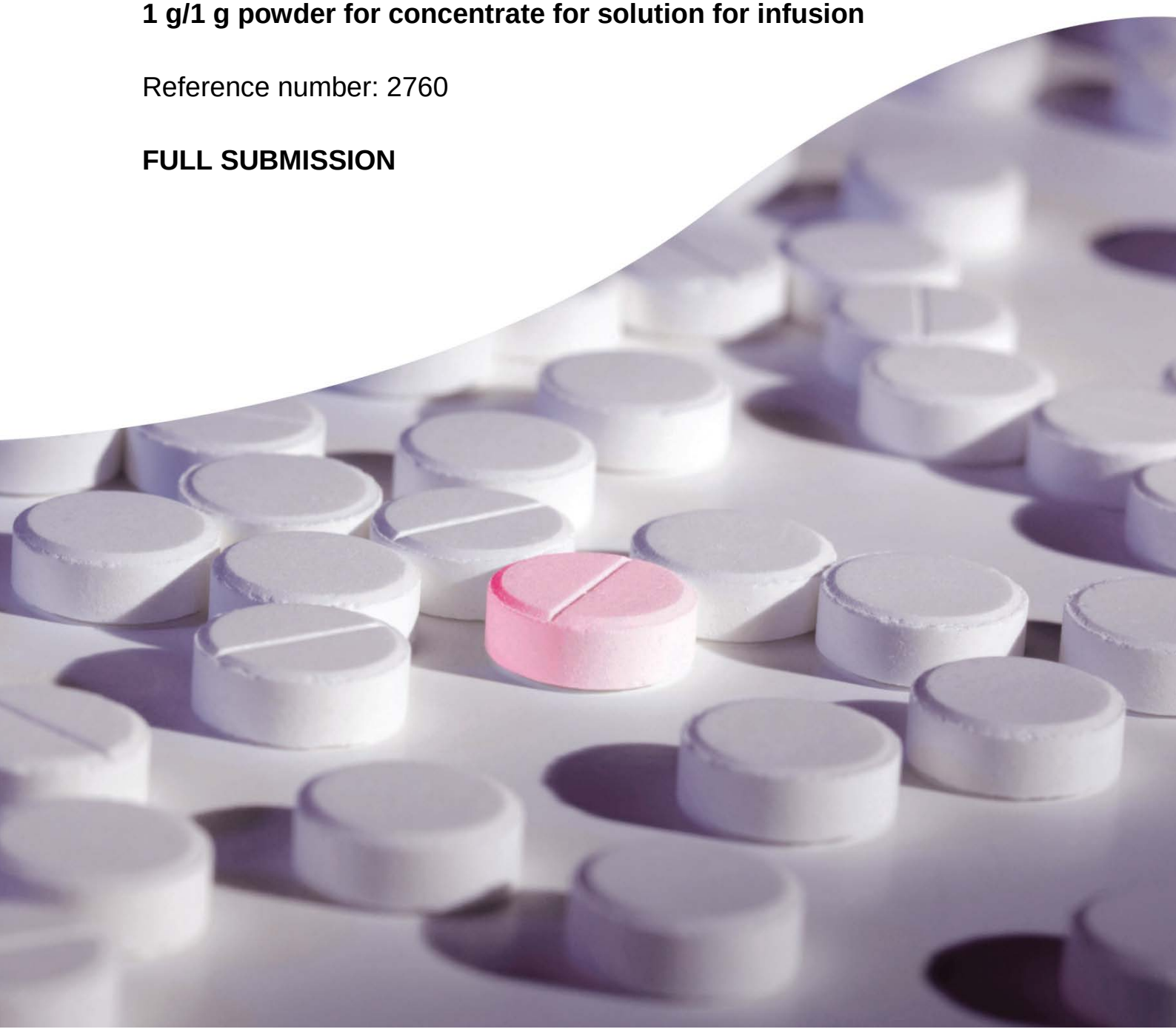
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Meropenem/vaborbactam (Vaborem®)
1 g/1 g powder for concentrate for solution for infusion

Reference number: 2760

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
The Routledge Academic Centre
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 218 26900

This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Meropenem/vaborbactam (Vaborem®) 1 g/1 g powder for concentrate for solution for infusion. Reference number: 2760. September 2020.

