AWMSG Secretariat Assessment Report
Ceftolozane/tazobactam (Zerbaxa®▼) 1 g/0.5 g powder for concentrate for solution for infusion

This assessment report is based on evidence submitted by Merck Sharp & Dohme Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ceftolozane/tazobactam (Zerbaxa®▼) is indicated for the treatment of the following infections in adults: • Complicated intra-abdominal infections (cIAIs) • Acute pyelonephritis • Complicated urinary tract infections (cUTIs)[2]
Dosing	For cIAI the recommended dosage is 1 g ceftolozane/0.5 g tazobactam, administered as an intravenous infusion over one hour, every eight hours for 4–14 days. This regimen is to be used in combination with metronidazole when anaerobic pathogens are suspected. For acute pyelonephritis and cUTI the recommended dosage is 1 g ceftolozane/0.5 g tazobactam, administered as an intravenous infusion over one hour, every eight hours for seven days. Refer to the Summary of Product Characteristics (SPC) for further dosing information[2].
Marketing authorisation date	18 September 2015[3]

2.0 DECISION CONTEXT

2.1 Background

Complicated intra-abdominal infections (cIAIs) cover a wide range of clinical conditions that progress beyond the abdominal cavity and cause localised abscesses or diffuse peritonitis[4,5]. The most common microbial pathogens that result in cIAIs are *Escherichia coli*, members of the *Enterobacteriaceae* family, *Pseudomonas aeruginosa* and *Bacteroides fragilis*[4].

Complicated urinary tract infections (cUTIs) involve a UTI in the presence of functional or anatomical abnormalities of the urinary tract, such as indwelling catheters or urinary obstruction[4]. Pyelonephritis is an infection of one or both kidneys and is considered a subset of cUTI regardless of the presence of anatomic abnormalities[4,6]. The most common uropathogens in UTIs are *E. Coli*, *Klebsiella* species (spp), *Pseudomonas* spp, *Proteus* spp, *Enterobacter* spp, and *Citrobacter* spp[4]. Pathogens responsible for healthcare-associated cUTIs are commonly resistant to multiple antimicrobial agents[4].

Increased resistance to commonly prescribed antibiotics is a recognised global problem[4]. Extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* spp confer resistance to most β-lactam antimicrobial agents and are a growing issue: susceptibility data from the Study for Monitoring Antimicrobial Resistance Trends indicate that 18% of *E. coli* collected worldwide from 2005 to 2007 produced ESBLs[4].

Current evidence links inappropriate use of broad-spectrum antibiotics with the selection of antibiotic resistant bacteria such as ESBL-producing Gram negative bacteria, methicillin-resistant *Staphylococcus aureus* and the induction of *Clostridium difficile* infection[7].

Ceftolozane is a cephalosporin that inhibits essential penicillin-binding proteins of bacteria, resulting in inhibition of cell wall synthesis, cell wall deterioration and cell death[4]. Inclusion of tazobactam, a β-lactamase inhibitor, can potentially protect ceftolozane from hydrolysis by some β-lactamases[4].

The applicant company has requested that the All Wales Medicine Strategy Group (AWMSG) consider ceftolozane/tazobactam for use in a subgroup of patients within its licensed indication. The proposed subgroup is patients with a confirmed cIAI or cUTI (including acute pyelonephritis) following non-responsive first-line therapy due to resistance, i.e. where susceptibility has been confirmed and ceftolozane/tazobactam is considered the most clinically appropriate option[1].

2.2 Comparators

The comparators for cIAI included in the company submission were meropenem and piperacillin/tazobactam[1].

The comparators for cUTI (including acute pyelonephritis) included in the company submission were meropenem, levofloxacin, ciprofloxacin and piperacillin/tazobactam[1].

