

Antimicrobial prescribing: Meropenem with vaborbactam



This evidence review sets out the best available evidence on meropenem with vaborbactam for treating complicated urinary tract infection, complicated intra-abdominal infection, hospital-acquired pneumonia (including ventilator-associated pneumonia), bacteraemia associated with these infections, or infections due to aerobic Gram-negative organisms where there are limited treatment options. It should be read in conjunction with the evidence summary, which gives the key messages.

Disclaimer

The content of this evidence review was up-to-date in November 2019. See summaries of product characteristics (SPCs), British national formulary (BNF), 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 meropenem with vaborbactam for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options, particularly those with the following infections, or bacteraemia associated with these:

- complicated urinary tract infection (cUTI), including pyelonephritis
- complicated intra-abdominal infection (cIAI)
- hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Complicated UTIs are often associated with anatomical abnormalities or foreign bodies in the urinary tract, such as catheters and renal stents, and can occur in the upper or lower urinary tract. Acute pyelonephritis is a subset of cUTI, which can occur in people with or without abnormalities of the urinary tract. Acute pyelonephritis can affect one or both kidneys, and usually results from an ascending uncontrolled bladder infection. Gram-negative organisms account for approximately 60–80% of complicated and hospital-acquired UTIs. The most common pathogens are *Escherichia coli* (*E. coli*), *Klebsiella* species, *Pseudomonas* species, *Proteus* species, *Enterobacter* species and *Citrobacter* species ([Vaborem European public assessment report](#) [EPAR]).

Complicated IAI occurs when infection in a single abdominal organ progresses beyond that organ and causes either localised or diffuse peritonitis. This can occur after perforation (for example, appendicitis, perforated ulcer or diverticulitis), surgical intervention or trauma. CIAIs have been estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit and overall mortality rates may be as high as 25%. Pathogens most commonly seen in cIAI are *E. coli*, other Enterobacterales (formerly known as Enterobacteriaceae), *Pseudomonas aeruginosa* and *Bacteroides fragilis* (Vaborem EPAR).

HAP and VAP occur when bacteria colonise the respiratory tract. HAP is pneumonia that develops 48 hours or more after hospital admission, which was not incubating at hospital admission. VAP is HAP in people receiving mechanical ventilation. These infections are a serious risk for people with an underlying illness or medical

intervention who are in hospital for 48 hours or more. Mortality rates can be around 20% in HAP and VAP depending on the severity of the underlying disease.

Examples of pathogens include Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, and Gram-negative bacteria such as *Klebsiella pneumoniae* (*K. pneumoniae*), other Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter* species (Vaborem EPAR).

NICE has produced the following antimicrobial prescribing guidelines on cUTIs and pneumonia, which includes recommendations on choosing an antibiotic:

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

A NICE guideline on [pneumonia in adults](#) is also available. NICE has not currently published any guidance on cAIs, although an antimicrobial prescribing guideline on [diverticular disease](#) is expected in November 2019, which will include recommendations on choosing an antibiotic for acute diverticulitis.

Treating cUTIs, cAIs, HAP and VAP has become increasingly more challenging because of rising rates of antimicrobial resistance among the pathogens commonly involved. Effective management of cUTI requires a combination of early diagnosis, appropriate surgical intervention (if necessary) and empiric, broad-spectrum antibiotics. Second or third generation cephalosporins in combination with metronidazole, extended-spectrum penicillins with beta-lactamase inhibitors or carbapenems are commonly used for the treatment of cAI. The NICE guideline on HAP recommends single antibiotics, although, 2 or more antibiotics may sometimes be used in HAP and VAP, at least until the susceptibility of the organisms has been clarified (Vaborem EPAR).

According to the [English Surveillance Programme for Antimicrobial Utilisation and Resistance \(ESPAUR\) Report 2018 to 2019](#), 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 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 *E. coli*). The burden of resistance remained unchanged for Gram-positive infections over the same period.

Carbapenems are beta-lactam antibiotics that have a broad spectrum of activity against both Gram-positive and Gram-negative bacteria. They are often referred to as 'antibiotics of last resort' due to their activity against multiresistant bacteria. The ESPAUR report notes there was an increase in the total number of carbapenemase (a type of beta-lactamase)-producing Enterobacterales referred to laboratories in 2018, with more than 4,000 isolates confirmed as positive for at least 1 carbapenemase. Despite the increase in detections, less than 150 bloodstream infections were caused by carbapenemase-producing Gram-negative bacteria. The report states this is in marked contrast to the situation in other countries, reflecting the implementation of antimicrobial stewardship initiatives in the UK.

The antibiotic considered in this evidence review is a combination of the carbapenem, meropenem, and a new beta-lactamase inhibitor, vaborbactam.

Product overview

Mode of action

Meropenem is a broad-spectrum carbapenem antibacterial, which belongs to the class of beta-lactam antibiotics and covers Gram-positive, Gram-negative and anaerobic bacteria. Meropenem binds with penicillin-binding proteins to inhibit bacterial cell wall synthesis.

Vaborbactam is a beta-lactamase inhibitor from a new class (cyclic boronates) ([Vaborem European public assessment report](#)), which binds with beta-lactamases (enzymes that cause resistance to beta-lactam antibiotics) to prevent them working. Vaborbactam has no antibacterial activity ([Vaborem summary of product characteristics](#)).

Regulatory status

Meropenem with vaborbactam ([Vaborem](#), Menarini) has a marketing authorisation for treating the following infections in adults:

- complicated urinary tract infection (cUTI), including pyelonephritis
- complicated intra-abdominal infection (cIAI)
- hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Meropenem with vaborbactam is also indicated for treating:

- adults with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above
- infections due to aerobic Gram-negative organisms in adults with limited treatment options (only after consulting a doctor with appropriate experience in managing infectious diseases).

Consideration should be given to official guidance on the appropriate use of antibacterial agents (summary of product characteristics).

The marketing authorisation was granted in November 2018 and meropenem with vaborbactam was launched in the UK in November 2019.

Dosing information

- Meropenem with vaborbactam is administered by intravenous infusion. Each vial contains meropenem trihydrate equivalent to 1 g meropenem, and 1 g vaborbactam. In adults with creatinine clearance of 40 ml/minute or more, the recommended dosage is 2 g/2 g infused over 3 hours, every 8 hours. Lower dosages are recommended in people with renal impairment and creatinine clearance below 40 ml/minute (summary of product characteristics). No dosage adjustment is needed based on age or hepatic impairment.

The duration of treatment recommended in the summary of product characteristics varies according to the indication:

- cUTI, including pyelonephritis, and cIAI: 5 to 10 days (may continue up to 14 days)
- HAP, including VAP: 7 to 14 days
- Bacteraemia associated, or suspected to be associated with, any of the infections listed above, and infections due to aerobic Gram-negative organisms in adults with limited treatment options: duration is in accordance with the site of infection.

Resistance

According to the summary of product characteristics, the inhibitory spectrum of vaborbactam includes class A and class C carbapenemases. Vaborbactam does not inhibit class B or class D carbapenemases (such as metallo-beta-lactamases and oxacillinases, respectively) and cannot protect meropenem against these.

According to the [English Surveillance Programme for Antimicrobial Utilisation and Resistance \(ESPAUR\) Report 2018 to 2019](#), OXA-48 carbapenemases (class D) were the most frequently identified carbapenem-resistant Enterobacterales, accounting for 52.0% of confirmed carbapenemase-producing Enterobacterales in 2018. In that year, the rates of NDM, IMP and VIM (class B) carbapenemases 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%).

