Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2278

meropenem/vaborbactam 1 gram/1 gram powder for concentrate for solution for infusion (Vaborem®)

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04 September 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

meropenem/vaborbactam (Vaborem®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of 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)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem/vaborbactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

SMC restriction: for adults with confirmed carbapenem-resistant Enterobacteriaceae (CRE), which is involved in the production of *Klebsiella pneumoniae* carbapenemase (KPC) associated with cUTI (including acute pyelonephritis [AP]), cIAI, HAP (including VAP) and bacteraemia that occurs in association with, or is suspected to be associated with any of the infections previously mentioned. Use should be on the advice of local microbiologists or specialists in infectious disease.

In a randomised, double-blind, phase III study, meropenem/vaborbactam was non-inferior to a beta-lactamase/beta-lactamase inhibitor for the treatment of adults with cUTI, including AP. A smaller, randomised, open-label, phase III study suggested that meropenem/vaborbactam compared favourably with best available therapy for the treatment of adults with infections due to confirmed/suspected CRE.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of 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)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Meropenem/vaborbactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.[1]

Dosing Information

The recommended dose for meropenem/vaborbactam for the treatment of complicated infections in patients with a creatinine clearance (CrCl) ≥40mL/min is 2g/2g every 8 hours administered by intravenous infusion over 3 hours.

The recommended duration of treatment ranges from 5 to 10 days for cUTIs (including pyelonephritis) and cIAIs, and may continue up to 14 days, if needed. For HAP (including VAP), the recommended duration of treatment ranges from 7 to 14 days. For bacteraemia and infections due to aerobic Gram-negative organisms in patients with limited treatment options, the recommended duration of treatment is defined in accordance with the site of the infection.

Meropenem/vaborbactam should be used to treat infections due to aerobic Gram-negative organisms in adult patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Please refer to the Summary of Product Characteristics (SPC) for more information regarding dosage in special populations and contraindications.[1]

Product availability date

22 November 2019

Summary of evidence on comparative efficacy

Meropenem is an established broad-spectrum carbapenem antibacterial, part of the class of beta-lactam antibiotics, which covers Gram-positive, Gram-negative and anaerobic bacteria. It exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis as a result of binding to and inhibition of activity of essential penicillin-binding proteins. Vaborbactam is a new, non-beta-lactam inhibitor of class A and C serine beta-lactamases, including *Klebsiella pneumoniae* carbapenemase (KPC). Vaborbactam has no antibacterial activity itself and it does not inhibit class B or class D carbapenemases. The addition of vaborbactam to meropenem aims to protect the

efficacy of meropenem against Class A and C beta-lactamases, including KPC-producing carbapenem-resistant Enterobacteriaceae (CRE-KPC).[1, 2] The combination of meropenem plus vaborbactam has been licensed for the treatment of 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 these infections and for infections due to aerobic Gram-negative organisms in adults with limited treatment options. The submitting company has asked SMC to consider the use of meropenem/vaborbactam when positioned for use in adults with confirmed CRE, which is involved in the production of KPC associated with cUTI (including acute pyelonephritis [AP]), cIAI, HAP (including VAP) and bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections previously mentioned.