AWMSG Secretariat Assessment Report
Meropenem/vaborbactam (Vaborem®▼) 1 g/1 g powder for concentrate for solution for infusion

1.0 KEY FACTS

Assessment details	Meropenem/vaborbactam (Vaborem®▼) for the treatment of complicated urinary tract infection (cUTI) including acute pyelonephritis (AP), complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP) in adults; and for the 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. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. The applicant company has highlighted a subpopulation where it considers meropenem/vaborbactam (Vaborem®▼) may be particularly advantageous. The company requests that AWMSG consider meropenem/vaborbactam only in adults with confirmed carbapenem-resistant Enterobacteriaceae-*Klebsiella pneumoniae* carbapenemase (CRE-KPC) associated with cUTI including AP, cIAI, HAP including VAP, and bacteraemia that occurs in association with, or is suspected to be in associated with, any of the infections listed above.
Current clinical practice	A wide range of antibiotics, alone or in combination, are used for treating cUTI, AP, cIAIs, HAP and VAP, including beta-lactam antibacterial agents (such as the carbapenems) when they involve Gram-negative pathogens. Regimens may be changed based on response to treatment or results from microbiological susceptibility testing. There is increasing antimicrobial resistance to beta-lactams and although carbapenem resistance remains relatively low, increasing trends have been observed.

	Clinical experts agree that there is an unmet need for well-tolerated antibacterial agents for patients infected with carbapenem-resistant Enterobacteriaceae (CRE). Meropenem/vaborbactam is a new antimicrobial, and therefore data on resistance and the impact in clinical practice in the UK are limited. Local antibiotic resistance patterns need to be taken into account because meropenem/vaborbactam may not be appropriate in regions where Class B or Class D carbapenemase resistance is common. Currently, there are no medicines recommended for use specifically for the treatment of adults with confirmed CRE-KPC associated infections.
Clinical effectiveness	TANGO II is the first prospective phase III study with a pathogen focus, specifically designed for CRE-KPC. TANGO II provides support for using meropenem/vaborbactam as monotherapy versus best available treatment (BAT), to treat adults with infections suspected or documented to be caused by CRE. This was an open-label descriptive study only, and has a number of limitations, including a small number of participants and no power calculations performed. The marketing authorisation for cIAI and HAP or VAP was granted based on experience with meropenem alone, and pharmacokinetic and pharmacodynamic data.
Cost-effectiveness	A cost-utility analysis compares meropenem/vaborbactam with BAT in the treatment of confirmed CRE-KPC associated infection in adults. The company base case suggests that meropenem/vaborbactam is £2,106 more costly and produces an additional 0.338 quality-adjusted life-years (QALYs) over the 5-year time horizon resulting in an incremental cost-effectiveness ratio (ICER) of £6,231 per QALY gained.

	Whilst the model structure is robust to sensitivity and scenario analyses provided by the company, with estimates for meropenem/vaborbactam ranging from dominant to an ICER of £11,292 per QALY gained, the cost-utility analyses are subject to considerable uncertainty due to the paucity of high-quality available data and the small sample size of the pivotal study.
Budget impact	The company estimates that [commercial in confidence figure removed] patients would receive treatment with meropenem/vaborbactam in Wales in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The company base case suggests that introducing meropenem/vaborbactam would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings valued at £6,091 in Year 1, increasing to £15,228 in Year 5. These result from reduced cost of adverse events. Sensitivity analysis changing uptake rates and acquisition costs by 10% resulted in cost differences between [commercial in confidence figures removed] in Year 1 and between [commercial in confidence figures removed] in Year 5. The budget impact analysis is hampered by the small sample size of 15 patients used to calculate the mean cost of BAT which introduces uncertainty.

This assessment report is based on evidence submitted by Menarini International Operations Luxembourg S.A[1] and an evidence search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 18–19 May 2020.

2.0 BACKGROUND

2.1 Condition and clinical practice

A wide range of antibiotics, alone or in combination, are used for treating complicated urinary tract infection (cUTI), acute pyelonephritis (AP), complicated intra-abdominal infection (cIAI), hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP). These include carbapenems which are beta-lactam antibiotics that have a broad spectrum of activity against both Gram-positive and Gram-negative bacteria[2]. Regimens may be changed based on response to treatment or results from microbiological susceptibility testing.

Growing resistance to the current major Gram-negative antibiotic classes has resulted in the increased use of carbapenems, which have traditionally been held in reserve as a 'last resort' treatment[3]. The emergence of carbapenem-resistance in certain Enterobacteriaceae is therefore a concern[3].

There are many different mechanisms that can result in carbapenem resistance[4]. Carbapenem-resistant Enterobacteriaceae (CRE) that produce carbapenemases, enzymes that break down carbapenems and related antimicrobials making them ineffective, are called carbapenemase-producing CRE, and are therefore a subset of all CRE[4].