Mechanisms of resistance in Gram-negative bacteria that are known to affect meropenem with vaborbactam include organisms that produce metallo-beta-lactamases or oxacillinases with carbapenemase activity. Mechanisms of bacterial resistance that could decrease the antibacterial activity of meropenem with vaborbactam include porin mutations affecting outer membrane permeability and overexpression of efflux pumps.

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

Monitoring the usage of new antibiotics and detecting emerging resistance to these medicines is a crucial component of antimicrobial usage surveillance to inform antimicrobial stewardship activities and preserve treatment effectiveness. Effective infection prevention and control remains essential and it is crucial that guidelines for carbapenemase-producing Enterobacterales remain relevant to the emerging situation ([ESPAUR report 2018 to 2019](#)).

Effectiveness

This evidence review discusses the best available evidence for meropenem with vaborbactam ([Vaborem](#)) for its licensed indications, which is 2 phase 3 randomised controlled trials ([Tango I](#) and [Tango II](#)).

Tango I was a multicentre, randomised, double-blind, double-dummy noninferiority trial, which compared the efficacy and safety of meropenem with vaborbactam (2 g/2 g intravenously [IV] over 3 hours, every 8 hours) with piperacillin with tazobactam (4 g/0.5 g over 30 minutes, every 8 hours) in 550 adults with complicated urinary tract infection (cUTI), including acute pyelonephritis. Treatment could be switched to oral levofloxacin after 15 or more doses of IV treatment if improvement criteria were met. The total length of antibiotic treatment was 10 days. The primary efficacy outcome was assessed using different criteria for the FDA and the EMA. For the FDA, the primary outcome was overall success, a composite outcome of clinical cure (complete resolution or significant improvement of baseline signs and symptoms) and microbial eradication at the end of IV treatment. For the EMA, the primary outcome was microbial eradication.

Tango II was a multicentre, randomised, open-label trial comparing meropenem with vaborbactam (2 g/2 g IV over 3 hours, every 8 hours for 7 to 14 days) with best available antibiotic treatment in 77 adults with cUTI or acute pyelonephritis, complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) or bacteraemia, suspected or documented to be caused by carbapenem-resistant Enterobacterales. Best available antibiotic treatment was chosen by the investigator before randomisation and included polymyxin, carbapenem, aminoglycoside or tigecycline antibiotics alone or in combination; or ceftazidime with avibactam alone. Primary efficacy outcomes

included all-cause mortality in the HAP or VAP and bacteraemia subgroups; microbial eradication (EMA) and overall success (FDA; a composite of clinical cure and microbial eradication) in the cUTI subgroup; and clinical cure in the cIAI subgroup. Tango II was a descriptive study only and no formal power or sample size calculations were performed.

[Appendix A](#) summarises details of the included studies. [Appendix B](#) gives an overview of the results for clinical effectiveness. [Appendix E](#) gives details of studies identified in the literature search that were then excluded.

Overall success

In Tango I, in people with cUTI and acute pyelonephritis, overall success (the FDA primary outcome) was a composite outcome of clinical cure (complete resolution or significant improvement of baseline signs and symptoms) and microbial eradication (baseline pathogens reduced to less than 10^4 colony-forming units [CFU] per millilitre of urine). For a primary outcome in Tango I, overall success was assessed at the end of the IV treatment visit in the microbiologic modified [intention-to-treat](#) (MITT) population. The MITT population included participants who received 1 or more doses of study treatment (n=545). The microbiologic MITT population included all participants in the MITT population with 1 or more bacterial pathogens of 10^5 CFU/ml or more in baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures (n=374).

The definition of overall success was similar in Tango II. However, outcomes in this study were primarily assessed in participants with microbiologically confirmed carbapenem-resistant Enterobacterales who received 1 or more doses of study treatment (the CRE-MITT population, n=47 for all infections [n=22 for bacteraemia, n=16 for cUTI or acute pyelonephritis, n=5 for HAP or VAP and n=4 for cIAI]).

At the end of IV treatment in Tango I (mean 8 days), the overall success rate in the microbiologic MITT population was 98.4% (189/192) with meropenem with vaborbactam compared with 94.0% (171/182) with piperacillin with tazobactam (difference 4.5%, 95% [confidence interval](#) [CI] 0.7% to 9.1%; $p < 0.001$ for noninferiority) in people with cUTI or acute pyelonephritis. The lower limit of the 95% CI was greater than the prespecified noninferiority margin of -15%, showing that

meropenem with vaborbactam was statistically noninferior to piperacillin with tazobactam for the FDA primary outcome. A prespecified statistical analysis showed that meropenem with vaborbactam was also statistically significantly better than piperacillin with tazobactam (the lower limit of the 95% CI exceeded 0, $p=0.01$). Similar overall success rates were seen in subgroups of people with acute pyelonephritis, cUTI and a removable source of infection (such as a urinary catheter or removable kidney stones) or cUTI and a nonremovable source of infection. However, the study was not powered to assess noninferiority or superiority in these subgroups.

In Tango I, the rate of overall success in the microbiologic MITT population was lower in both groups at the test of cure visit (7 days after the end of treatment; a secondary outcome) compared with the end of IV treatment visit (74.5% [143/192] in the meropenem with vaborbactam group and 70.3% [128/182] in the piperacillin with tazobactam group; difference 4.1%, 95% CI -4.9% to 9.1%; no statistically significant difference). The [Vaborem European public assessment report](#) (EPAR) notes that these results suggest that colony counts in samples taken at the end of IV treatment resulted in falsely optimistic eradication rates in both treatment groups, possibly because of substantial concentrations of study treatment persisting in the urine. Residual live organisms were identified in cultures at the test of cure visit 7 days after treatment was stopped in both groups, a pattern that the EPAR notes has been seen in other studies in cUTI and acute pyelonephritis.

In Tango II, in participants with cUTI or acute pyelonephritis ($n=16$) in the CRE-MITT population, the overall success rate at the test of cure visit (7 days \pm 2 days after the end of treatment; a primary outcome) was numerically lower in the meropenem with vaborbactam group than in the best available antibiotic treatment group (33.3% [4/12] compared with 50.0% [2/4] respectively; difference -16.7%; no statistical analysis). The Tango II study was descriptive only and no formal power or sample size calculations were performed, which means no robust statistical analyses can be undertaken and firm conclusions cannot be drawn.

Microbial eradication

For the primary outcomes in people with cUTI and acute pyelonephritis in Tango I, microbial eradication (the EMA primary outcome) was defined as baseline pathogens reduced to less than 10^3 CFU/ml urine. It was assessed at the test of cure visit in the microbiologic MITT population and the microbiologic evaluable population. The microbiologic evaluable population included all participants in the microbiologic MITT population who had a clinical outcome and a microbiologic outcome at the end of IV treatment who had received enough study treatment according to a prespecified range (n=347). This outcome was also assessed in Tango II and was a primary outcome in the subgroup of people with cUTI and pyelonephritis in the CRE-MITT population (n=16).

