2 (47.9)
C _{max} (μM)	159.1 (62.3)	87.6 (43.8)
CL (L/hr)	8.2 (59.4)	4.4 (47.9)
AUC _{0-24hr} =area under the concentration time curve from 0 to 24 hours; C _{max} =maximum concentration; CL=plasma clearance		

Distribution

The binding of imipenem and cilastatin to human plasma proteins is approximately 20 % and 40 %, respectively. The binding of relebactam to human plasma proteins is approximately 22 % and is independent of concentration.

The steady-state volume of distribution of imipenem, cilastatin, and relebactam is 24.3 L, 13.8 L, and 19.0 L, respectively, in subjects following multiple doses infused over 30 minutes every 6 hours.

The penetration into pulmonary epithelial lining fluid (ELF) expressed as the total ELF-to-unbound plasma exposure ratio was 55 % and 54 % for imipenem and relebactam, respectively.

Biotransformation

Imipenem, when administered alone, is metabolised in the kidneys by dehydropeptidase-I, resulting in low levels of imipenem (average of 15-20 % of the dose) recovered in human urine. Cilastatin, an inhibitor of this enzyme, effectively prevents renal metabolism so that when imipenem and cilastatin are given concomitantly, adequate levels of imipenem (approximately 70 % of the dose) are achieved in the urine to enable antibacterial activity.

Cilastatin is mainly eliminated in the urine as unchanged parent drug (approximately 70 - 80 % of the dose), with 10 % of the dose recovered as an N-acetyl metabolite, which has inhibitory activity against dehydropeptidase-I comparable to the parent medicinal product.

Relebactam is cleared primarily via renal excretion as unchanged parent drug (greater than 90 % of the dose) and is minimally metabolised. Unchanged relebactam was the only drug-related component detected in human plasma.

Elimination

Imipenem, cilastatin, and relebactam are mainly excreted by the kidneys.

Following multiple-dose administration of 500 mg imipenem, 500 mg cilastatin, and 250 mg relebactam to healthy male subjects, approximately 63 % of the administered imipenem dose, and 77 % of the administered cilastatin dose are recovered as unchanged parent in the urine. The renal excretion of imipenem and cilastatin involves both glomerular filtration and active tubular secretion. Greater than 90 % of the administered relebactam dose was excreted unchanged in human urine. The mean renal clearance for relebactam is 135 mL/min, close to the plasma clearance (148 mL/min), indicating nearly complete elimination of relebactam by the renal route. The unbound renal clearance of relebactam is greater than the glomerular filtration rate, suggesting that in addition to glomerular filtration, active tubular secretion is involved in the renal elimination, accounting for ~ 30 % of the total clearance.

Linearity/non-linearity

The pharmacokinetics of relebactam are linear across the 25 mg to 1 150 mg dose range studied for a single intravenous administration, and 50 mg to 625 mg dose range studied for multiple intravenous administration every 6 hours up to 7 days. Minimal accumulation of imipenem, cilastatin or relebactam was observed following multiple 30-minute intravenous infusions of relebactam (50 to 625 mg) co-administered with 500 mg imipenem/500 mg cilastatin every 6 hours up to 7 days in healthy adult males with normal renal function.

Drug metabolising enzymes

Studies evaluating the potential for imipenem or cilastatin to interact with CYP450 enzymes have not been conducted.

Relebactam at clinically relevant concentrations does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro* in human liver microsomes. Relebactam showed no potential for *in vitro* induction of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. Thus, relebactam is unlikely to cause clinical drug-drug interactions via CYP-mediated pathways.

Imipenem, cilastatin, and relebactam are all cleared primarily via renal excretion unchanged, with metabolism as a minor elimination route. Thus, Recarbrio is unlikely to be subject to drug-drug interactions when co-administered with CYP inhibitors or inducers.