The Welsh Antimicrobial Resistance Programme oversee the surveillance of antimicrobial resistance in Wales[5]. National Prescribing Indicators have also been used to encourage and monitor appropriate prescribing of antibiotics in primary care for several years[6]. Increasing antimicrobial resistance however, has resulted in a critical need for new antibiotics[7,8].

2.2 Medicine

The antibiotic considered in this report is a combination of the carbapenem, meropenem, and a new beta-lactamase inhibitor, vaborbactam. Meropenem/vaborbactam (Vaborem®) is the first fixed-dose antibiotic combination of this type. Meropenem exerts bactericidal activity by inhibiting peptidoglycan cell wall synthesis as a result of binding to and inhibition of activity of essential penicillin-binding proteins[9]. Vaborbactam is a non-beta-lactam inhibitor of Class A and Class C serine beta-lactamases, including *Klebsiella pneumoniae* carbapenemase (KPC). It acts by forming a covalent adduct with beta-lactamases and is stable to beta-lactamase-mediated hydrolysis. It has no antibacterial activity, but markedly enhances the antimicrobial potency of meropenem against KPC-producers as demonstrated in *in vitro* and *in vivo* studies[9]. Vaborbactam does not inhibit Class B or Class D carbapenemases[3,10].

This novel fixed-dose combination is given as a three-hour intravenous (IV) infusion every eight hours and the duration of treatment recommended varies according to the indication[9]. Marketing authorisation was granted in 2018 for treating adults with: cUTI including AP, cIAI, HAP including VAP in adults; and for the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of these infections listed[9]. Meropenem/vaborbactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options[9].

In their submission the company highlight that it is expected meropenem/vaborbactam will be used to treat adults who have serious infections proven to be caused by CRE-KPC[1]. The company have therefore requested that the All Wales Medicines Strategy Group (AWMSG) consider meropenem/vaborbactam only in adults with confirmed CRE-KPC associated with infections of cUTI including AP, cIAI, HAP including VAP, and bacteraemia that occurs in association with, or is suspected to be in associated with, any of the infections listed above[1].

2.3 Comparators

The comparator included in the company's submission is best available therapy (BAT). This is the standard of care comparator for meropenem/vaborbactam monotherapy. In the pivotal study (TANGO II), BAT includes (alone or in combination) a carbapenem, aminoglycoside, polymyxin B, colistin, tigecycline, or ceftazidime-avibactam (monotherapy only).

2.4 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Antimicrobial prescribing: meropenem with vaborbactam. Evidence summary (ES21). 2019[3].
- Hawkey PM, Warren RE, Livermore DM, et al. Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/ British Infection Association Joint Working Party. Journal of Antimicrobial Chemotherapy. 2018[11].
- The Scottish Antimicrobial Prescribing Group (SAPG). Position paper on optimising antimicrobial prescribing in possible or suspected infections due to multi-drug resistant Gram-negative bacteria. 2016[12].
- Welsh Government. Together for health. Tackling antimicrobial resistance and improving antibiotic prescribing: a delivery plan for NHS Wales and its partners. 2016[13].

In the absence of a submission from the marketing authorisation holder, ceftazidime-avibactam (Zavicefta®) for the treatment of adults with cIAI, cUTI including pyelonephritis, HAP including VAP, and infections due to aerobic Gram-negative organisms in patients with limited treatment options, is not endorsed for use within NHS Wales[14].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, meropenem/vaborbactam (Vaborem®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Meropenem/vaborbactam should be used 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[3,9].

3.0 CLINICAL EFFECTIVENESS

The company's submission includes evidence from two phase III randomised controlled studies (TANGO I and TANGO II)[1]. TANGO II was a multinational, open-label study and provides supportive evidence regarding the efficacy and safety of meropenem/vaborbactam monotherapy versus BAT in adults with infections suspected or documented to be caused by CRE. TANGO I was not designed to evaluate meropenem/vaborbactam for treating carbapenem-resistant pathogens, so evaluation of clinical efficacy from this study will not be discussed; however, the study did evaluate the safety of this medicine which is therefore included below[1].

3.1 TANGO II

A total of 47 adult patients (mean age 62.5 years) with bacteraemia (47%), cUTI or AP (34%), HAP or VAP (11%), or cIAI (8%), and had Enterobacteriaceae confirmed to be meropenem resistant, formed the primary analysis population (microbiologic-CRE modified intent-to-treat [mCRE-mITT])[7]. The Gram-negative pathogen isolated was most commonly (87%) *klebsiella pneumoniae*[7].

Patients were randomised 2:1 to meropenem/vaborbactam (2 g/2 g over three hours, every eight hours for 7–14 days; n = 32) or BAT (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime-avibactam alone; n = 15)[7].