The main clinical evidence for meropenem/vaborbactam comes from the TANGO I study but this is limited to patients with cUTI.[3] It was a multicentre, randomised, double-blind, phase III study which compared the efficacy and safety of meropenem plus vaborbactam with piperacillin plus tazobactam in 550 adults with confirmed or suspected cUTI including AP. Patients were aged ≥18 years and were considered to need ≥5 days of IV antibiotic treatment. They were randomised equally to receive meropenem plus vaborbactam (2g/2g intravenously every 8 hours) or piperacillin plus tazobactam (4g/0.5g intravenously every 8 hours). Study treatment was given for a total of 10 days and patients could be switched to oral levofloxacin after 15 doses of intravenous study treatment to complete 10 days of total treatment provided improvement criteria were met. The primary efficacy outcome was assessed using different criteria for the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). For the EMA, the primary outcome was microbial eradication (defined as baseline pathogens reduced to less than 10^3 colony-forming units [CFU]/mL urine) at the test of cure (TOC) visit in the microbiologic modified intention to treat (MITT) population (all treated patients with baseline bacterial pathogen(s) of ≥10^5 CFU/mL in urine or the same pathogen in blood and urine, excluding those with only Gram-positive pathogens in urine) and microbiologic evaluable population (all treated patients with no major selection criteria violations, with a clinical outcome having received ≥80% to ≤120% of IV doses or ≥6 doses if failed or ≥9 doses if cured). In each group, approximately 59% of patients had AP and approximately 41% had cUTI, with about half of the latter having a removable source of infection (for example a catheter or kidney stones). At baseline, the most common pathogen in both groups was *Escherichia coli* (65%) followed by *Klebsiella pneumoniae* (15%). However the majority of organisms were sensitive to meropenem and approximately 12% were resistant to piperacillin/tazobactam.

Microbiologic eradication at TOC was achieved by 67% (128/192) in the meropenem/vaborbactam group compared with 58% (105/182) in the piperacillin/tazobactam group in the microbiologic MITT population and by 66% (118/178) compared with 60% (102/169) respectively in the microbiologic evaluable population. The non-inferiority margin of 10% was met in both populations. Secondary outcomes were also similar: overall success (defined as a composite of clinical cure and microbial eradication) at TOC (74% and 70%), clinical cure at TOC (91% and 86%) and at the end of intravenous treatment (98% and 96%).[3]

The evidence to support the proposed positioning comes from an open-label, randomised, phase III study (TANGO II) which compared meropenem/vaborbactam with best available therapy (BAT) in 77 patients with suspected or confirmed CRE infections. Eligible patients were aged ≥18 years with a serious infection, specifically cUTI or AP, cIAI, HAP, VAP, or bacteraemia with a confirmed or suspected CRE pathogen requiring intravenous treatment for a minimum of 7 days and had an Acute Physiology and Chronic Health Evaluation II (APACHE II) prognostic score ≤30. They were randomised, in a ratio of 2:1 to receive meropenem/vaborbactam (2g/2g by intravenous infusion over 3 hours, every 8 hours, n=52) or BAT (n=25). BAT was selected by the investigator before randomisation and could include polymyxins, carbapenems, aminoglycosides and tigecycline given as monotherapy or in combination, or monotherapy with ceftazidime/avibactam. Study treatment was continued for 7 to 14 days. Randomisation was stratified by type of infection and by geographic region.

TANGO II was a descriptive study only and was not powered for statistical analyses. The primary analysis population comprised 47 patients with confirmed CRE infection who formed the microbiologic-CRE-modified intent-to-treat (mCRE-MITT) population, of which 32 patients were randomised to meropenem/vaborbactam and 15 patients were randomised to BAT. The primary efficacy outcomes varied across infection types. For patients with cUTI or AP, it was the proportion of patients achieving microbial eradication (defined as $<10^3$ colony forming units [CFU]/mL urine for the EMA) or overall success rate (defined as a composite outcome of clinical cure and microbial eradication [defined as $<10^4$ CFU/mL urine] for the FDA) at TOC visit (7 days ± 2 days following end of treatment [EOT]). For cIAI, the primary efficacy outcome was the proportion of patients achieving clinical cure (defined as complete resolution of symptoms of infection to the point that no further antimicrobial therapy and/or surgical intervention for cIAI was necessary) at TOC. For HAP/VAP and bacteraemia, it was the proportion of patients with all-cause mortality at day 28. Secondary outcomes included the proportion of patients achieving clinical cure at EOT and TOC visits for the overall mCRE-MITT population and the HAP/VAP and bacteraemia subpopulations; all-cause mortality at day 28 in the mCRE-MITT population and the cUTI/AP, HAP/VAP and bacteraemia subpopulations; clinical cure at EOT/TOC and day-28 mortality in all patients who received at least one dose of study drug (MITT population).