At the test of cure visit in Tango I, the rate of microbial eradication in the microbiologic MITT population was 66.7% (128/192) in the meropenem with vaborbactam group compared with 57.7% (105/182) in the piperacillin with tazobactam group (difference 9.0%, 95% CI -0.9% to 18.7%; $p < 0.001$ for noninferiority). At the same visit in the microbiologic evaluable population, the rate of microbial eradication was 66.3% (118/178) in the meropenem with vaborbactam group compared with 60.4% (102/169) in the piperacillin with tazobactam group (difference 5.9%, 95% CI -4.2% to 16.0%; $p < 0.001$ for noninferiority). Meropenem with vaborbactam was noninferior to piperacillin with tazobactam in both populations because the lower limit of the 95% CIs for the differences between the groups was greater than the prespecified noninferiority margin of -15%.

At the test of cure visit in Tango II, the rate of microbial eradication in the CRE-MITT population with cUTI or acute pyelonephritis was 25.0% (3/12) in the meropenem with vaborbactam group compared with 50.0% (2/4) in the piperacillin with tazobactam group (difference 25.0%; no statistical analysis).

In the total CRE-MITT population in Tango II, there was no significant difference in rates of microbial eradication between meropenem with vaborbactam and best available antibiotic treatment at the end of treatment visit (65.6% [21/32] compared with 40.0% [6/15] respectively; difference 25.6%, 95% CI -4.1% to 55.4%; $p = 0.09$) or test of cure visit (53.1% [17/32] compared with 33.3% [5/15]; difference 19.8%,

95%CI -9.7% to 49.3%; p=0.19) (secondary outcomes). The Tango II study was descriptive only and no formal power or sample size calculations were performed, which means the statistical analyses are not robust and firm conclusions cannot be made.

Clinical cure

In Tango I, clinical cure was defined as complete resolution or significant improvement of baseline signs and symptoms of cUTI or acute pyelonephritis (secondary outcome). This outcome was also assessed in Tango II and was a primary outcome in the small subgroup of people with cIAI (n=4 in the CRE-MITT population). In Tango II, clinical cure was defined as complete resolution of signs and symptoms of the index infection such that no further antimicrobial therapy (and/or surgical intervention for cIAI) was needed.

At the end of IV treatment visit in Tango I, the rate of clinical cure in the microbiologic MITT population was 98.4% (189/192) in the meropenem with vaborbactam group and 95.6% (174/182) in the piperacillin with tazobactam group (difference 2.8%, 95% CI -0.7% to 7.1%; no statistically significant difference). At the test of cure visit the rates were 90.6% (174/192) and 86.3% (157/182) respectively (difference 4.4%, 95% CI -2.2% to 11.1%; no statistically significant difference).

At the test of cure visit in Tango II, the rate of clinical cure in the CRE-MITT population with cIAI was 100% (2/2) in the meropenem with vaborbactam group and 0% (0/2) in the best available antibiotic treatment group (difference 100%; no statistical analysis).

In the total CRE-MITT population in Tango II, meropenem with vaborbactam was associated with higher rates of clinical cure than best available antibiotic treatment at both the end of treatment visit (65.6% [21/32] compared with 33.3% [5/15] respectively; difference 32.3%, 95% CI 3.3% to 61.3%; p=0.03) and the test of cure visit (59.4% [19/32] compared with 26.7% [4/15]; difference 32.7%, 95% CI 4.6% to 60.8%; p=0.02) (secondary outcomes).

All-cause mortality

All-cause mortality was not assessed in Tango I. In Tango II, the rate of all-cause mortality at day 28 in the HAP or VAP and bacteraemia subgroups (n=27) was a primary outcome. Mortality was also assessed in the complete CRE-MTT population (secondary outcome).

The rate of all-cause mortality in people with HAP or VAP or bacteraemia in the CRE-MITT population was numerically lower in the meropenem with vaborbactam group than in the best available antibiotic treatment group (22.2% [4/18] compared with 44.4% [4/9] respectively; difference -22.2%, 95% CI -59.9% to 15.5%; p=0.25). However, noting that analyses are not robust because of the trial design and small number of people, there was no statistically significant difference between the groups.

Similar results were seen in the total CRE-MITT population (meropenem with vaborbactam 15.6% [5/32] compared with best available antibiotic treatment 33.3% [5/15]; difference -17.7%, 95% CI -44.7% to 9.3%; p=0.20). One of the 5 deaths in the meropenem with vaborbactam group was associated with sepsis compared with 4 of the 5 deaths in the best available antibiotic treatment group.

Safety

In people with complicated urinary tract infection (cUTI) or acute pyelonephritis in [Tango I](#) who received at least 1 dose of study treatment (n=545), the proportions of people who experienced the following were broadly similar between the meropenem with vaborbactam and piperacillin with tazobactam groups (no statistical analyses reported):

- any adverse events (39.0% [106/272] and 35.5% [97/273] respectively)
- study treatment-related adverse events (15.1% [41/272] and 12.8% [35/273] respectively)
- serious adverse events (4.0% [11/272] and 4.4% [12/273] respectively)
- severe adverse events (2.6% [7/272] and 4.8% [13/273] respectively)

- life-threatening adverse events (congestive cardiac failure, septic shock secondary to salpingo-oophoritis and an infusion-related reaction; 1.1% [3/272] and 0% [0/273] respectively)
- death (0.7% [2 people] in each group)
- adverse events leading to study treatment discontinuation (2.6% [7/272] and 5.1% [14/273] respectively)
- adverse events leading to study discontinuation (1.1% [3 people] in each group).

The most common adverse event reported with meropenem with vaborbactam in Tango I was headache (8.8% [24/272] compared with 4.4% [12/273] with piperacillin with tazobactam), all instances of which were mild or moderate in severity.

In people with documented or suspected carbapenem-resistant Enterobacterales in [Tango II](#) who received at least 1 dose of study treatment (n=75), overall, meropenem with vaborbactam was generally associated with a smaller proportion of adverse events than best available antibiotic treatment (no statistical analyses reported):

- any adverse events (84% [42/50] and 92.0% [23/25] respectively)
- study treatment-related adverse events (24.0% [12/50] and 44.0% [11/25] respectively)
- serious adverse events (34.0% [17/50] and 44.0% [11/25] respectively)
- severe adverse events (14.0% [7/50] and 28.0% [7/25] respectively)
- life-threatening adverse events (6.0% [3/50] and 4.0% [1/25] respectively)
- death (20% [10/50] and 24% [6/25] respectively)
- adverse events leading to study treatment discontinuation (10.0% [5/50] and 12.0% [3/25] respectively)
- adverse events leading to study discontinuation (16.0% [8/50] and 20.0% [5/25] respectively).

The [summary of product characteristics](#) for meropenem with vaborbactam reports that the most common adverse reactions among 322 participants in the pooled phase 3 trials were headache (8.1%), diarrhoea (4.7%), infusion site phlebitis (2.2%) and nausea (2.2%). Severe adverse reactions were observed in 2 participants (0.6%; an infusion-related reaction and an increase in blood alkaline phosphatase). A serious infusion-related reaction was reported in an additional participant (0.3%).

The [Vaborem European public assessment report](#) concludes that the safety database for meropenem with vaborbactam is relatively small but does not indicate any major concerns resulting from addition of vaborbactam to meropenem.

[Appendix B](#) gives details of the results for safety and tolerability from the included studies.

Person-related factors

Meropenem with vaborbactam is administered by intravenous infusion over 3 hours, every 8 hours ([summary of product characteristics](#)). In practice, it is highly likely to be prescribed and administered in a hospital setting.