Primary efficacy endpoints varied for each infection type. For patients with cUTI/AP, the primary endpoint was defined as the proportion of patients that achieved overall success (composite endpoint of clinical cure plus microbiologic eradication) at End of Treatment (EOT) and Test of Cure (TOC [7 ± 2 days after End of Treatment]) Overall success rates at EOT were found to be numerically higher among patients who received meropenem/vaborbactam than those who received BAT [75.0% (9/12) vs. 50.0% (2/4)]. Overall success rates at TOC were 33.3% (4/12) for meropenem/vaborbactam and 50.0% (2/4) for BAT. The primary endpoint for patients with cIAI was defined as the proportion of patients with an outcome of clinical cure at Test of Cure (TOC [7 ± 2 days after End of Treatment]). Both patients with cIAI receiving meropenem/vaborbactam were reported to have had a clinical cure versus neither in the BAT group (0/2). The primary endpoint of Day-28 All-cause mortality rates in the combined HAP/VAP and bacteraemia subgroups were shown to be numerically lower in patients who received meropenem/vaborbactam than in those who received BAT [22.2% (4/18) vs. 44.4% (4/9), difference, - 22.2%; 95% CI - 59.9 to 15.5%; P = 0.25)].

Efficacy endpoints (shown in Table 1) across all infection types included: the proportion of patients with clinical cure and microbiologic eradication) at the End of Treatment (EOT) and Test of Cure (TOC) (7 ± 2 days after End of Treatment); also Day-28 all-cause mortality. Results showed that treatment with meropenem/vaborbactam monotherapy was associated with increased clinical cure and microbiologic eradication rate, as well as decreased mortality, when compared to BAT. Nine patients in the meropenem/vaborbactam group had prior antibiotic failure[7]. Sensitivity analysis across infection types showed an increase in the treatment effect of meropenem/vaborbactam over BAT for both clinical cure at TOC and Day-28 All-cause mortality in patients without prior antibiotic failure. Exploratory risk-benefit analyses of composite clinical failure or nephrotoxicity favoured meropenem/vaborbactam versus BAT[7].

This study was ongoing at the time of submission to the European Medicines Agency (EMA) for marketing authorisation[10]. During the primary assessment period the study was terminated on the advice of the Data Safety Monitoring Board, which agreed that their interim benefit-risk assessment did not support further randomisation of patients to BAT. At termination, there had been 77 patients randomised over 2.5 years[10].

Table 1. Results from TANGO II[7]

Efficacy endpoints among all patients with confirmed CRE				
Efficacy endpoint	M/V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)	Difference (95% CI)	P value
Clinical Cure at End of Treatment	21 (65.6)	5 (33.3)	32.3 (3.3 to 61.3)	0.03
Clinical Cure at Test of Cure	19 (59.4)	4 (26.7)	32.7 (4.6 to 60.8)	0.02
Microbiologic cure at End of Treatment †	21 (65.6)	6 (40.0)	25.6 (−4.1 to 55.4)	0.09
Microbiologic cure at Test of Cure †	17 (53.1)	5 (33.3)	19.8 (−9.7 to 49.3)	0.19
Day-28 mortality	5 (15.6)	5 (33.3)	−17.7 (−44.7 to 9.3)	0.20
Sensitivity analysis at day 28 across all infection types excluding prior antibiotic failure *				
Efficacy endpoint	M/V (*n* = 23) *n* (%)	BAT (*n* = 15) *n* (%)	Difference (95% CI)	P value
Clinical cure at TOC	16 (69.6)	4 (26.7)	42.9 (13.7 to 72.1)	0.004
Day-28 all-cause mortality	1 (4.3)	5 (33.3)	−29.0 (−54.3 to −3.7)	0.02
Exploratory analysis of risk-benefit profile of M/V compared to BAT				
Efficacy endpoint	M/V (*n* = 32) *n* (%)	BAT (*n* = 15) *n* (%)	Difference (95% CI)	P value
Clinical failure or nephrotoxicity	10 (31.3)	12 (80.0)	−48.7 (−74.6 to −22.9)	< 0.001

BAT: best available treatment; CI: confidence interval; CRE: carbapenem-resistant Enterobacteriaceae; M/V: meropenem/vaborbactam.
* Patients assessed as having prior antibiotic failure at randomisation (meropenem/vaborbactam, 9; BAT, 0) were excluded from this analysis.
† Composite of either microbiologic eradication or presumed eradication at respective visit

3.2 Comparative safety

Meropenem is a well-established antibiotic that has been used worldwide for over two decades for the treatment of serious infections; it's safety profile is well described[10]. The EMA concluded that the safety database pertaining to vaborbactam alone is limited, and for the combination it is relatively small but does not indicate any major concerns resulting from addition of vaborbactam to meropenem[10].