The primary outcomes numerically favoured meropenem/vaborbactam over BAT for clinical cure in patients with cIAI and for all-cause mortality in patients with HAP/VAP and bacteraemia. However the primary outcomes numerically favoured BAT over meropenem/vaborbactam for both the FDA and EMA outcomes in patients with cUTI/AP.[2, 4] Details of results for primary and selected secondary outcomes are presented in table 1 below.

Table 1. Proportions of patients achieving primary and selected secondary outcomes in TANGO II in the mCRE-MITT population

Outcome and infection	meropenem / vaborbactam	BAT	Difference (95% CI)
Primary Outcomes			
All-cause mortality at day-28 in patients with HAP/VAP and bacteraemia (combined); % (n/N)	22% (4/18)	44% (4/9)	-22% (-60 to 16)
Microbial eradication at TOC in patients with cUTI/AP (EMA); % (n/N)	25% (3/12)	50% (2/4)	-25%
Overall success at TOC in patients with cUTI/AP (FDA); % (n/N)	33% (4/12)	50% (2/4)	-16.7%
Clinical cure at TOC in patients with cIAI; % (n/N)	100% (2/2)	0% (0/2)	100%
Secondary outcomes			
All infections			
Clinical cure at EOT; % (n/N)	66% (21/32)	33% (5/15)	32% (3.3 to 61)
Clinical cure at TOC; % (n/N)	59% (19/32)	27% (4/15)	33% (4.6 to 61)
All-cause 28-day mortality; % (n/N)	16% (5/32)	33% (5/15)	-18% (-45 to 9.3)
Microbial eradication at TOC; % (n/N)	53% (17/32)	33% (5/15)	20% (-9.7 to 49)
cUTI or AP infections			
Clinical cure at EOT; % (n/N)	75% (9/12)	50% (2/4)	25%
Clinical cure at TOC; % (n/N)	42% (5/12)	50% (2/4)	-8.3%
All-cause 28-day mortality; % (n/N)	8.3% (1/12)	0% (0/4)	8.3%
Microbial eradication at TOC; % (n/N)	25% (3/12)	50% (2/4)	-25%
Bacteraemia			
Clinical cure at TOC; % (n/N)	57% (8/14)	25% (2/8)	32%
All-cause 28-day mortality; % (n/N)	29% (4/14)	38% (3/8)	-9%
Microbial eradication at TOC; % (n/N)	50% (7/14)	38% (3/8)	12%
HAP/VAP			
Clinical cure at TOC; % (n/N)	100% (4/4)	0% (0/1)	100%
All-cause 28-day mortality; % (n/N)	0% (0/4)	100% (1/1)	-100%
Microbial eradication at TOC; % (n/N)	75% (3/4)	0% (0/1)	75%

cIAI infection			
Clinical cure at TOC; % (n/N)	100% (2/2)	0% (0/2)	100%
All-cause 28-day mortality; % (n/N)	0% (0/2)	50% (1/2)	-50%
Microbial eradication at TOC; % (n/N)	50% (1/2)	0% (0/2)	50%
mCRE-MITT= microbiological carbapenem-resistant Enterobacteriaceae modified intent-to- treat, BAT = best available therapy; TOC = time of cure, EOT= end of treatment CI= confidence interval, cUTI/AP= complicated urinary tract infection, including acute pyelonephritis, cIAI = complicated intra-abdominal infection; HAP/VAP = hospital acquired pneumonia/ventilator acquired pneumonia			

An exploratory analysis compared the risk: benefit of meropenem/vaborbactam with BAT in terms of the composite of all-cause 28 day mortality and nephrotoxicity (post-baseline increase in serum creatinine ≥1.0mg/dL). The results favoured meropenem/vaborbactam (25% [8/32]) versus BAT (40% [6/15]).[2, 4]

Summary of evidence on comparative safety

The safety profile of meropenem is well-established and although the safety data for vaborbactam and its use in combination with meropenem are limited, no additional safety issues were identified.[2]