Evidence strengths and limitations

[Tango I](#) was a relatively large, well-designed and reported trial, which was undertaken in accordance with regulatory requirements. The [Vaborem European public assessment report](#) (EPAR) states that Tango I was generally of an adequate design, except that the final prespecified noninferiority margin for the EMA primary outcome was 15%, rather than 10%. However, analyses found that the lower limit of the 95% confidence interval around the difference in eradication rates was within –10% for both primary outcome populations.

Less than 15% of participants in Tango I had creatine clearance below 50 ml/min, only around 5% had bacteraemia, and less than 5% had previously received an antibiotic for the infection being studied. Also, the majority of participants in Tango I were European but not from the UK and it is unclear whether all would have met criteria for hospitalisation in the UK. However, the EPAR notes that the population in Tango I was generally acceptable.

Tango I was not designed to evaluate meropenem with vaborbactam for treating carbapenem-resistant pathogens, and very few meropenem-resistant but meropenem with vaborbactam-susceptible organisms were detected at baseline. Therefore, this trial cannot determine whether the vaborbactam dose was adequate to protect meropenem against class A and class C beta-lactamases.

Pharmacokinetic and pharmacodynamic data were used to support the marketing authorisation in this regard.

Nearly all pathogens recorded in Tango I were susceptible to meropenem but about 12% were resistant to piperacillin with tazobactam. The EPAR states that, although piperacillin with tazobactam was a suitable comparator for a study that was predominantly undertaken in European centres, the imbalance in resistance to the assigned treatment was of concern for the overall validity of the primary analysis. However, after excluding participants with piperacillin with tazobactam resistant organisms or pathogens resistant to the assigned treatment, a –10% noninferiority margin was still met. Note that TANGO I was not designed to look for noninferiority of meropenem with vaborbactam compared to piperacillin with tazobactam specifically in carbapenem-resistant Enterobacterales.

The EPAR concludes that the results of Tango I support the marketing authorisation for meropenem with vaborbactam for treating cUTI and acute pyelonephritis. Clinical evidence is available to confirm it is effective against 3 Gram-negative pathogens (*Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter cloacae* species complex) and in vitro evidence of efficacy is available for other pathogens.

The EPAR states that the [Tango II](#) trial may be regarded as supportive, although this open-label study was intended for a descriptive comparison of efficacy only and has several other limitations. It included a small number of participants, with outcomes assessed in only 47 people with confirmed carbapenem-resistant Enterobacterales. People with a variety of infection sites were included, which means it is difficult to interpret the results. Also, many different options were used as best available antibiotic treatment and only 9/47 people (19%, all in the meropenem with vaborbactam group) had previously experienced treatment failure with another antibiotic. Although treatment was not blinded, investigators were required to select best available antibiotic treatment before randomisation. In addition, outcomes were assessed using blinded local site evaluation and a separate blinded adjudication committee.

The EPAR notes that, although Tango II cannot provide definitive evidence of efficacy, the data safety monitoring board recommended early study termination

because there was evidence of benefit in the meropenem with vaborbactam group. However, the numbers of participants with cIAI and HAP or VAP were very small (n=4 and n=5 respectively). Therefore, the marketing authorisation for these conditions was granted based on experience with meropenem alone, and pharmacokinetic and pharmacodynamic data.

The EPAR points out that the safety profile of meropenem is well-established and the limitation of the safety database relates to vaborbactam. Exposure to the licensed dosage of meropenem with vaborbactam is limited to 364 people in clinical trials. However, The EPAR concludes that there are no major safety concerns.

Both trials included adults only and there is no evidence to support the use of meropenem with vaborbactam in children and young people. No randomised controlled trials have compared meropenem alone and meropenem with vaborbactam.

[Appendix C](#) summarises the quality assessment of the included studies.

Estimated impact for the NHS

Other treatments

A wide range of antibiotics, alone or in combination, are used for treating complicated urinary tract infection (cUTI), acute pyelonephritis, complicated intra-abdominal infection (cIAIs), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Examples include cephalosporins, metronidazole, extended-spectrum penicillins with beta-lactamase inhibitors and carbapenems. Regimens may be changed based on response to treatment or results from microbiological susceptibility testing. Local (or national) antimicrobial prescribing guidelines should be consulted when selecting treatment options for these indications.

NICE has produced antimicrobial prescribing guidelines on [catheter-associated UTI](#), [acute pyelonephritis](#) and [HAP](#), which include recommendations on choosing an antibiotic. NICE has not currently published any guidance on cIAIs, although a guideline on [diverticular disease](#) is expected to be published in November 2019,

which will include recommendations on choosing an antibiotic for acute diverticulitis. A NICE guideline on [pneumonia in adults](#) is also available.

Costs of treatment

The acquisition cost of meropenem with vaborbactam is £55.67 (excluding VAT) per vial, meaning the cost of 1 day's treatment at the usual dosage (2 g/2 g [2 vials] every 8 hours) is £334.02 (personal communication Menarini, October 2019).

The acquisition costs (excluding VAT) of other intravenous antibiotics that are used for cUTI, acute pyelonephritis, cIAI, HAP and VAP are generally lower than that of meropenem with vaborbactam. For example, ceftazidime with avibactam (2 g/0.5 g every 8 hours) costs £257.10 per day, ceftolozane with tazobactam (1 g/0.5 g every 8 hours) costs £201.09 per day, and piperacillin with tazobactam (4 g/0.5 g every 8 hours) costs from £14.40 per day ([BNF, October 2019](#)). The acquisition cost of meropenem alone is £17.78 (excluding VAT) for 1 vial containing 1 g of powder for solution for injection ([Drug Tariff, October 2019](#)). The cost of 1 day's treatment with 2 g (2 vials) every 8 hours is £106.68.

Depending on the proven pathogens contributing to the infection, meropenem with vaborbactam may need to be given in combination with other antimicrobials for which additional treatment costs would need to be considered.

Current or estimated usage

The manufacturer of meropenem with vaborbactam (Menarini) anticipates that usage will be low, following the principles of good antimicrobial stewardship and under the guidance of a microbiologist.

Specialists involved in producing this evidence summary expect that meropenem with vaborbactam will be used to treat people with limited treatment options who have serious infections suspected or proven to be caused by multi-drug resistant aerobic Gram-negative bacteria according to its licensed indications. Local antibiotic resistance patterns also need to be taken into account because meropenem with vaborbactam may not be appropriate in regions where class B or class D carbapenemase resistance is common.

Likely place in therapy

Meropenem with vaborbactam has a marketing authorisation for treating adults with complicated urinary tract infection (cUTI) including pyelonephritis, complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP), bacteraemia associated with (or suspected to be associated with) those infections, or infections due to aerobic Gram-negative organisms with limited treatment options. Commissioners and local decision makers need to take safety, efficacy, cost, patient factors and national guidance into account when considering the likely place in therapy of meropenem with vaborbactam.

The [Vaborem European public assessment report](#) (EPAR) concludes that the Tango I trial provides good evidence for meropenem (2 g over 3 hours, every 8 hours) for treating adults with cUTI or acute pyelonephritis. However, it cannot provide clinical evidence for the adequacy of the vaborbactam dosing regimen because the trial was not designed to assess efficacy against meropenem-resistant organisms. About 5% of people in Tango I had bacteraemia, providing some support for using meropenem with vaborbactam for this indication.