The applicant company's summary of clinical safety of meropenem/vaborbactam describes pooled data from TANGO I (n = 272) and TANGO II (n = 50)[1]. The overall incidence of adverse events was similar between groups over the two studies[1,10]. The most common adverse reactions were headache (8.1%), diarrhoea (4.7%), infusion site phlebitis (2.2%) and nausea (2.2%)[9]. Severe adverse reactions were observed in two patients (0.6 %), one infusion related reaction and one blood alkaline phosphatase increased respectively. In one additional patient, a serious adverse reaction of infusion related reaction was reported (0.3%)[9].

The Committee for Medicinal Products for Human Use (CHMP) concluded that there are no major safety concerns which would impact on the benefit-risk balance of meropenem/vaborbactam[10].

3.3 Ongoing studies

There are no ongoing studies from which additional evidence will be available in the next 6-12 months.

3.4 AWTTC critique

- TANGO II enrolled patients from 27 hospital sites in eight countries with known prevalence of Klebsiella pneumoniae carbapenemase (KPC)-producing CRE, and the majority of patients (36/47) in the microbiologic-CRE modified intent-to-treat group had confirmed KPC-producing infections.

- This is the first and only clinical study of a novel agent given as monotherapy, compared against BAT in patients with confirmed CRE-KPC infections[7].
- TANGO II was a descriptive study only with a number of limitations[3]. It included a small number of participants, with outcomes assessed in only 47 people with confirmed CRE[7]. No formal power or sample size calculations were performed[7], which means no robust statistical analyses could be undertaken and firm conclusions drawn.
- The Data Safety Monitoring Board recommended early study termination because there was evidence of benefit in the meropenem/vaborbactam group[10]. However, the numbers of participants with cIAI and HAP or VAP were very small (n = 4 and n = 5 respectively)[3]. Therefore, the marketing authorisation for these conditions was granted based on experience with meropenem alone, and pharmacokinetic and pharmacodynamic data[3].
- AWTTC- sought Welsh clinical expert opinion confirms BAT is the standard of care comparator for meropenem/vaborbactam monotherapy.
- CHMP highlight that the safety profile of meropenem is well-established and the limitation of the safety database relates to vaborbactam[10]. Despite the limited exposure to the licensed dosage of meropenem/vaborbactam there appears to be no major safety concerns[10].
- There are no randomised controlled trials that compare meropenem alone and meropenem/vaborbactam.
- Although no firm efficacy data could be drawn from Tango II as the study was not designed for inferential testing, the data showed a consistent trend in favouring meropenem/vaborbactam which showed broad support for the adequacy of the vaborbactam dose.
- CHMP acknowledge that the proposed list of organisms that have been successfully treated in clinical trials is short[10]. It is accompanied by a list of organisms against which efficacy has not been demonstrated in clinical trials, but which may be expected to respond to meropenem/vaborbactam[10].

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing meropenem/vaborbactam powder for solution for IV infusion (2 g/2 g every eight hours) with BAT including (alone or in combination) a carbapenem, aminoglycoside, polymyxin B, colistin or tigecycline alone or in combination and ceftazidime-avibactam (as monotherapy only) for the treatment of adult patients with confirmed CRE-KPC associated 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 listed above[1].

The CUA takes the form of a decision tree model, with a 5-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. The model was informed by a previously published model[15] and the model structure and duration of key events were ratified by clinical and health economics experts[16]. Two cohorts of 1,000 adult patients with confirmed CRE-KPC infection enter the model at a mean age of 62.5 years with all baseline characteristics (e.g. gender and comorbidity scores) matched to the TANGO II patient cohort[7].

Based on the average treatment duration in the pivotal trial[7], patients receive either meropenem/vaborbactam for the first [commercial in confidence figure removed] days or BAT for [commercial in confidence figure removed] days upon model entry. On both treatments, patients can develop antibiotic-induced nephrotoxicity and require short-term renal replacement therapy (RRT) for six days or long-term RRT where nephrotoxicity causes irreversible damage. Following treatment, patients can be cured and discharged or, if not, receive a course of BAT antibiotics and remain in hospital for the duration of treatment. After the initial 28 days, all alive patients are followed for the remaining five years of the time horizon after they were either discharged home or into long-term care and can die at any point from any cause[1].