2.3 Guidance and related advice

- Public Health Wales Antimicrobial Resistance Programme Surveillance Unit. Antibacterial Resistance in Wales 2005–2014 (2015)[8].
- All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC). National Prescribing Indicators 2015–2016. Supporting information for prescribers (2015)[9].
- National Institute for Health and Care Excellence. Quality Standard 90. Urinary tract infection in adults (2015)[10].
- Welsh Analytical Prescribing Support Unit (WAPSU). National Prescribing Indicators. Analysis of antibacterial prescribing data to March 2014 (2014)[11].
- National Institute for Health and Care Excellence. Quality Standard 61. Infection prevention and control (2014)[12].
- Welsh Government. Code of practice for the prevention and control of healthcare associated infections (2014)[13,14].
- National Institute for Health and Care Excellence. Clinical Guideline 139. Infection: Prevention and control of healthcare-associated infections in primary and community care (2012)[15].
- Public Health Wales. Guidance for Antimicrobial Stewardship for Hospitals in Wales. Antimicrobial Stewardship: "Stay Smart – then Focus" (2011)[7].
- National Institute for Health and Care Excellence. Public Health Guidance 36. Prevention and control of healthcare-associated infections: quality improvement guide (2011)[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included evidence from two phase III studies: ASPECT-cIAI, designed to compare the efficacy and safety of ceftolozane/tazobactam with intravenous (IV) meropenem in adult patients with cIAI; and ASPECT-cUTI, designed to compare the efficacy and safety of ceftolozane/tazobactam with intravenous levofloxacin in adult patients with cUTI or acute pyelonephritis[1].

3.1 ASPECT-cIAI

The ASPECT-cIAI trial was a randomised, double-blind, placebo-controlled, multinational phase III non-inferiority trial that compared the efficacy and safety of ceftolozane/tazobactam with meropenem in patients with cIAI[1,4,17]. Patients included in the study were ≥ 18 years of age with clinical evidence of cIAI[17]. Operative or percutaneous drainage of an infectious focus was either planned or had been performed within 24 hours, confirming the presence of cIAI[17]. Patients were excluded if one of the following criteria applied: presence of cIAI managed by staged abdominal repair in which the fascia was not closed; low likelihood of adequate source control at surgery; severe renal failure (creatinine clearance of < 30 ml/minute); or use of systemic antimicrobial therapy for IAI for > 24 hours prior to the first dose of study drug (unless this treatment failed, defined by the need for additional intervention and persistent signs of ongoing infection with positive culture of intra-abdominal abscess or peritonitis fluid, despite > 48 hours of antimicrobial therapy)[1,4,17].

Patients (n = 993) were randomised 1:1 to receive either 1.5 g IV ceftolozane/tazobactam (1 g ceftolozane and 0.5 g tazobactam) with 0.5 g metronidazole every eight hours or 1 g IV meropenem with placebo every eight hours for 4–10 days[1,4,17]. Treatment could be continued for up to 14 days in patients who had one of the following: multiple abscesses, non-appendix-related diffuse peritonitis, failure of prior antimicrobial therapy, or hospital acquired infection[17].

The primary outcome of the study was clinical cure rate of the microbiological intent-to-treat (MITT; see glossary) population (n = 806) at test-of-cure (TOC) visit (24–32 days after start of therapy)[1,17]. Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antimicrobials or interventions were required. Clinical failure included death due to cIAI prior to the TOC visit, persisting or recurrent infection requiring additional antimicrobials for ongoing symptoms of IAI, and/or surgical site infection. To determine non-inferiority, a two-sided 95% confidence interval (CI) for the weighted difference in cure rates between ceftolozane/tazobactam with metronidazole (n = 389) and meropenem (n = 417) in the MITT population was calculated. If the lower limit of the 95% CI was above −10 percentage points, non-inferiority was claimed. As shown in Table 1, based on this analysis non-inferiority was met in the MITT group.

ESBL-producing *Enterobacteriaceae* isolates were identified in 29 patients in each MITT treatment arm. Per pathogen clinical cure rates for ESBL-producing *Enterobacteriaceae* spp were 95.8% (23/24) in the ceftolozane/tazobactam plus metronidazole group and 88.5% (23/26) in the meropenem group[17].

Table 1. Primary and secondary endpoints of the ASPECT-cIAI trial at TOC visit[1,17]

	Ceftolozane/tazobactam plus metronidazole n (%)	Meropenem n (%)	Difference (%, 95% CI)
MITT population	**N = 389**	**N = 417**	
Cure	323 (83.0)	364 (87.3)	−4.2 (−8.91–0.54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
CI: confidence interval; MITT: microbiological intent-to-treat.			