Membrane transporters

Relebactam does not inhibit the following hepatic and renal transporters *in vitro* at clinically relevant concentrations: OATP1B1, OATP1B3, OAT1, OAT3, OCT2, P-gp, BCRP, MATE1, MATE2K, or BSEP.

Relebactam is actively secreted into the urine. It is not a substrate of OAT1, OCT2, P-gp, BCRP, MRP2, or MRP4 transporters, but is a substrate of OAT3, OAT4, MATE1 and MATE2K transporters. The active tubular secretion accounts for only approximately 30 % of the total clearance of relebactam, thus, the extent of drug-drug interaction due to inhibition of

the tubular transporters is expected to be of minimal clinical significance, which was confirmed with a clinical drug-drug interaction study with probenecid and Recarbrio (see section 4.5).

Special populations

Renal impairment

In a clinical pharmacokinetic study and population pharmacokinetic analysis, clinically relevant differences in exposure (AUC) were observed for imipenem, cilastatin, and relebactam based on the extent of renal impairment.

In the clinical study in adults, imipenem geometric mean AUCs were up to 1.4 - fold, 1.5 - fold, and 2.5 - fold higher in patients with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects with normal renal function. The respective cilastatin geometric mean AUCs were up to 1.6 - fold, 1.9 - fold, and 5.6 - fold higher. Relebactam geometric mean AUCs were up to 1.6 - fold, 2.2 - fold, and 4.9 - fold higher in patients with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects with normal renal function. In patients with End Stage Renal Disease (ESRD) on haemodialysis, imipenem, cilastatin, and relebactam are efficiently removed by haemodialysis.

To maintain systemic exposures similar to patients with normal renal function, dose adjustment is recommended for patients with renal impairment. ESRD patients on haemodialysis should receive Recarbrio after haemodialysis session (see section 4.2).

Hepatic impairment

Imipenem, cilastatin, and relebactam are primarily cleared renally; therefore, hepatic impairment is not likely to have any effect on Recarbrio exposures (see section 4.2).

Elderly/gender

In a geriatric/gender study and population pharmacokinetic analysis no clinically relevant differences in exposure (AUC) were observed for imipenem, cilastatin, and relebactam based on age or gender, apart from the effect of renal function (see section 4.2).

Race

Only a limited number of non-white patients were included in the clinical studies, but no major effect of race on imipenem, cilastatin, and relebactam pharmacokinetics is expected.

Paediatric population

The steady-state pharmacokinetic parameters of imipenem and relebactam in paediatric patients (birth to less than 18 years of age) with HAP/VAP, cUTI or cIAI following the recommended paediatric dosing regimens are summarised in Table 8.

Population pharmacokinetic analyses and target attainment simulations in paediatric patients with HAP/VAP, cUTI or cIAI demonstrated that the recommended paediatric dosing regimens for patients from birth to less than 18 years with normal renal function resulted in generally similar systemic exposures to adults with normal renal function given 1.25 g of imipenem/cilastatin/relebactam. These analyses, including the assumption of proportional effects of renal impairment in adults and paediatric patients, also predict that the recommended dose adjustments for patients weighing at least 30 kg with eGFR less than 90 mL/min/1.73 m² result in systemic exposures similar to that in adult patients (see section 4.2).

Dose adjustments are recommended for paediatric patients from birth to less than 18 years of age weighing at least 30 kg with eGFR less than 90 mL/min/1.73 m² (see section 4.2). There is insufficient information to recommend a dose adjustment in paediatric patients weighing less than 30 kg with renal impairment.