The probabilities of developing nephrotoxicity, being cured, surviving beyond 28 days and being discharged either home or into long-term care were taken from the TANGO II study[7,17]. Values reported in published literature were used for the probabilities of requiring short-term[18] and long-term RRT[19]. Welsh general population mortality data[20] was used to calculate all-cause mortality beyond 28 days by adjusting for the population's multiple co-morbidities and the increased risk of death in case of RRT[21,22].

In addition to nephrotoxicity, the model also accounts for septic shock. The incidence of both adverse events was based on TANGO II patient-level data[17].

Costs considered in the model are treatment acquisition and administration costs, disease management costs (including length and type of hospital stay including intensive care), disease complication costs (including resulting long-term care and clinical failure) and adverse event costs (including cost of treatment of nephrotoxicity and septic shock). Meropenem/vaborbactam acquisition costs were based on an average treatment duration of [commercial in confidence figure removed][23] at a total cost per course of [commercial in confidence figure removed]. Comparator costs were based on a weighted average cost of treatments informed by the BAT arm of TANGO II. The published unit costs of amikacin, gentamicin, ertapenem, meropenem, ceftazidime-avibactam, polymyxin B, colistin and tigecycline[2] and an average patient weight of [commercial in confidence figure removed][23] were used to calculate a comparator cost of £819.52 per treatment course based on average dosing recommended in the British National Formulary. Administration costs comprised of the cost of inserting a central venous catheter[24].

Hospitalisation costs were applied as a weighted per patient cost based on the proportions and length of stay of patients admitted to hospital and ICU in the TANGO II study[17] and published unit costs[24,25]. Following treatment failure, one further additional treatment course was costed as BAT plus hospitalisation (excluding ICU). The annual cost of long-term care was based on Scottish unit costs[26]. Nephrotoxicity and septic shock were costed using published unit costs[24,25,27]. Haemodialysis costs[24] were applied for six days for patients with short-term RRT and for 90 days for patients who would eventually develop the need for chronic RRT based on published Scottish data[19]. Cost of chronic RRT dependency was costed using the cost of one annual spell of exacerbated chronic kidney disease[25] and annual cost of dialysis[28]. No other healthcare resource use was considered.

No utility data were collected in the pivotal study[7]. Utilities during hospitalisation, nephrotoxicity, post-hospitalisation, chronic RRT and after discharge to home or long- term care (LTC) were therefore taken from national and international publications identified as part of a systematic literature review[15,29-32].

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. Scenario analysis explored the cost-differences between meropenem/vaborbactam and BAT taking into account different time horizons, discount rates, 28-day mortality rates, and cost of BAT.

4.2 Results

The results of the base case are detailed in Table 2. When compared with BAT, meropenem/vaborbactam is £2,106 more costly and produces an additional 0.338 quality-adjusted life-years (QALYs) over the 5-year time horizon. The higher cost is predominantly driven by a higher treatment acquisition costs of meropenem/vaborbactam and higher costs for LTC in the meropenem/vaborbactam arm due to higher survival. The higher number of QALYs is caused by the higher likelihood of meropenem/vaborbactam patients to survive beyond 28 days and be cured after treatment with lower probability of nephrotoxicity.

Table 2. Results of the base case analysis

	Meropenem/vaborbactam	BAT	Difference
Medicine acquisition costs*	¶¶	£820	¶¶
Administration costs	¶¶	£485.16	¶¶
Healthcare costs (including hospitalisations, adverse events, clinical failure, nephrotoxicity, RRT in hospital, chronic RRT and long-term care)	¶¶	£27,509	¶¶
Total costs	**£30,920**	**£28,813**	**£2,106**
Total life years	**2.151**	**1.701**	**0.450**
Total QALYs	**1.598**	**1.260**	**0.338**
ICER (£/QALY gained)	**£6,231**		

*Acquisition costs include costs of meropenem/vaborbactam and BAT as first-line treatments. Costs associated with BAT in second-line for patients who experience treatment failure in first-line treatment are included within healthcare costs.
¶¶ commercial in confidence figure removed.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year RRT: renal replacement therapy

In deterministic sensitivity analysis, the incremental cost-effectiveness ratios (ICERs) for meropenem/vaborbactam compared to BAT ranged from dominating to £11,292. The 28-day mortality rate, health state utilities after discharge, probability of nephrotoxicity and LTC and LTC annual costs (as the key cost driver) impacted most on cost-effectiveness results. The results of the scenario analyses are assessed in order of plausibility in Table 3.