3.2 ASPECT-cUTI

ASPECT-cUTI was a randomised, double-blind, placebo-controlled, multinational phase III non-inferiority trial comparing the efficacy and safety of

ceftolozane/tazobactam and levofloxacin in patients with cUTI (including patients with acute pyelonephritis)[1,4,18]. Patients included in the study were ≥ 18 years of age, had pyuria, a diagnosis of pyelonephritis or complicated lower-urinary-tract infections (cLUTIs), had been admitted to hospital for IV antibiotic therapy and had a pre-treatment baseline urine culture specimen obtained within 36 hours before the first dose of the study drug[1,18]. Exclusion criteria included patients with concomitant infections that required treatment with non-study antibacterial agents that had Gram-negative activity, an infection at baseline that the investigator determined would require more than a seven day course of treatment, or severe renal failure[1,18].

Patients (n = 1,083) were randomised in a 1:1 ratio to receive 1.5 g IV ceftolozane/tazobactam (1 g ceftolozane and 0.5 g tazobactam) every eight hours or 750 mg IV levofloxacin once daily for seven days[1,18]. Double dummy saline infusions were used to mask treatments.

The primary outcome of the study was the composite cure rate (combined microbiological eradication and clinical cure; see glossary) of the microbiological modified intention-to-treat (mMITT; see glossary) population (n = 800) at TOC visit (5–9 days after treatment)[1,18]. Clinical failure was defined as the presence of one or more signs or symptoms of cLUTIs or pyelonephritis requiring additional antibiotics, or an adverse event leading to premature discontinuation of the study drug and the initiation of additional antibiotic therapy[18].

To determine non-inferiority, a two-sided 95% CI for the weighted difference in composite cure rates between ceftolozane/tazobactam (n = 398) and levofloxacin (n = 402) in the mMITT population was calculated. If the lower limit of the 95% CI was above −10 percentage points, non-inferiority was claimed. Based on this analysis, non-inferiority was met in the mMITT group (Table 2). Results for the mMITT population also suggest that ceftolozane/tazobactam is more effective than levofloxacin in terms of composite cure and microbiological eradication rates; the results for clinical cure also favour ceftolozane/tazobactam, but the difference between treatments was not statistically significant.

Table 2. Primary and secondary endpoints of the ASPECT-cUTI trial at TOC visit[1,18]

	Ceftolozane/tazobactam n (%)	Levofloxacin n (%)	Difference (%, 95% CI)
mMITT population	**N = 398**	**N = 402**	
Composite cure	306 (76.9)	275 (68.4)	8.5 (2.3–14.6)
Microbiological eradication	320 (80.4)	290 (72.1)	8.3 (2.4–14.1)
Clinical cure	366 (92.0)	356 (88.6)	3.4 (−0.8–7.6)
CI: confidence interval; mMITT: microbiological modified intention-to-treat.			

Of the 800 patients in the mMITT population, 656 (82.0%) had pyelonephritis and 144 (18.0%) had cLUTI[18]. Composite cure was reported within each subgroup, and non-inferiority of ceftolozane/tazobactam to levofloxacin was demonstrated in both disease populations (Table 3). Results for the cLUTI subgroup suggest significantly improved composite cure rates with ceftolozane/tazobactam compared to levofloxacin, but the difference between treatments was not statistically significant for the pyelonephritis subgroup[18].

Table 3. Primary outcome results of the ASPECT-cUTI trial, by diagnosis subgroup[18]

	Diagnosis	Number of patients/total (%)		Difference (95% CI)
		Ceftolozane/tazobactam	Levofloxacin	
mMITT population				
Composite cure at TOC visit (5–9 days after therapy)	cLUTI	47/70 (67.1%)	35/74 (47.3%)	19.8 (3.7–34.6)
	Pyelonephritis	259/328 (79.0%)	240/328 (73.2%)	5.8 (−0.7–12.3)

CI: confidence interval; mMITT: microbiological modified intention-to-treat; cLUTI: complicated-lower-urinary-tract-infection; TOC: test-of-cure.