TANGO I provided safety data versus another beta-lactamase/beta-lactamase inhibitor combination. The incidence of adverse events reported during TANGO I was 39% (106/272) of meropenem/vaborbactam patients and 36% (97/273) of piperacillin/tazobactam patients; these were related to study medication in 15% and 13% of patients respectively and were serious in 4.0% and 4.4% of patients respectively. An adverse event led to discontinuation of study medication in 2.6% and 5.1% of patients respectively. Two patients in each treatment group died due to an adverse event. The most frequently reported adverse events were headache (8.8% versus 4.4%) and diarrhoea (3.3% versus 4.4%).[3]

In the safety population of TANGO II, treatment emergent adverse events were reported by 84% (42/50) of patients in the meropenem/vaborbactam and 92% (23/25) of patients in the BAT group and were serious in 34% and 44% of patients respectively. Adverse events were considered treatment related in 24% and 44% of patients respectively and 0% and 8.0% of these were serious. There were five (10%) patients in the meropenem/vaborbactam group and three (12%) patients in the BAT group who discontinued treatment due to an adverse event; while eight (16%) and five (20%) patients in the respective groups discontinued the study due to an adverse event.[2, 4]

The most frequently reported treatment-related adverse events of any grade in the meropenem/vaborbactam group versus the BAT group respectively were: diarrhoea (12% versus 16%), anaemia (10% versus 12%), hypokalaemia (10% versus 8.0%), hypotension (8.0% versus 12%), sepsis (4.0% versus 20%), septic shock (2.0% versus 16%). Adverse events indicative of renal failure occurred in a lower proportion of subjects in the meropenem-vaborbactam group compared with the BAT group (more than half received colistin); these events included renal

failure (0% and 4.0%, respectively), renal failure acute (2.0% and 12.0%, respectively) and renal impairment (2.0% and 8.0%, respectively).[4]

In the pooled phase III studies, the most common adverse reactions among 322 patients treated with meropenem/vaborbactam were headache (8.1%), diarrhoea (4.7%), infusion site phlebitis (2.2%) and nausea (2.2%). Severe adverse reactions were observed in 2 patients (0.6%) (an infusion-related reaction and an increase in blood alkaline phosphatase) and a serious infusion-related reaction was reported in one additional patient (0.3%).[1]

The European Public Assessment Report (EPAR), concluded that the safety evidence for meropenem with vaborbactam is relatively small but does not indicate any major concerns resulting from addition of vaborbactam to meropenem.[2]

Summary of clinical effectiveness issues

Meropenem/vaborbactam has a marketing authorisation for the treatment of a number of serious infections. Beta-lactam antibacterials, alone or in combination, are commonly used to treat these infections, particularly when they involve Gram-negative bacteria. However, the increasing rates of antimicrobial resistance, including CRE, has made successful treatment more challenging. The English surveillance program for antimicrobial utilisation and resistance from 2018 to 2019 found that 52% of confirmed CRE were class D carbapenemases, 26% were class B and 11% were class A (KPC).[5] The submitting company has requested that SMC considers meropenem/vaborbactam when positioned for use in adult with confirmed CRE-KPC associated with cUTI (including AP), cIAI, HAP (including VAP) and bacteraemia that occurs in association with, or is suspected to be associated with any of the infections previously mentioned. Clinical experts consulted by SMC stressed the need for new/novel agents with activity against multidrug resistant Gram negative infections, and the limited treatment options currently available for CRE-KPC bacterial infections.

Clinical evidence from TANGO I demonstrated that meropenem/vaborbactam was non-inferior to piperacillin/tazobactam in patients with cUTIs, including AP. However, there were few patients with meropenem-resistant, meropenem/vaborbactam sensitive pathogens at baseline. Therefore the EMA noted that this study primarily compared a higher dose of meropenem (2g every 8 hours) with piperacillin plus tazobactam and did not support the dose of vaborbactam which provides protection to meropenem against class A or C beta-lactamases.