Probabilistic sensitivity analyses indicate that meropenem/vaborbactam has a 97.7% and 98.8% probability of being cost-effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 3. Results of scenario analyses

Scenarios	ICER	Plausibility
28-day mortality rate the same in both treatment arms	**£4,210**	This is a plausible scenario as the difference in 28-day mortality was not statistically significant in the TANGO II study[7].
Treatment duration changed within 95% confidence interval[7]	**£4,933 to £7,637**	This is a plausible scenario as treatment duration is likely to differ between individuals.
Using most recent NHS reference unit costs instead of 2013/14 Scottish data	**£5,977**	This is a plausible scenario as current NHS reference costs will be less biased and may more accurately reflect the Welsh context.
BAT cost per course taken from TANGO II[7]	**£5,585**	The plausibility of this scenario is uncertain as real-life data would reflect actual dosing and usage but sample size was small and may not accurately reflect the patient population.
BAT cost per course taken from TANGO II[7] and Welsh experts	**£5,823**	The plausibility of this scenario is uncertain as real-life data would reflect actual dosing and usage but sample size was small and may not accurately reflect the patient population.
Time horizon of 1 year	**Meropenem/vaborbactam dominant**	This scenario is less plausible considering the long-term impact of RRT requirement and long-term care in some patients.
Discount rate 0%	**£6,427**	This scenario is less plausible than the base case as the time horizon exceeds 1 year and discounting of 3.5% is considered standard.
Discount rate 1.5%	**£6,342**	This scenario is less plausible than the base case as discounting of 3.5% is considered standard.
Discount rate 6%	**£6,096**	This scenario is less plausible than the base case as discounting of 3.5% is considered standard.
Time horizon 28 days	**Meropenem/vaborbactam dominant**	This scenario is implausible considering that patients may need multiple treatment courses to resolve the infection and it does not allow for the long-term implications of nephrotoxic adverse events.
BAT: best available treatment; ICER: incremental cost-effectiveness ratio; RRT: renal replacement therapy.		

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model and the model is well presented and appears robust and well-structured.
- The company has made an effort to use the best available data.

Limitations:

- A considerable limitation of the CUA is the lack of high-quality data available to populate the model. Many of the input parameters are based on the modified intent-to-treat (mITT) population of the TANGO II study[7] of patients with confirmed CRE-KPC infection which contains 32 patients in the meropenem/vaborbactam arm and 15 in the BAT arm and efficacy analyses were based on descriptive statistics only; no formal power or sample size calculations were performed.
- Inputs not available from the TANGO II study are taken from Scottish data[22,25] or from publications that appear dated[18,19,21]. While this can be explained by a lack of published evidence for this particular patient population and costs were adequately inflated where required, it introduces uncertainty into the results of the analysis.
- The choice of comparator is reasonable and has been confirmed to be relevant to the Welsh context by Welsh experts. However, the breadth of comparator treatments used in the TANGO II study[7] and the small sample size (n = 15 in the comparator arm) means that comparator input data is not adequately powered to provide confidence in the values used in the model. Furthermore, cost data of individual BAT treatments were often based on treatment duration data sourced from single patients. The company states that a weighted average was used to calculate treatment costs, using patient level data to inform treatment duration across BAT of [commercial in confidence figure removed] days. They assert that this provides a conservative approach as it is lower than the duration of treatment with meropenem/vaborbactam. However, if these data are not representative of the wider population, the efficacy and costs presented may not accurately reflect comparator treatment in routine practice.
- One of the main drivers of the cost-effectiveness of meropenem/vaborbactam is the lower mortality rate at 28 days compared to BAT (15.6% vs. 33.3%). However, this difference was not statistically significant (p = 0.20). This is particularly important as sensitivity analysis showed that the model is most sensitive to changes in the 28-day mortality rate which will introduce considerable uncertainty. The company provided a scenario analysis that assumes no difference in mortality at 28 days which results in an ICER of £4,210.
- Due to the lack of evidence regarding the efficacy of a second round of meropenem/vaborbactam, the model assumes that all second round treatments are administered as BAT and no treatment beyond a second course are considered. This will underestimate the total cost in both arms. However, this is most likely a conservative approach considering the higher cure rate of meropenem/vaborbactam.
- Hospitalisation costs were based on [commercial in confidence figure removed] general ward and [commercial in confidence figure removed] ICU[17]. Patients in ICU were assumed to spend their entire hospital stay in intensive care (i.e. being admitted to and discharged from ICU directly), which will considerably overestimate hospitalisation cost for these patients. However, the company asserts that the ICER will remain unaffected since the same hospitalisation costs are applied to both the meropenem/vaborbactam and BAT treatment arms and the incremental hospitalisation cost would remain at £0.
- Furthermore, patients in ICU were assumed to have the same quality of life as patients in the general ward which may overestimate their QALYs.