Table 8: Population pharmacokinetic model based geometric mean (% geometric coefficient of variation) steady-state plasma pharmacokinetic parameters

Body Weight	Age	Imipenem				Relebactam			
		AUC _{0-24hr} (µM.hr)	C _{max} (µM)	t _{1/2} (hr)	CL (L/hr/kg)	AUC _{0-24hr} (µM.hr)	C _{max} (µM)	t _{1/2} (hr)	CL (L/hr/kg)
≥30 kg	<18 years (N=38)	662 (38.8)	116 (23.3)	1.67 (26.6)	0.235 (25.9)	428 (45)	61.1 (27.2)	1.85 (26.3)	0.156 (28.7)
<30 kg	≥3 months and <18 years (N=66)	715 (27.4)	104 (15.1)	1.37 (19.6)	0.28 (24.2)	474 (49.9)	57.2 (23.2)	1.57 (29.2)	0.182 (32.8)
<30 kg	Birth to <3 months (N=27)	749 (21.6)	111 (13.2)	1.55 (20.3)	0.201 (20.1)	545 (44.5)	59.9 (21.6)	2.09 (39.4)	0.119 (35.3)

AUC_{0-24hr}=area under the concentration time curve from 0 to 24 hours; C_{max}=maximum concentration;
t_{1/2}=elimination half-life; CL=body weight normalised plasma clearance

5.3 Preclinical safety data

Imipenem/cilastatin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity studies.

Animal studies showed that the toxicity produced by imipenem, as a single entity, was limited to the kidney. Co-administration of cilastatin with imipenem in a 1:1 ratio prevented the nephrotoxic effects of imipenem in rabbits and monkeys. Available evidence suggests that cilastatin prevents the nephrotoxicity by preventing entry of imipenem into the tubular cells.

A teratology study in pregnant cynomolgus monkeys given imipenem/cilastatin sodium at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem/cilastatin sodium (approximately 100/100 mg/kg/day or approximately 3 times the recommended daily human intravenous dose) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups (see section 4.6).

Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem/cilastatin.

Relebactam

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity, or genotoxicity. Carcinogenicity studies have not been conducted with relebactam.

Relebactam administered intravenously to lactating rats at a dose of 450 mg/kg/day (GD 6 to LD 14), was excreted into the milk with concentration of approximately 5 % that of maternal plasma concentrations.

Animal studies show that relebactam given as a single entity caused renal tubular degeneration in monkeys at AUC exposure 7-fold the human AUC exposure at the maximum recommended human dose (MRHD). Renal tubular degeneration was shown to be reversible after dose discontinuation. There was no evidence of nephrotoxicity at AUC exposures less than or equal to 3-fold the human AUC exposure at the MRHD.

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Imipenem/cilastatin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity studies.

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Long term studies in animals have not been performed to evaluate carcinogenic potential of imipenem/cilastatin.

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Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity, or genotoxicity. Carcinogenicity studies have not been conducted with relebactam.

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Animal studies show that relebactam given as a single entity caused renal tubular degeneration in monkeys at AUC exposure 7-fold the human AUC exposure at the maximum recommended human dose (MRHD). Renal tubular degeneration was shown to be reversible after dose discontinuation. There was no evidence of nephrotoxicity at AUC exposures less than or equal to 3-fold the human AUC exposure at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Dry powder

30 months.

After reconstitution and dilution

Diluted solutions should be used immediately. The time interval between the beginning of reconstitution and the end of intravenous infusion should not exceed two hours.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Keep vials in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 mL glass vial, with 20 mm rubber stopper and aluminium crimp cap seal.

This medicinal product is supplied in packs of 25 vials.

6.6 Special precautions for disposal and other handling

Recarbrio is supplied as a dry powder in a single-dose vial that must be reconstituted and further diluted using aseptic technique prior to intravenous infusion as outlined below:

Adult patients

To prepare infusion solution, contents of the vial must be transferred to 100 mL of an appropriate infusion solution (see sections 6.2 and 6.3): 9 mg/mL (0.9 %) sodium chloride. In exceptional circumstances where 9 mg/mL (0.9 %) sodium chloride cannot be used for clinical reasons 5 % glucose may be used instead. **Please note that pre-filled infusion bags are overfilled and, to obtain a correct concentration, it is important to be assured that exactly 100 mL of the diluent is used in this step when a part of the content of the infusion bag is administered (e.g., in the case of paediatric weight-based dosing).**

- Withdraw 20 mL (10 mL times 2) of diluent from the appropriate infusion bag and reconstitute the vial with 10 mL of the diluent. The reconstituted suspension must not be administered by direct intravenous infusion.
- After reconstitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.
- Add the additional 10 mL of infusion diluent to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.