The main evidence to support the positioning proposed by the company comes from the TANGO II study. However this study had a number of limitations including its open-label design which allowed investigators to pre-select BAT, but aimed to minimise potential bias through assessment of clinical outcomes by both a local blinded investigator and a blinded adjudication committee. It enrolled a small number of patients with a range of infections and was not powered for statistical analyses. In addition, the different types of infections and treatments used within BAT make interpretation of the results difficult. The number of patients with confirmed CRE-associated cIAIs and HAP/VAP included in the primary analysis of TANGO II was limited to four and five patients,

respectively. There were also imbalances between the treatment groups in the numbers of patients with specific infections and in patients' baseline characteristics, including gender, renal function and co-morbidities. In the BAT group, 73% (11/15) of patients had a Charlson Comorbidity Index (CCI) ≥6 compared to 44% (14/32) patients in the meropenem/vaborbactam group indicating a higher level of co-morbidity and poorer prognosis status. Nine patients in the meropenem/vaborbactam group of the mCRE-MITT population of TANGO II had previous antibiotic failure and a post-hoc sensitivity analysis, excluding these patients, confirmed the results of the primary analysis.[4, 6]

In TANGO II, the comparator was BAT, pre-selected by the investigator from polymyxins, carbapenems, aminoglycosides, tigecycline and ceftazidime plus avibactam. Of the selected BAT, 47% of patients received dual therapy, 27% monotherapy and the remaining one and two patients received triple and quadruple therapy respectively. Advice from the Scottish Antimicrobial Prescribing Group suggests that monotherapy is less appropriate for patients with CRE-KPC infections.

The EMA concluded that there were limited clinical data from TANGO II to support the use of meropenem/vaborbactam for the treatment of cIAI and HAP/VAP. Therefore, the marketing authorisation for these indications is based on the efficacy of meropenem alone, and microbiological and pharmacokinetic/pharmacodynamic analyses.[2]

The introduction of meropenem plus vaborbactam provides an additional treatment option for patients with CRE-KPC associated infections, where options are limited. Clinical experts consulted by SMC considered meropenem plus vaborbactam to be a therapeutic advancement for CRE bacterial infections and noted that it may provide an option with potentially less renal toxicity. The addition of vaborbactam can protect the efficacy of meropenem against class A and C beta-lactamases but offers no protection against class B or D beta-lactamases or other types of carbapenem resistance. There are currently limited data on resistance to meropenem/vaborbactam. There may be service implications for laboratories in terms of sensitivity testing.

Summary of comparative health economic evidence

The submitting company provided an economic analysis of meropenem/vaborbactam within its licensed indication, with an additional restriction to patients who have had confirmed CRE-KPC associated infections. BAT was used as the key comparator, which comprised of a weighted average of the one to four-drug regimens utilised in the TANGO-II clinical study, with the proportions in the weighted average as noted in the clinical effectiveness section.

A cohort-based decision-tree model structure was used to represent the short-term (up to 28 days) and long-term (28 days to 5 years) patient pathway. Decision nodes over the short-term covered the occurrence of nephrotoxicity, receipt of renal replacement therapy (RRT) in hospital, and the probability of achieving a cure and dying by 28 days. Longer-term nodes covered the

receipt of chronic renal-replacement therapy (for patients receiving RRT in the first 28 days), probability of discharge to home versus long-term care, and probability of dying by 5 years. A perspective of NHS Scotland and social work was used for costs. A time horizon of 5 years was used.