In the mMITT population, 100 patients in the ceftolozane/tazobactam treatment arm and 112 patients in the levofloxacin treatment arm had levofloxacin-resistant uropathogens isolated from baseline culture[18]. At the primary endpoint (TOC visit), composite cure was achieved in 60% (60/100) and 39.3% (44/112) of these patients in the ceftolozane/tazobactam and levofloxacin treatment arms, respectively[18]. Of the baseline pathogens isolated from the mMITT population 8.4% (65/776) were resistant to ceftolozane/tazobactam: 2.7% (20/731) of Gram-negative and 100% (45/45) of Gram-positive isolates were resistant. ESBL-producing uropathogens were isolated in 61 patients from the ceftolozane/tazobactam treatment arm and 57 patients from the levofloxacin treatment arm. Composite cure rates of ESBL-positive patients were 62.3% (38/61) and 35.1% (20/57) for ceftolozane/tazobactam and the levofloxacin treatment groups, respectively (percentage difference 27.2, 95% CI 9.2–42.9)[18].

3.3 Systematic review and network meta-analysis

To address the lack of direct comparative evidence, the company included two systematic reviews (SRs) and network meta-analyses (NMAs) designed to estimate the relative efficacy and safety of ceftolozane/tazobactam compared to other antibiotic treatments for cIAI and cUTI (including pyelonephritis)[1].

[Commercial in confidence information removed.]

3.4 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) considered that there were no major concerns regarding safety in the use of ceftolozane/tazobactam[4]. The primary data included to support the safety of ceftolozane/tazobactam come from the ASPECT-cIAI and ASPECT-cUTI phase III trials[1,4]. Due to differences in administration, comparators and patient characteristics the safety data were reviewed by indication as well as overall[4].

Cephalosporins are associated with a risk of developing *C. difficile* associated diarrhoea[18]. The rate of *C. difficile* infection was low in both studies, but two drug-related *C. difficile* serious AEs (SAEs) were recorded in the ASPECT-cIAI study (one in each treatment arm) and two in the ceftolozane/tazobactam arm in ASPECT-cUTI study: incidents of events relating to *C. difficile* were considered low and comparable between treatments[4,17,18].

3.4.1 ASPECT-cIAI

In the ASPECT-cIAI trial, overall incidence of treatment-emergent adverse events (TEAEs) was similar between ceftolozane/tazobactam plus metronidazole and meropenem (44% and 42.7%, respectively[1,4]). Overall rates did not increase with duration of therapy and the majority of TEAEs recorded were mild to moderate in severity[4]. The most common TEAEs (reported in ≥ 2% of patients) were nausea,

diarrhoea, vomiting and pyrexia, of which vomiting was reported less frequently in the ceftolozane/tazobactam with metronidazole group than in the meropenem group. Overall, more patients treated with ceftolozane/tazobactam and metronidazole reported gastrointestinal TEAEs compared with patients treated with meropenem (20.3% versus 16.9%, respectively). SAEs, discontinuations and mortality were not significantly different between the two treatment arms[1,4].

3.4.2 ASPECT-cUTI

In the ASPECT-cUTI trial the incidence of TEAEs was similar between ceftolozane/tazobactam and levofloxacin (34.7% and 34.4%, respectively)[1,4]. Overall rates of TEAEs did not increase with duration of therapy and the majority of TEAEs recorded were mild to moderate in severity. The most common TEAEs (recorded in ≥ 2% of patients) were headache, constipation and nausea. Overall, a similar proportion of patients treated with ceftolozane/tazobactam reported gastrointestinal TEAEs compared with patients treated with levofloxacin (11.8% versus 11.4%, respectively)[1,4].