The Tango II trial provides limited support for using meropenem with vaborbactam to treat adults with infections due to aerobic Gram-negative organisms and limited treatment options. According to the EPAR, pharmacokinetic and pharmacodynamic data suggest that the dose of vaborbactam is enough to cover the majority of enterobacteria that produce class A or class C carbapenemases. The scientific justification for the vaborbactam dose for treating adults with cIAI and HAP or VAP is also based on pharmacokinetic and pharmacodynamic data.

The safety profile of meropenem is well-established and, although the safety database for meropenem with vaborbactam is relatively small, the EPAR concludes it does not indicate any major concerns resulting from addition of vaborbactam to meropenem.

The EPAR reports that successful treatment of cUTI, HAP and VAP is threatened by rising rates of antimicrobial resistance among common pathogens. The threat is less for acute pyelonephritis and cIAI because they often have an acute onset outside of

hospital settings, which makes it less likely that the causative pathogens have been subjected to the degree of selective pressure that typically affects nosocomial organisms. Beta-lactam antibacterial agents are commonly used to manage these infections when they involve Gram-negative pathogens. However, resistance to beta-lactams, including carbapenems, is increasing, and may co-exist with resistance to other classes of antibacterial agents.

The EPAR states that there is an unmet need for well-tolerated antibiotics that are active against aerobic Gram-negative organisms that express class A and class C carbapenemases. It reports that vaborbactam can protect meropenem from inactivation by these beta-lactamases in the absence of other types of carbapenem resistance, and concludes that, although meropenem with vaborbactam cannot wholly solve the problem of carbapenem resistance, it provides a potentially useful alternative for treating infections due to carbapenem-resistant enterobacteria.

Vaborbactam cannot protect meropenem against class B and class D beta-lactamases or restore susceptibility when resistance is wholly or partly due to impermeability or efflux mechanisms. The EPAR stresses that it is important that these limitations are understood. Therefore, using meropenem with vaborbactam to treat adults with limited treatment options should be under the guidance of an appropriately experienced infection specialist (such as a clinical microbiologist or infectious diseases consultant).

Commissioners and local decision makers will need to consider where meropenem with vaborbactam fits within local antimicrobial prescribing guidelines for managing the infections covered by the marketing authorisation, taking the principles of antimicrobial stewardship and national guidance into account. As stated in the approved indications, consideration should be given to official guidance on the appropriate use of antibacterial agents. The NICE guideline on [antimicrobial stewardship](#): systems and processes for effective antimicrobial medicine use makes recommendations for local decision-making groups on factors to take into account when evaluating a new antimicrobial for local use and for inclusion in the local formulary. This includes: assessing the need for the new antimicrobial; clinical effectiveness; the population in which it will be used; the specific organisms or conditions for which it will be used; local rates and trends of resistance; whether use

should be restricted and, if so, how use will be monitored; any urgent clinical need for the new antimicrobial; and any plans for introducing the new antimicrobial.

Other factors to consider are the risks and benefits of treatment, the type of setting to administer intravenous antimicrobials, for example hospital or homecare, antimicrobial monotherapy versus combination therapy, frequency and duration of intravenous administration and monitoring requirements associated with some antimicrobials.

Appropriate use of antimicrobials is important to reduce the serious threat of antimicrobial resistance. Public Health England’s [‘Start smart – then focus’](#) toolkit outlines best practice in antimicrobial stewardship in the secondary care setting.

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 and declarations of interest

Name, job title/organisations	DOI
Dr Rowland Bright-Thomas, Consultant Respiratory Physician, Manchester University Hospitals NHS Foundation Trust	No relevant interests declared
Dr Anastasios Lekkas, Consultant Respiratory Physician, University Hospital Southampton NHS Foundation Trust	No relevant interests declared
Preet Panesar, Lead Pharmacist – Microbiology, University College London Hospital NHS Foundation Trust	No relevant interests declared
Professor Ian Pearce, Consultant Urological Surgeon, Central Manchester University Hospitals NHS Foundation Trust; Honorary Professor, University of Salford; Honorary Senior Lecturer, University of Manchester; Editor Journal of Clinical Urology	Director of Pearce Urology: Provider of private medical care (Financial interest 2012 – ongoing) Director of Pearce Consultancy: Provider of private medical care advice (Financial interest 2012 – ongoing) British Association Urological Surgeons (Trustee, 2015 – ongoing) Director of Fortify Clinic Limited (Financial, 2019 – ongoing)

Name, job title/organisations	DOI
Dr Natasha Ratnaraja, Consultant in Infection, University Hospitals Coventry and Warwickshire NHS Trust	No relevant interests declared

Appendices

Appendix A: Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
Tango I ¹ Randomised double-blind double-dummy trial 60 sites in 17 countries ^a	n=550 (n=545 in the MITT population ^b) Mean duration of treatment 10 days (IV 8 days and oral 2 days ^c), mean study duration 25 days	Adults (≥18 years, mean age 53 years, 66% female, 93% white) with estimated creatinine clearance <30 ml/min (mean about 90 ml/min) who had documented or suspected cUTI ^d (41%) or acute pyelonephritis ^d (59%) needing at least 5 days of IV antibiotics ^c <i>E. coli</i> (65%) and <i>K. pneumoniae</i> (16%) were the most commonly isolated urinary pathogens	Meropenem with vaborbactam 2 g/2 g IV over 3 hours, every 8 hours ^c (n=272) Blinded dose adjustment was made for participants with estimated creatinine clearance less than 50 ml/min	Piperacillin with tazobactam 4 g/0.5 g over 30 minutes, every 8 hours ^c (n=273)	The US and EU have different regulatory requirements that are reflected in the primary outcomes For the FDA, the primary outcome was overall success (a composite outcome of clinical cure ^e and microbial eradication ^f) at the end of IV treatment visit for the microbiologic MITT population ^g For the EMA, the primary outcome was microbial	The majority of participants were European but not from the UK and it is unclear whether all would have met criteria for hospitalisation in the UK 31% of participants did not have a baseline pathogen of 10 ⁵ CFU/ml or more, despite meeting the inclusion criteria, and therefore were not included in the primary analysis population (the microbiologic MITT population) The trial was not designed to evaluate meropenem with vaborbactam for treating carbapenem-resistant pathogens Nearly all pathogens were susceptible to meropenem but about 12% were resistant to piperacillin with tazobactam

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
					eradication ^h at the test of cure visit ⁱ for the microbiologic MITT and microbiologic evaluable populations ^j	
Tango II ² Open-label randomised controlled trial 27 sites in 8 countries ^k	n=77 (n=47 in the microbiologic CRE-MITT population ^l) Mean duration of treatment 9 days Study duration is unclear but mortality was assessed at 28 days	Adults ≥18 years (mean age 62.5 years, 49% female, 85% white) with cUTI or acute pyelonephritis (34%), HAP or VAP (11%), bacteraemia (47%) or cIAI (8%) and confirmed or suspected CRE ^l requiring ≥7 days of IV antibiotics <i>K. pneumoniae</i> (87%) was the most commonly isolated pathogen	Meropenem with vaborbactam 2 g/2 g IV over 3 hours, every 8 hours for 7 to 14 days (n=32) Dose adjustment was made for participants with estimated creatinine clearance less than 50 ml/min	Best available antibiotic treatment (including polymyxins, carbapenems, aminoglycosides or tigecycline alone or in combination; or ceftazidime with avibactam alone; n=15). Choice was left up to the investigator and documented before randomisation. The dose was according to local protocols	Primary efficacy outcomes included all-cause mortality at day 28 in the HAP or VAP and bacteraemia subgroups; microbial eradication ^m (EMA) and overall success (a composite outcome of clinical cure ⁿ and microbial eradication ^m [FDA]) at the test of cure visit ^o in the cUTI subgroup; and clinical cure ^p at the test of cure	The study was open-label and included a small number of participants, with outcomes assessed in only 47 people The study was descriptive and no formal power or sample size calculations were performed The data safety monitoring board reviewed interim data and recommended early study termination due to evidence of benefit in the meropenem with vaborbactam group