The primary source of data for modelling clinical effectiveness (clinical cure at TOC and mortality at 28 days) came from a subgroup of the TANGO-II study within a modified intention-to-treat population. This study was also used to derive the frequency of nephrotoxicity and septic shock. Supplementary published evidence sources were used to estimate the probability of downstream events such as receipt of RRT in hospital and chronic RRT, and mortality (all-cause and due to chronic RRT).[7, 8] Utility estimates were taken from a range of sources, with the baseline utility of 0.730 (for hospitalisation) derived from a time trade-off study conducted in patients with serious conditions in the United States.[9]

Costs included medicines acquisition and administration alongside costs of healthcare resource use due to hospitalisation (inpatient and intensive care unit), treatment-emergent adverse events (septic shock and nephrotoxicity) and disease complications (long-term care and clinical failure). Treatment duration of meropenem/vaborbactam and the weighted comparator was based on the mean duration in the TANGO-II mCRE-MITT analysis, whilst treatment duration for the weighted comparator appeared to be based on the licensed indications of individual treatments. Duration and proportion of patients receiving RRT in hospital was obtained from the published literature.[8]

The base case results are shown in table 2. Acquisition costs and costs of long-term care represent the main additional costs, whilst savings are predominantly due to management of nephrotoxicity and avoidance of adverse events. Quality adjusted life year (QALY) gains are driven by increased proportions of patients discharged home or into long-term care without requiring chronic RRT.

Table 2: Base case results

Treatment	**Total**			**Incremental**			**ICER (cost per QALY gained) £**
	Costs (£)	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	
BAT	28,600	1.675	1.241	-	-	-	-
Meropenem/ vaborbactam	30,643	2.118	1.574	2,043	0.443	0.332	6,146
BAT=best available therapy, ICER=incremental cost-effectiveness ratio, LY=life years, QALYs=quality adjusted life years.							

A number of scenario analyses were provided, as shown in table 3.

Table 3: Scenario analyses

	Parameter	Meropenem/ vaborbactam total costs (£)	Meropenem / vaborbactam total QALYs	Incremental costs (£)	Incremental QALYs	ICER (Cost per QALY gained) (£)
	Base case	30,643	1.574	2,043	0.332	6,146
1.	Time horizon: 28 days	12,952	0.056	-1,109	0.001	Dominant
2.	BAT cost per course: TANGO II dosing data	30,710	1.574	1,825	0.332	5,489
3.	Utility estimates: disutility applied for diabetes at baseline	30,643	1.536	2,043	0.331	6,175
4.	Utility estimates: disutility for CCI ≥ at baseline	30,643	1.518	2,043	0.349	5,862

QALY= quality-adjusted life year, ICER= incremental cost-effectiveness ratio, BAT= best available therapy, CCI= Charlson comorbidity index

The submission is associated with the following limitations:

- Comparator: the analysis uses a weighted average comparator based on the TANGO-II study. Clinical expert input received by SMC suggests that ceftolozane/tazobactam and ceftazidime/avibactam may represent the key comparators. It was not possible to obtain additional scenarios in the timeline, however, NDC were satisfied that the relative costs of these comparators are unlikely to influence the ICER to a significant degree.
- Reliability of clinical evidence: the use of a small subgroup analysis risks the introduction of confounding factors, which potentially introduce bias in favour of meropenem/vaborbactam. Examples of potentially important covariate imbalances include higher proportions of BAT patients with diabetes mellitus, a higher average CCI and a greater number of immunocompromised patients. No adjustment has been performed to account for any differences. This increases the uncertainty in the estimates of clinical effectiveness but could also have implications for the cost estimates (such as by increasing the duration of treatment required with BAT).

- Multiple evidence sources have been used for the estimation of utilities, some of which may not be directly comparable to each other. Longer-term utilities, which comprise the majority of the QALY gain, may have been overestimated as they do not account for the baseline comorbidities observed in the patient population. However, the application of disutilities to account for comorbidities does not appear to unduly influence the results (Scenarios 3 and 4).