3.5 AWTTC critique

- The applicant company suggests that ceftolozane/tazobactam should be considered for use in a subgroup of patients within its licensed indication. The subgroup of interest is patients with confirmed cIAI or cUTI (including acute pyelonephritis) following non-responsive first-line therapy due to resistance (where susceptibility of ceftolozane/tazobactam has been confirmed)[1]. The evidence to support the clinical effectiveness of ceftolozane/tazobactam is not specific to this subgroup of patients. For the majority of patients included in the ASPECT-cIAI and ASPECT-cUTI trials ceftolozane/tazobactam was given as a first-line treatment[1,17,18]. Furthermore, the NMAs included trials investigating the use of antibiotics in any patients with cUTI or cIAI: line of therapy was not specified. The company has acknowledged this discrepancy between the clinical evidence and the proposed positioning of ceftolozane/tazobactam sought by their submission[1]. The company claim that line of therapy and/or disease severity would not be expected to have an impact on efficacy; this conclusion is based on company sought clinical expert opinion[1].
- It is recommended that broad spectrum antibiotics such as cephalosporins should be avoided unless there are clear indications for their use[7]. Public Health Wales guidelines recommend that broad spectrum antibiotics are used within one hour of diagnosis where there is urgent need to start treatment (severe or life threatening infection) particularly when the source of infection is unknown. Microbiological investigation (e.g. susceptibility testing) can lead to prompt de-escalation of any broad spectrum therapy and more tailored treatment[7]. This conflicts with the place in therapy that the company have proposed for ceftolozane/tazobactam[1].
- The inclusion of tazobactam broadens the application of ceftolozane to include antimicrobial-resistant bacteria, such as ESBL-producing *Enterobacteriaceae* spp[1,4]. Both ASPECT-cIAI and ASPECT-cUTI included data on a subgroup of patients with ESBL-producing isolates: overall these subgroups reported improved cure rates with ceftolozane/tazobactam (plus metronidazole in ASPECT-cIAI) compared against the respective comparator[1,17,18]. However, this evidence is taken from small patient subgroups: 7.2% of patients in the ASPECT-cIAI trial MITT population (58 patients) and 14.8% of patients (118 patients) in the ASPECT-cUTI trial mMITT population were ESBL-positive[1,17,18]. No statistical analysis of comparative efficacy was provided for this subgroup, possibly due to a lack of statistical power to detect a difference in such a small population.
- No UK or Welsh patients were included in either the ASPECT-cIAI or ASPECT-cUTI trials[1,17,18]. The applicant company state that the demographics of the study populations could be considered broadly comparable to the Welsh

healthcare setting. However, variation in treatment pathways for cIAI and cUTI across European healthcare systems means that the care received by patients in addition to, or prior to, ceftolozane/tazobactam may differ from the Welsh healthcare setting. There was a higher proportion of females with cUTI, which is reflective of patients that would present in the clinical setting[1].

- Due to similar pathophysiology and treatment approach, the company included patients with acute pyelonephritis in the cUTI cohort[1]. In the mMITT population of the ASPECT-cUTI trial patients had a primary diagnosis of pyelonephritis (82.0%) or lower-urinary-tract infection (18.0%)[18]. Current CHMP guidelines recommend that cUTI and pyelonephritis patients should be stratified at enrolment in clinical trials and the proportion with pyelonephritis should be limited[19]. However, the studies included in this submission predate current CHMP guidelines, and the approach of grouping cUTI and pyelonephritis patients together was consistent with CHMP guidelines available at the time and validated by clinicians in an advisory board (company data on file, not verified)[1,4].
- The most appropriate comparators for the indications in this submission are difficult to determine: several different guidelines are in use within the Welsh Health Boards. Clinical expert opinion sought by AWTTC suggests that the most appropriate comparators for the subgroup of patients highlighted by the company are carbapenems (imipenem and meropenem) and piperacillin/tazobactam. For the treatment of both cIAI and cUTI, the company has suggested that ceftolozane/tazobactam will primarily displace use of meropenem following confirmed susceptibility testing[1].
- The safety profile of ceftolozane/tazobactam versus levofloxacin was broadly comparable[4]. However, the levofloxacin dose used in the ASPECT-cUTI trial was 750 mg; this is the licensed dose in the USA and is higher than the recommended licensed dose in the UK (500 mg)[20]. Higher dosing carries the potential of increased or more severe side effects. In addition, for cUTI the SPC recommends that a combination of IV and oral levofloxacin be used, with patients normally switching to oral treatment after 2–4 days[20], whereas patients included in ASPECT cUTI received IV levofloxacin throughout the trial (for seven days)[18].
- To address the lack of direct comparative evidence between ceftolozane/tazobactam and the outlined comparators, the applicant company included NMAs to compare the efficacy and safety of ceftolozane/tazobactam with alternative antibiotics in both cIAI and cUTI[1]. No detail was provided on the search terms used or the bibliographic databases searched in the SRs, and it is therefore unclear whether comprehensive attempts have been made to identify evidence to inform the NMAs. Both NMAs included trials of antibiotics used at any point in therapy; results were not restricted to the company's proposed use of ceftolozane/tazobactam after a lack of response to first line therapy due to resistance. The authors of the analyses concluded that ceftolozane/tazobactam appeared to have broadly comparable efficacy and safety outcomes with the outlined comparators[1]. However, the evidence base identified by the SRs conducted to inform the NMAs was limited, and many of the effect estimates have very wide credible intervals, indicating considerable uncertainty, and should therefore be interpreted with caution[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission included, as the base case, a cost-minimisation analysis (CMA) of ceftolozane/tazobactam with metronidazole versus meropenem in patients

with cIAIs and a CMA of ceftolozane/tazobactam versus meropenem in patients with cUTIs[1]. The company estimates that, if recommended, ceftolozane/tazobactam would be expected to displace a level of meropenem usage in both cIAIs and cUTIs, following confirmed susceptibility testing[1].