Adult patients with renal impairment and paediatric patients weighing at least 30 kg with renal impairment

A reduced dose of Recarbrio will be administered according to the patient's CrCl or eGFR, as determined from Table 9.

- Prepare 100 mL of infusion solution as directed above for adult patients.
- Select the volume (mL) of the final infusion solution needed for the appropriate dose of Recarbrio as shown in Table 9.

Paediatric patients weighing 2 kg to less than 30 kg with normal renal function

- Prepare 100 mL of infusion solution as directed above for adult patients.
- The volume of the final infusion solution (with a concentration of 12.5 mg/mL) to be administered is calculated based on patient weight as follows:
 - Infusion volume (mL) = (Weight (kg) x 37.5 mg/kg) / 12.5 mg/mL
 - Note: The entire volume in the infusion bag (100 mL) will not be required.
- Transfer the calculated infusion volume from the prepared 100 mL solution to an adequately sized infusion bag or infusion syringe.
- The infusion volume will be administered over 60 minutes via infusion or infusion syringe pump.

Table 9: Preparation of Recarbrio solution for intravenous infusion in adult and paediatric patients (weighing at least 30 kg)

Estimated renal function (CrCl [mL/min]* or eGFR [mL/min/1.73 m ²] [†])	Dose of Recarbrio (imipenem/cilastatin/relebactam) (mg)	Volume (mL) of solution to be removed and discarded from preparation	Volume (mL) of final infusion solution needed for dose
Greater than or equal to 90	500/500/250	N/A	100
Less than 90 to greater than or equal to 60	400/400/200	20	80
Less than 60 to greater than or equal to 30	300/300/150	40	60
Less than 30 to greater than or equal to 15 or ESRD on haemodialysis	200/200/100	60	40
*CrCl calculated using the Cockcroft-Gault formula for adult patients			
[†] eGFR calculated using the bedside Schwartz formula for paediatric patients weighing ≥ 30 kg			

Reconstituted solutions of Recarbrio range from colourless to yellow. Variations of colour within this range do not affect the potency of the product. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Discard if discolouration or visible particles are observed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Compatible medicinal products

The physical compatibility of Recarbrio with selected injectable medicinal products was evaluated in two commonly available diluents at a Y-infusion site. Compatible medicinal products with the corresponding compatible diluent (i.e. 5 % Dextrose Injection or 0.9 % Sodium chloride Injection) are listed below. Recarbrio should not be co-administered through the same intravenous line (or cannula), with other medicinal products not listed below, as no compatibility data are available. Refer to the respective prescribing information of the co-administered medicinal product(s) to confirm compatibility of simultaneous co-administration. This medicinal product must not be mixed with other medicinal products except those mentioned below.

List of Compatible Injectable Medicinal Products for use with 5 % Dextrose or 0.9 % Sodium chloride Injection as Diluents

- dexmedetomidine
- dopamine
- epinephrine
- fentanyl
- heparin
- midazolam
- norepinephrine
- phenylephrine

Compatible intravenous bags and infusion set materials

Recarbrio is compatible with the following intravenous container bags and infusion set materials. Any intravenous bags or infusion set materials not listed below should not be used.

Intravenous Container Bag Materials

Polyvinyl chloride (PVC) and polyolefin (polypropylene and polyethylene)

Intravenous Infusion Set Materials (with tubing)

PVC + Di-(2-ethylhexyl)phthalate (DEHP) and polyethylene (PE)-lined PVC

Incompatible medicinal products

Recarbrio for solution for infusion is physically incompatible with propofol in 5 % Dextrose (also named Glucose) or 0.9 % Sodium chloride.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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