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
					visit ^o in the cIAI subgroup	

References:

¹ Kaye KS, Bhowmick T, Metallidis S et al. (2018) [Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection. The TANGO I randomized clinical trial.](#) JAMA 319(8): 788–99

² Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G et al. (2018) [Effect and safety of meropenem–vaborbactam versus best-available therapy in patients with carbapenem-resistant enterobacteriaceae infections: the TANGO II randomized clinical trial.](#) Infect Dis Ther 7(4): 439–55

^a Belarus, Brazil, Bulgaria, Czech Republic, Greece, Hungary, Italy, Peru, Poland, Romania, Slovakia, Slovenia, South Korea, Spain, Taiwan, Ukraine and the US

^b The MITT population included participants who received 1 or more doses of study treatment (n=545)

^c After 15 or more doses, if they met prespecified criteria for improvement, participants could be switched from their IV study treatment to oral levofloxacin (500 mg daily), to complete 10 days of total treatment

^d Complicated UTI was defined as having at least 2 of chills, rigors, or fever; elevated white blood cell count or left shift; nausea or vomiting; dysuria, increased urinary frequency or urinary urgency; or lower abdominal pain or pelvic pain **and** the presence of pyuria **and** at least 1 associated risk factor, such as an indwelling catheter, neurogenic bladder or obstructive uropathology. Signs or symptoms of acute pyelonephritis could also be defined by flank pain or costovertebral angle tenderness on physical examination. Around half of participants with cUTI had a removable source of infection such as a urinary catheter or removable kidney stones

^e Complete resolution or significant improvement of baseline signs and symptoms of cUTI or acute pyelonephritis

^f Baseline pathogens reduced to <10⁴ CFU/ml urine

^g The microbiologic MITT population included all participants in the MITT population with 1 or more bacterial pathogens of 10⁵ CFU/ml or more in baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures (n=374)

^h Baseline pathogens reduced to <10³ CFU/ml urine

ⁱ 7 days after the end of treatment

^j The microbiologic evaluable population included all participants in the microbiologic MITT population who had a clinical outcome and a microbiologic outcome at the end of IV treatment who had received enough study treatment according to a prespecified range (n=347)

^k Argentina, Brazil, Colombia, Greece, Israel, Italy, the UK and the US

^l Patients were enrolled if carbapenem resistance was suspected or confirmed but the primary study population was the microbiologic CRE-MITT population, defined as participants who received at least 1 dose of study treatment and had a baseline qualifying isolate confirmed as CRE by a local or central laboratory

^m Baseline pathogens reduced to <10³ CFU/mL urine (EMA) or <10⁴ CFU/mL urine (FDA)

ⁿ Complete resolution of signs and symptoms of the index infection such that no further antimicrobial therapy (and/or surgical intervention for cIAI) was needed

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
° 7 days ±2 days after the end of treatment						
Abbreviations: CFU, colony-forming units; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; IV, intravenous; MITT, modified intention-to-treat ; VAP, ventilator-associated pneumonia						

Appendix B: Results tables

Tango I (2018)

	Meropenem with vaborbactam	Piperacillin with tazobactam	Analysis
Primary outcomes			
FDA: Percentage of participants with overall success ^a at the end of IV treatment ^b in the microbiologic MITT population ^c	98.4% (189/192)	94.0% (171/182)	Difference 4.5% (95% CI 0.7% to 9.1%) p<0.001 for noninferiority ^d and p=0.1 for superiority Meropenem with vaborbactam statistically significantly better
EMA: Percentage of participants with microbial eradication ^e at test of cure ^f in the microbiologic MITT population ^c	66.7% (128/192)	57.7% (105/182)	Difference 9.0% (95% CI -0.9% to 18.7%) p<0.001 for noninferiority ^d Meropenem with vaborbactam was noninferior to piperacillin with tazobactam
EMA: Percentage of participants with microbial eradication ^e at test of cure ^f in the microbiologic evaluable population ^g	66.3% (118/178)	60.4% (102/169)	Difference 5.9% (95% CI -4.2% to 16.0%) p<0.001 for noninferiority ^d Meropenem with vaborbactam was noninferior to piperacillin with tazobactam
Secondary outcomes			
Percentage of participants with overall success ^a at test of cure ^f in the microbiologic MITT population ^c	74.5% (143/192)	70.3% (128/182)	Difference 4.1% (95% CI -4.9% to 9.1%) No statistically significant difference
Percentage of participants with overall success ^a at the end of IV treatment ^b in people with acute pyelonephritis	97.5% (117/120)	94.1% (95/101)	Difference 3.4% (95% CI -2.0% to 10.2%) No statistically significant difference
Percentage of participants with overall success ^a at the end of IV treatment ^b in people with cUTI	100% (35/35)	92.1% (35/38)	Difference 7.9% (95% CI -2.5% to 20.9%) No statistically significant difference

	Meropenem with vaborbactam	Piperacillin with tazobactam	Analysis
and a removable source of infection ^h			
Percentage of participants with overall success ^a at the end of IV treatment ^b in people with cUTI without a removable source of infection	100% (37/37)	95.3% (41/43)	Difference 4.7% (95% CI –5.1% to 15.6%) No statistically significant difference
Percentage of participants with clinical cure ⁱ at the end of IV treatment ^b	98.4% (189/192)	95.6% (174/182)	Difference 2.8% (95% CI –0.7% to 7.1%) No statistically significant difference
Percentage of participants with clinical cure ⁱ at test of cure ^d	90.6% (174/192)	86.3% (157/182)	Difference 4.4% (95% CI –2.2% to 11.1%) No statistically significant difference
Safety and tolerability outcomes (MITT population^c)			
Percentage of participants experiencing treatment-emergent adverse events	39.0% (106/272)	35.5% (97/273)	No statistical analysis reported
Percentage of participants experiencing adverse events considered related to the study treatment	15.1% (41/272)	12.8% (35/273)	No statistical analysis reported
Percentage of participants experiencing life-threatening adverse events	1.1% (3/272)	0.0% (0/273)	No statistical analysis reported
Percentage of participants experiencing serious adverse events	4.0% (11/272)	4.4% (12/273)	No statistical analysis reported
Percentage of participants who died	0.7% (2/272)	0.7% (2/273)	No statistical analysis reported
Percentage of participants who stopped their study treatment because of treatment-emergent adverse events	2.6% (7/272)	5.1% (14/273)	No statistical analysis reported