- No utility data were collected in the pivotal study[7]. Utilities are therefore sourced from several national and international publications, some of which are quite dated[15,29-32]. Furthermore, these utilities, derived from different countries, settings and populations, were directly applied to the model. While the company argues that this was the best available evidence, it may cause bias due to likely heterogeneity and lack of generalisability to the current Welsh population.
- The pivotal study[7] was conducted in 27 hospitals in eight countries known to have a high prevalence of CRE-KPC including Argentina, Brazil, Colombia, Greece, Israel, Italy, UK and US. No information is available on the number of patients recruited in Wales. Depending on differences in healthcare systems and population, the results may therefore not be generalisable to the Welsh population. However, the company states that baseline patient characteristics of the mCRE-MITT population in TANGO II were confirmed to be reflective of the patient population in Wales by two microbiologist consultants at Public Health Wales.
- A large proportion of clinical outcomes, unit costs and utilities were based on data from Scotland, England, the Netherlands, other European countries and the US. While this was required due to the scarcity of available data, it may not accurately reflect the Welsh context.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of meropenem/vaborbactam versus BAT in the treatment of adult patients with confirmed CRE-KPC associated infection.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates an annual incidence of CRE-KPC infections in Wales of [commercial in confidence figure removed] people. This estimate is obtained from company data on file based on Welsh patient data and has been ratified by two microbiologist consultants at Public Health Wales[33]. This incidence is assumed to be constant over the 5-year time horizon taking into account population growth but not mortality. Of these patients 100% are assumed to be eligible for treatment with meropenem/vaborbactam. Discontinuation is not taken into account and an uptake rate of [commercial in confidence figure removed] is assumed in the first year, increasing to [commercial in confidence figure removed] in Year 5. This results in an estimated [commercial in confidence figure removed] patients receiving meropenem/vaborbactam in Year 1, increasing to [commercial in confidence figure removed] patients in Year 5. A dose of meropenem/vaborbactam of 2 g/2 g every eight hours[7] with a mean average treatment duration of [commercial in confidence figure removed] days in the microbiologic-CRE-mITT population[23] resulted in a cost per course of [commercial in confidence figure removed]. BAT was costed at a weighted amount of £819.52 as per the cost-utility analysis[1].

The company performed basic sensitivity analysis altering uptake rates and medicine acquisition costs by 10%.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing meropenem/vaborbactam would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of currently available BAT.

Sensitivity analysis changing uptake rates and medicine acquisition costs by 10% resulted in cost differences between [commercial in confidence figures removed] in Year 1 and between [commercial in confidence figures removed] in Year 5.

Table 4. Company-reported costs associated with use of meropenem/vaborbactam for the treatment of confirmed CRE-KPC infections

	Year 1	Year 2	Year 3	Year 4	Year 5
Sub-population of eligible patients (indication under consideration)	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Medicines acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0.00	£0.00	£0.00	£0.00	£0.00
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed.					

The company estimated that net resource implications arising from the introduction of meropenem/vaborbactam will lead to a saving of £6,091 in Year 1, increasing to £15,228 in Year 5. This is a consequence of reduced adverse events costs due to a lower rate of nephrotoxicity and septic shock. These resource-type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission is overly complicated. However, the numbers reported have been recalculated and confirmed by AWTTC.
- Input parameters are derived from company data on file based on Welsh patient data and ratified by two microbiologist consultants at Public Health Wales[33] but are based on small patient numbers and therefore subject to considerable uncertainty.

- The sensitivity analysis provided by the company does not address the considerable uncertainty surrounding BAT composition and cost caused by the small sample size (n = 15) in the comparator arm of the relevant sub-population of the TANGO II study[7]. This may cause bias considering that the study population may not accurately reflect the Welsh population and routine practice. In a scenario analysis based upon the opinion of two microbiologist consultants at Public Health Wales, the composition of BAT was aligned with Welsh clinical practice whereby the cost of BAT increased from £819.52 to £923.46 per course. This reduced the cost impact to £3,831 in Year 1 and £9,578 in Year 5.

6.0 ADDITIONAL FACTORS TO CONSIDER

6.1 Other

The applicant company state that when selected based on efficacy from antibiotic susceptibility testing, treatment with meropenem/vaborbactam as monotherapy is generally sufficient based on evidence provided from TANGO II and real world evidence on file[16,17,34,35]. Depending on the severity of the infection, meropenem/vaborbactam may be given in combination with other antimicrobials, at the discretion of the clinicians involved, in which case additional treatment costs would need to be considered.

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