Two separate simple decision analytic models were used to estimate the difference in cost between ceftolozane/tazobactam treatment versus meropenem treatment for both cIAIs and cUTIs. In both models it is assumed that ceftolozane/tazobactam and the comparators are used in a second-line context, i.e. after culture and sensitivity results have confirmed that the bacterial organism is resistant to or non-susceptible to the initial treatment. Since the indication for ceftolozane/tazobactam covers adults with cIAIs, acute pyelonephritis or cUTIs, the modelled scenario reflects a subset of the licensed population. Patients, who are assumed to be hospitalised, enter the models when a change in antibiotic is in progress and the bacterial organism has been confirmed as susceptible to ceftolozane/tazobactam. In the cIAI model, patients are treated with either a combination of IV ceftolozane/tazobactam with metronidazole or IV meropenem. This differs to the advice given in the SPC, which states that ceftolozane/tazobactam should be used in combination with metronidazole specifically where anaerobic pathogens are suspected. In the cUTI model, patients are treated with either a combination of IV ceftolozane/tazobactam or with IV meropenem[1].

The model adopts an NHS/Personal Social Services perspective and a time horizon corresponding to the duration of antibiotic treatment. Costs for a full course of antibiotic treatment were calculated as the sum of the costs of medicine acquisition, medicine administration and monitoring. All antibiotics used require reconstitution for IV administration. Costs were dependent on the dosing regimens of the antibiotics. Administration costs include the cost of reconstitution fluids, pharmacist and nursing time to prepare the infusion, and nursing time to administer the infusion[21,22]. Unit personnel costs were derived from Personal Social Services Research Unit costs for the UK (2015)[23]. The SPC for meropenem advises close monitoring of hepatic function during treatment[24]. Monitoring costs were not included in the base case but were included in a sensitivity analysis. No discounting was applied given the short time horizon of the model.

The company conducted scenario/sensitivity analyses as follows:
For cIAIs:

- Varying the duration of ceftolozane/tazobactam (2 and 15 days, reflecting the minimum and maximum durations of treatment in the ASPECT-cIAI trial[2])
- Including hepatic monitoring for meropenem as per SPC[24]
- Using piperacillin/tazobactam as a comparator

For cUTIs:

- Including hepatic monitoring for meropenem as per SPC[24]
- Using ciprofloxacin as a comparator
- Using levofloxacin as a comparator
- Using piperacillin/tazobactam as a comparator

4.1.2 Results

The results of the base case analysis and scenario/sensitivity analyses for cIAIs and cUTIs are given in Tables 4 and 5 respectively. Ceftolozane/tazobactam is more costly in the base cases and in the majority of scenario/sensitivity analyses conducted.

Table 4. Results of the base case analysis and scenario/sensitivity analyses for cIAIs.