In conclusion, as the economic results are robust to variations in the majority of inputs, the economic case has been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The Scottish Antimicrobial Prescribing Group (SAPG) has published a position paper on optimising antimicrobial prescribing in possible or suspected infections due to multi-drug resistant Gram-negative bacteria in April 2016. This includes details for specific approach for infections due to CRE. This includes the use of combination therapy to reduce the risk of treatment failure. This recommends a minimum of two antibiotics for bacteraemias and severe infection including respiratory tract infections; although there is insufficient evidence to conclude which combinations are most effective but colistin plus a carbapenem may be a suitable first choice. Temocillin and aztreonam may be used in combination with non-beta-lactams if they appear to be sensitive. Temocillin is not active against most CPE but remains effective against KPC-producing Enterobacteriaceae in in vitro studies. Rifampicin has been shown to have synergistic activity with meropenem and colistin, and may also be considered for combination therapy.[10]

The Scottish Intercollegiate Guidelines Network (SIGN) published guidelines for the management of suspected bacterial urinary tract infection in adults in 2012. However, these guidelines do not make any recommendations on treating specific pathogens.[11]

The National institute for Health and Care Excellence (NICE) antimicrobial guidelines provide guidance and advice to help manage common infections and tackle antimicrobial resistance for a wide range of infection types. However, none of these is relevant for the indication under review.[12]

Additional information: comparators

Various combinations of antibiotics depending on sensitivities and local resistance patterns.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Meropenem plus vaborbactam	2g/2g by intravenous infusion every 8 hours	1,670 to 4,676

Costs from BNF online on 13 May 2020. Costs are calculated based on a course of 5 to 14 days.

Additional information: budget impact

The submitting company estimated there would be 13 patients eligible for treatment with meropenem/vaborbactam in year 1, rising to 35 patients in year 5 to which confidential uptake rates were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards.

*Other data were also assessed but remain confidential.**

References

1. A. Menarini Farmaceutica Internazionale SRL. Meropenem/vaborbactam (Vaborem) Summary of Product Characteristics. [cited April 16,2020] Available from: https://www.medicines.org.uk/emc/product/10813.
2. European Medicines Agency (EMA). EPAR: Assessment Report Vabomere 2018 [cited 2020 Feb 11]; Available from: https://www.ema.europa.eu/en/documents/assessment-report/vabomere-epar-public-assessment-report_en.pdf.
3. Kaye KS, Bhowmick T, Metallidis S, Bleasdale SC, Sagan OS, Stus V*, et al.* 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 - Journal of the American Medical Association. 2018;319(8):788-99.
4. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, Mathers AJ, Bassetti M, Vazquez J*, et al.* Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infectious Diseases and Therapy. 2018;7(4):439-55.
5. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018 – 2019, November 2019.
6. Bassetti M, Giacobbe DR, Patel N, Tillotson G, Massey J. Efficacy and Safety of Meropenem–Vaborbactam Versus Best Available Therapy for the Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Patients Without Prior Antimicrobial Failure: A Post Hoc Analysis. Advances in therapy. 2019:1-7.
7. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S*, et al.* Acute Renal Failure in Critically Ill Patients: A Multinational, Multicenter Study. JAMA. 2005;294(7):813-8.
8. Prescott GJ, Metcalfe W, Baharani J, Khan IH, Simpson K, Smith WCS*, et al.* A prospective national study of acute renal failure treated with RRT: incidence, aetiology and outcomes. Nephrol Dial Transplant. 2007;22(9):2513-9.
9. Tsevat J, Cook EF, Green ML, Matchar DB, Dawson NV, Broste SK*, et al.* Health values of the seriously ill. SUPPORT investigators. Annals of internal medicine. 1995;122(7):514-20.
10. Scottish Antimicrobial Prescribing Group, Healthcare Improvement Scotland. Position Paper on Optimising Antimicrobial Prescribing in Possible or Suspected Infections Due to Multi-Drug Resistant Gram Negative Bacteria. SAPG 2016 April [accessed May 2020];Available from: https://www.sapg.scot/quality-improvement/hospital-prescribing/gram-negative-infection/.
11. Scottish Intercollegiate Guidelines N. Management of suspected bacterial urinary tract infection in adults : a national clinical guideline. Edinburgh: Sign; 2013.
12. NICE. Antimicrobial prescribing guidelines. [cited; Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/antimicrobial-prescribing-guidelines.

This assessment is based on data submitted by the applicant company up to and including 13 August 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via

the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.