

Antimicrobial prescribing: meropenem with vaborbactam

Evidence summary

Published: 20 November 2019

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Key messages

The content of this evidence review was up-to-date in November 2019. See summaries of product characteristics (SPCs), British national formulary (BNF), or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Meropenem with vaborbactam (Vaborem, Menarini) is a combination of a broad-spectrum carbapenem antibiotic, which covers gram-positive, gram-negative and anaerobic bacteria, and a new beta-lactamase inhibitor, which protects against class A and class C (but not class B and class D) carbapenemases (enzymes that cause resistance to carbapenem antibiotics). It is given as a 3-hour intravenous (IV) infusion every 8 hours and 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).

Evidence is from 2 phase 3 randomised controlled trials ([Tango I](#) and [Tango II](#)). Tango I provides evidence for meropenem for treating adults with cUTI and acute pyelonephritis, but 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 (for the marketing authorisation, the dosage of vaborbactam was supported by pharmacokinetic and pharmacodynamic data). About 5% of people in Tango I had bacteraemia, providing some support for using meropenem with vaborbactam for this indication. Tango II provides limited support for using meropenem with vaborbactam to treat adults with infections due to aerobic gram-negative organisms and limited treatment options. The marketing authorisation for cIAI and HAP or VAP was granted based on experience with meropenem alone, and pharmacokinetic and pharmacodynamic data.

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

Likely place in therapy

The [Vaborem European public assessment report](#) (EPAR) states that there is an unmet need for well-tolerated antibacterial agents 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. 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 carbapenem-resistant 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 carbapenem-resistant Enterobacterales (11.2%).

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 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. Therefore, using meropenem with vaborbactam in this way should be under the guidance of an appropriately experienced infection specialist (such as a clinical microbiologist or infectious diseases consultant), following the principles of good antimicrobial stewardship.

Local (or national) antimicrobial prescribing guidelines should be consulted when selecting treatment options for these indications.

Factors for decision making

Effectiveness

Tango I was a randomised, double-blind, double-dummy trial that compared meropenem with vaborbactam (2 g/2 g IV [intravenous] over 3 hours, every 8 hours) with piperacillin with tazobactam (4 g/0.5 g IV over 30 minutes, every 8 hours) in adults with complicated urinary tract infection (cUTI), including acute pyelonephritis. The primary outcomes were overall success, a composite outcome of clinical cure (complete resolution or significant improvement of baseline signs and symptoms) and microbial eradication (baseline pathogens reduced to below 10³–10⁴ colony-forming units/ml urine) at the end of IV treatment or microbial eradication at the test of cure visit (7 days after the end of treatment).

Tango II was an open-label, randomised trial that compared meropenem with vaborbactam

(2 g/2 g IV over 3 hours, every 8 hours) with best available antibiotic treatment (polymyxin, carbapenem, aminoglycoside or tigecycline antibiotics alone or in combination; or ceftazidime with avibactam alone) in 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. Tango II was a descriptive study only and no formal power or sample size calculations were performed.

Overall success

At the end of treatment in Tango I (mean 8 days, n=374), the overall success rate 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 non-inferiority), in adults with cUTI or acute pyelonephritis. The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of -15%, showing that meropenem with vaborbactam was statistically non-inferior to piperacillin with tazobactam.

A pre-specified 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, $p = 0.01$).

Microbial eradication

Meropenem with vaborbactam was statistically non-inferior to piperacillin with tazobactam for microbial eradication at the test of cure visit in Tango I in adults with cUTI or acute pyelonephritis (66.7% [128/192] compared with 57.7% [105/182] respectively; difference 9.0%, 95% CI -0.9% to 18.7; $p < 0.001$ for non-inferiority).

In adults with cUTI or acute pyelonephritis (n=16), cIAI (n=4), HAP or VAP (n=5), or bacteraemia (n=22) caused by carbapenem-resistant Enterobacterales in Tango II, there was no 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).

However, the design of Tango II means the statistical analyses performed are not robust and no firm conclusions can be drawn based on this trial.

Clinical cure

In Tango I, in adults with cUTI or acute pyelonephritis, there was no statistically significant difference between meropenem with vaborbactam, and piperacillin with tazobactam, in the rate of clinical cure at the:

- end of treatment visit (98.4% [189/192] compared with 95.6% [174/182] respectively; difference 2.8%, 95% CI -0.7% to 7.1%) **or**
- test of cure visit (90.6% [174/192] compared with 86.3% [157/182] respectively; difference 4.4%, 95% CI -2.2% to 11.1%).

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).

All-cause mortality

All-cause mortality was not assessed in Tango I. In Tango II, there was no significant difference between meropenem with vaborbactam and best available antibiotic treatment in all-cause mortality at 28 days (15.6% [5/32] compared with 33.3% [5/15]; difference -17.7%, 95% CI -44.7% to 9.3%; p=0.20). However, the design of the trial means that analyses are not robust and firm conclusions cannot be made.

Safety

In people with cUTI or acute pyelonephritis in Tango I who took at least 1 dose of study treatment (n=545), the proportions of people who experienced adverse events were

broadly similar between the groups:

- Treatment-related adverse events were reported by 15.1% (41/272) of people receiving meropenem with vaborbactam, and 12.8% (35/273) of people receiving piperacillin with tazobactam.
- Adverse events leading to study treatment discontinuation occurred in 2.6% (7/272) and 5.1% (14/273) of people respectively.

In people with suspected or documented carbapenem-resistant Enterobacterales in Tango II who took at least 1 dose of study treatment (n=75):

- Treatment-related adverse events were reported by 24.0% (12/50) of people receiving meropenem with vaborbactam, and 44.0% (11/25) of people receiving best available antibiotic treatment.
- Adverse events leading to study treatment discontinuation occurred in 10.0% (5/50) and 12.0% (3/25) of people respectively.

Statistical analyses were not reported for safety outcomes in either trial.

The [summary of product characteristics](#) for meropenem with vaborbactam reports that the most common adverse reactions among 322 participants in 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](#) (EPAR) 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.

Limitations of the evidence

Tango I was a relatively large, well-designed and reported trial, which was undertaken in accordance with regulatory requirements. However, it was not designed to evaluate meropenem with vaborbactam for treating carbapenem-resistant pathogens, and very few organisms that were resistant to meropenem but susceptible to meropenem with vaborbactam 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.

Tango II was a supportive, open-label descriptive study with several other limitations. It included a small number of participants, with outcomes assessed in only 47 people with confirmed carbapenem-resistant Enterobacterales.

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.

Meropenem with vaborbactam is a new antimicrobial and therefore data on resistance and the impact in clinical practice in the UK are limited.

Person-related factors

Meropenem with vaborbactam is administered by IV infusion over 3 hours, every 8 hours and, in practice, it is highly likely that it will be prescribed and administered in a hospital setting.

Resource implications

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 of other IV antibiotics that are used for cUTI, acute pyelonephritis, cIAI, HAP and VAP are generally lower than that of meropenem with vaborbactam. 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.

The manufacturer of meropenem with vaborbactam (Menarini) anticipates that usage will be low, following the principles of good antimicrobial stewardship, and will be under the guidance of a microbiologist. A wide range of antibiotics, alone or in combination, are used for treating cUTI, acute pyelonephritis, cIAI, HAP and VAP, and regimens may be changed

based on response to treatment or results from microbiological susceptibility testing.

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.

See the [full evidence review](#) for more information.

ISBN: 978-1-4731-3594-9