	Meropenem with vaborbactam	Piperacillin with tazobactam	Analysis
Percentage of participants who left the study because of treatment-emergent adverse events	1.1% (3/272)	1.1% (3/273)	No statistical analysis reported
Percentage of participants experiencing any severe adverse event	2.6% (7/272)	4.8% (13/273)	No statistical analysis reported
Percentage of participants experiencing headache	8.8% (24/272)	4.4% (12/273)	No statistical analysis reported
Percentage of participants experiencing diarrhoea	3.3% (9/272)	4.4% (12/273)	No statistical analysis reported

Reference:

Kaye KS, Bhowmick T, Metallidis S et al. (2018) [Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection. The TANGO I randomized clinical trial](#). JAMA 319(8): 788–99

^a Overall success was defined as clinical cure (complete resolution or significant improvement of baseline signs and symptoms) and microbial eradication (baseline pathogens reduced to <10⁴ CFU/ml urine)

^b The mean duration of IV treatment was 8.0 days in both groups (1 to 15 days for meropenem with vaborbactam and 2 to 15 days for piperacillin with tazobactam)

^c The MITT population included participants who received 1 or more doses of study treatment (n=545). The microbiologic MITT population included all participants in the MITT population with 1 or more bacterial pathogens of 10⁵ CFU/ml or more in baseline urine culture or the same bacterial pathogen present in concurrent blood and urine cultures (n=374)

^d The lower limit of the 95% CI was greater than the prespecified noninferiority margin of – 15%, demonstrating that meropenem with vaborbactam was noninferior to piperacillin with tazobactam for the FDA and EMA primary outcomes

^e Baseline pathogens reduced to <10³ CFU/ml urine

^f 7 days after the end of treatment

^g The microbiologic evaluable population included all participants in the microbiologic MITT population who had a clinical outcome and a microbiologic outcome at the end of IV treatment who had received enough study treatment according to a prespecified range (n=347)

^h Includes urinary catheter or removable kidney stones

ⁱ Clinical cure was defined as complete resolution or significant improvement of baseline signs and symptoms of cUTI or acute pyelonephritis

Abbreviations: CFU, colony-forming units; CI, [confidence interval](#); cUTI, complicated urinary tract infection; IV, intravenous; MITT, modified [intention-to-treat](#); p, [p value](#)

Tango II (2018)

	Meropenem with vaborbactam	Best available antibiotic treatment	Analysis
Primary outcomes (CRE-MITT population^a)			
Percentage of participants with all-cause mortality at day 28 in the HAP or VAP and bacteraemia subgroups	22.2% (4/18)	44.4% (4/9)	Difference -22.2% (95% CI -59.9% to 15.5%, p=0.25) No statistically significant difference
EMA: Percentage of participants with microbial eradication ^b at test of cure ^c in the cUTI subgroup ^d	25.0% (3/12)	50.0% (2/4)	Difference -25.0% in favour of best available antibiotic treatment No statistical analysis
FDA: Percentage of participants with overall success (a composite outcome of clinical cure ^e and microbial eradication ^b) at test of cure ^c in the cUTI subgroup	33.3% (4/12) ^f	50.0% (2/4)	Difference -16.7% in favour of best available antibiotic treatment No statistical analysis
Percentage of participants with clinical cure ^e at test of cure ^c in the cIAI subgroup	100% (2/2)	0% (0/2)	Difference 100% in favour of meropenem with vaborbactam No statistical analysis
Secondary outcomes (microbiologic CRE-MITT population^a)			
Percentage of participants with any confirmed CRE with all-cause mortality at day 28	15.6% (5/32)	33.3% (5/15)	Difference -17.7% (95% CI -44.7% to 9.3%, p=0.20) No statistically significant difference
Percentage of participants with any confirmed CRE with clinical cure ^e at end of treatment ^g	65.6% (21/32)	33.3% (5/15)	Difference 32.3% (95% CI 3.3% to 61.3%, p=0.03) in favour of meropenem with vaborbactam
Percentage of participants with any confirmed CRE with clinical cure ^e at test of cure ^c	59.4% (19/32)	26.7% (4/15)	Difference 32.7% (95% CI 4.6 to 60.8%, p=0.02) in favour of meropenem with vaborbactam
Percentage of participants with any confirmed CRE with microbial eradication ^b at end of treatment ^g	65.6% (21/32)	40.0% (6/15)	Difference 25.6% (95% CI -4.1% to 55.4%, p=0.09) No statistically significant difference

	Meropenem with vaborbactam	Best available antibiotic treatment	Analysis
Percentage of participants with any confirmed CRE with microbial eradication ^b at test of cure ^c	53.1% (17/32)	33.3% (5/15)	Difference 19.8% (95% CI -9.7% to 49.3%, p=0.19) No statistically significant difference
Safety and tolerability outcomes (MITT population^h)			
Percentage of participants experiencing treatment-emergent adverse events	84.0% (42/50)	92.0% (23/25)	No statistical analysis reported
Percentage of participants experiencing adverse events considered related to the study treatment	24.0% (12/50)	44.0% (11/25)	No statistical analysis reported
Percentage of participants experiencing life-threatening adverse events	6.0% (3/50)	4.0% (1/25)	No statistical analysis reported
Percentage of participants experiencing serious adverse events	34.0% (17/50)	44.0% (11/25)	No statistical analysis reported
Percentage of participants who died	20.0% (10/50)	24.0% (6/25)	No statistical analysis reported
Percentage of participants who stopped their study treatment because of treatment-emergent adverse events	10.0% (5/50)	12.0% (3/25)	No statistical analysis reported
Percentage of participants who left the study because of treatment-emergent adverse events	16.0% (8/50)	20.0% (5/25)	No statistical analysis reported
Percentage of participants experiencing any severe adverse event	14.0% (7/50)	28.0% (7/25)	No statistical analysis reported
Percentage of participants experiencing renal adverse events	4.0% (2/50)	24.0% (6/25)	No statistical analysis reported

	Meropenem with vaborbactam	Best available antibiotic treatment	Analysis
Percentage of participants experiencing diarrhoea	12.0% (6/50)	16.0% (4/25)	No statistical analysis reported
<p>Reference: Wunderink RG, Giamarellou-Bourboulis EJ, Rahav G et al. (2018) Effect and safety of meropenem–vaborbactam versus best-available therapy in patients with carbapenem-resistant enterobacteriaceae infections: the TANGO II randomized clinical trial. Infect Dis Ther 7(4): 439–55</p> <p>^a Participants with microbiologically confirmed CRE who received 1 or more doses of study treatment (the CRE-MITT population, n=47 for all infections, [n=22 for bacteraemia, n=16 for cUTI/or acute pyelonephritis, n=5 for HAP or VAP and n=4 for cIAI])</p> <p>^b Baseline pathogens reduced to <10³ CFU/mL urine (EMA) or <10⁴ CFU/mL urine (FDA)</p> <p>^c 7 days ±2 days after the end of treatment. Mean duration of treatment was 9 days</p> <p>^d This outcome was not reported in the Tango II paper and has been obtained from the Vaborem European public assessment report</p> <p>^e Complete resolution of signs and symptoms of the index infection such that no further antimicrobial therapy (and/or surgical intervention for cIAI) was needed</p> <p>^f 4 participants treated with meropenem with vaborbactam were not assessed at the test of cure visit</p> <p>^g Mean duration of treatment was 9 days</p> <p>^h All participants who received 1 or more doses of study treatment (n=75)</p> <p>Abbreviations: CFU, colony-forming units; CI, confidence interval; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacteriales; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; MITT, modified intention-to-treat; p, p value; VAP, ventilator-associated pneumonia</p>			

Appendix C: Quality assessment of included studies

Quality assessment question	Tango I (2018)
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes ^a
Were patients, health workers and study personnel blinded?	Yes ^b
Were the groups similar at the start of the trial?	Yes ^c
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes ^d
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 ^e
Were all clinically important outcomes considered?	Yes ^f
Are the benefits worth the harms and costs?	See Evidence Summary
^a Eligible patients were randomised 1:1 using a computer-generated central randomisation code, using a dynamic randomisation algorithm and interactive voice/web response system	
^b It was a double-blind, double-dummy trial. As well as the study treatment, participants received a 30-minute or 3-hour saline infusion to maintain blinding	
^c Overall, baseline characteristics were similar in the 2 treatment groups. However, nearly all pathogens were susceptible to meropenem but about 12% were resistant to piperacillin with tazobactam	
^d Note that 31% of participants did not have a baseline pathogen of 10 ⁵ CFU/ml or more, despite meeting the inclusion criteria, and therefore were not included in the primary analysis population	
^e Although the majority of 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	
^f The primary outcomes were selected to meet FDA and EMA regulatory requirements. They include patient- and disease-oriented outcomes	
Checklist used: CASP RCT checklist	

Quality assessment question	Tango II (2018)
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes ^a
Were patients, health workers and study personnel blinded?	No ^b
Were the groups similar at the start of the trial?	Yes ^c
Aside from the experimental intervention, were the groups treated equally?	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 ^d
Were all clinically important outcomes considered?	Yes ^e
Are the benefits worth the harms and costs?	See Evidence Summary

Quality assessment question**Tango II (2018)**

^a Eligible patients were randomised 2:1 to meropenem with vaborbactam or best available antibiotic treatment using a computer-generated central randomisation code and interactive voice/web response system

^b The study was open-label. However, although treatment was not blinded, investigators were required to select best available antibiotic treatment before randomisation. Also, outcomes were assessed using blinded local site evaluation and a separate blinded adjudication committee

^c Overall, baseline characteristics appear similar in the 2 treatment groups. However, the treatment groups included people with a range of infections, making the results difficult to interpret. Also, many different options were used as best available antibiotic treatment

^d The study included centres in the UK and 56% of participants in the study were European

^e The primary outcomes were selected to meet FDA and EMA regulatory requirements. They include patient- and disease-oriented outcomes

Checklist used: [CASP RCT checklist](#)

Appendix D: Literature search strategy

Database search strategies

Database: Medline

Platform: Ovid

Version: 1946 to June 10, 2019

Search date: 12 June 19

Number of results retrieved: 48

Search strategy:

- 1 (vabomere or carbavance).ti,ab. (5)
- 2 (Meropenem and vaborbactam).ti,ab. (37)
- 3 Meropenem/ and vaborbactam.ti,ab. (26)
- 4 (RPX-2014 or RPX-7009).ti,ab. (0)
- 5 (RPX2014 or RPX7009).ti,ab. (19)
- 6 (RPX 2014 or RPX 7009).ti,ab. (0)
- 7 or/1-6 (48)

Database: Medline in-process Other Non-Indexed Citations

Platform: Ovid

Version: 1946 to June 11

Search date: 12 June 19

Number of results retrieved: 34

Search strategy:

- 1 (vabomere or carbavance).ti,ab. (3)
- 2 (Meropenem and vaborbactam).ti,ab. (34)
- 3 (RPX-2014 or RPX-7009).ti,ab. (0)
- 4 (RPX2014 or RPX7009).ti,ab. (1)
- 5 (RPX 2014 or RPX 7009).ti,ab. (0)
- 6 or/1-5 (34)

Database: Embase

Platform: Ovid

Version: 1974 to 2019 June 11

Search date: 12 June 19

Number of results retrieved: 122

Search strategy:

- 1 (vabomere or carbavance).ti,ab. (9)
- 2 (Meropenem and vaborbactam).ti,ab. (80)
- 3 meropenem plus vaborbactam/ (113)
- 4 (RPX-2014 or RPX-7009).ti,ab. (1)
- 5 (RPX2014 or RPX7009).ti,ab. (24)
- 6 (RPX 2014 or RPX 7009).ti,ab. (1)
- 7 or/1-6 (144)
- 8 limit 7 to english language (139)
- 9 8 not (letter or editorial).pt. (132)

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- 10 limit 9 to conference abstracts (10)
- 11 9 not 10 (122)

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

Platform: Wiley

Cochrane Database of Systematic Reviews

Issue 6 of 12, June 2019

Cochrane Central Register of Controlled Trials

Issue 6 of 12, June 2019

Search date: 12 June 19

Number of results retrieved: CDSR 0 ; CENTRAL 10.

ID	Search	Hits
#1	(vabomere or carbavance):ti,ab	3
#2	(Meropenem and vaborbactam):ti,ab	13
#3	MeSH descriptor: [Meropenem] explode all trees	167
#4	vaborbactam:ti,ab	13
#5	#3 and #4	2
#6	(RPX-2014 or RPX-7009):ti,ab	0
#7	(RPX2014 or RPX7009):ti,ab	7
#8	(RPX 2014 or RPX 7009):ti,ab	0
#9	#1 or #2 or #5 or #6 or #7 or #8 in Cochrane Reviews	0
#10	#1 or #2 or #5 or #6 or #7 or #8 in Trials	18
#11	"clinicaltrials.gov":so	140837
#12	"www.who.int":so	114462
#13	#11 or #12	255299
#14	#10 not #13	10

Database: HTA

Platform: CRD

Version:

Search date: 11 June 19

Number of results retrieved: 0

Search strategy:

#1	(vabomere) OR (carbavance) IN HTA (all fields)	0
#2	(Meropenem and vaborbactam) IN HTA (all fields)	0
#3	((RPX-2014) OR (RPX-7009)) IN HTA (all fields)	0
#4	((RPX2014) OR (RPX7009)) IN HTA (all fields)	0

Trials registry search strategies

Clinicaltrials.gov

Search date: 10 June 19

Number of results retrieved: 3

Search strategy: vabomere; carbavance; meropenem-vaborbactam; Meropenem and vaborbactam (Phase 3, 4, Not Applicable)

Evidence review: Antimicrobial prescribing: Meropenem with vaborbactam (November 2019)

Clinicaltrialsregister.eu

Search date: 10 June 19

Number of results retrieved: 2

Search strategy: phase II/III/IV: vabomere OR carbavance; "meropenem-vaborbactam"; Meropenem AND vaborbactam

Appendix E: Excluded studies

A literature search for meropenem with vaborbactam was conducted which identified 3 references (see [search strategy](#) for full details). These references were screened using their titles and abstracts and all 3 references were obtained and assessed for relevance to the meropenem with vaborbactam (Vaborem) product.

Two references identified from the search are included in this evidence review. These are [Tango I](#) and [Tango II](#), which are the key phase 3 randomised controlled trials. The third paper that was identified ([Bassetti M et al. 2019](#)) is a post hoc analysis of Tango II. This has not been included because of its limitations (post hoc analysis of a small, descriptive study) and limited applicability to UK clinical practice.

A summary of the included phase 3 studies is shown in [Appendix A](#).