Scenario	Costs	Ceftolozane /tazobactam+ metronidazole	Comparator	Difference	Plausibility
Base case					
7 days of treatment with ceftolozane /tazobactam + metronidazole* versus 7 days meropenem	Medicine acquisition costs	£1,472.94	£336.00	£1,136.94	
	Administration costs	£812.05	£701.59	£110.46	
	Total costs	£2,284.99	£1,037.59	**£1,247.40**	
Sensitivity analysis: 2 days ceftolozane/tazobactam + metronidazole					
2 days of treatment with ceftolozane /tazobactam + metronidazole* versus 7 days meropenem	Medicine acquisition costs	£420.84	£336.00	£84.84	Minimum duration in ASPECT-cIAI trial. therefore represents a best case scenario in terms of ceftolozane/ tazobactam costs.
	Administration costs	£232.01	£701.59	−£469.57	
	Hospitalisation costs†	£826.00	£2,891.00	−£2,065.00	
	Total costs	£1,478.85	£3,928.59	**−£2,449.73**	
Sensitivity analysis: 15 days ceftolozane/tazobactam + metronidazole					
15 days of treatment with ceftolozane /tazobactam + metronidazole* versus 7 days meropenem	Medicine acquisition costs	£3,156.30	£336.00	£2,820.30	Maximum duration in ASPECT-cIAI trial.-therefore represents a worst case scenario in terms of ceftolozane/ tazobactam costs.
	Administration costs	£1,740.10	£701.59	£1,038.51	
	Hospitalisation costs†	£6,195.00	£2,891.00	£3,304.00	
	Total costs	£11,091.40	£3,928.59	**£7,162.81**	
Sensitivity analysis: includes hepatic monitoring for meropenem					
7 days of treatment with ceftolozane /tazobactam + metronidazole* versus 7 days meropenem.	Medicine acquisition costs	£1,472.94	£336.00	£1,136.94	Highly plausible alternative to the base case given that this scenario represents standard practice[24].
	Administration & monitoring costs	£812.05	£726.48	£85.57	
	Total costs	£2,284.99	£1,062.48	**£1,222.51**	
Scenario analysis: versus piperacillin/tazobactam					
7 days of treatment with ceftolozane /tazobactam + metronidazole* versus 7 days with piperacillin /tazobactam	Medicine acquisition costs	£1,472.94	£43.30	£1,429.64	The dose used is consistent with the SPC [25]
	Administration costs	£812.05.	£629.98	£182.07	
	Total costs	£2,284.99	£673.28	**£1,611.71**	

*all patients with cIAI were assumed to be given metronidazole in addition to ceftolozane/tazobactam, although the SPC specifies that metronidazole be used in combination with ceftolozane/tazobactam when anaerobic pathogens are suspected[2]
† hospitalisation costs included for scenarios which did not have durations of 7 days

Table 5. Results of the base case analysis and scenario/sensitivity analyses for cUTIs.

Scenario	Costs	Ceftolozane /tazobactam	Comparator	Difference	Plausibility
Base case					
7 days of treatment with ceftolozane /tazobactam versus 7 days meropenem	Medicine acquisition costs	£1,407.63	£336.00	£1071.63	
	Administration costs	£528.97	£701.59	−£172.62	
	Total costs	£1,936.60	£1,037.59	**£899.01**	
Sensitivity analysis: includes hepatic monitoring for meropenem					
7 days of treatment with ceftolozane /tazobactam versus 7 days meropenem. Includes hepatic monitoring costs for meropenem	Medicine acquisition costs	£1,407.63	£336.00	£1,071.63	Highly plausible alternative to the base case given that this scenario represents standard practice[24].
	Administration & monitoring costs	£528.97	£726.48	−£197.51	
	Total costs	£1,936.60	£1,062.48	**£874.12**	
Scenario analysis: versus 10 days ciprofloxacin					
7 days of treatment with ceftolozane /tazobactam versus 10 days ciprofloxacin	Medicine acquisition costs	£1,407.63	£600.00	£807.63	The 10 day duration is typical of the studies included in the NMA.
	Administration costs	£528.97	£506.70	22.27	
	Hospitalisation costs†	£2,891.00	£4,130	−£1,239	
	Total costs	£4,827.60	£5,236.70	**−£409.10**	
Scenario analysis: versus 21 days ciprofloxacin					
7 days of treatment with ceftolozane /tazobactam versus 21 days ciprofloxacin	Medicine acquisition costs	£1,407.63	£1,260.00	£147.63	SPC has treatment duration of 7–21 days. No studies in the NMA had a ciprofloxacin duration beyond 10 days .Less plausible scenario. Extended duration possibly biases in the company's
	Administration costs	£528.97	£1,064.07	−£535.10	
	Hospitalisation costs†	£2,891.00	£8,673.00	−£5,782.00	
	Total costs	£4,827.60	£10,997.07	**−£6,169.47**	

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Scenario analysis: versus 7 days levofloxacin					
7 days of treatment with ceftolozane /tazobactam versus 7 days levofloxacin	Medicine acquisition costs	£1,407.63	£175.70	£1,231.93	Company state that based on clinical expert opinion levofloxacin was not considered to be current clinical practice in NHS Wales for cUTIs.
	Administration & monitoring costs	£528.97	£133.56	£395.41	
	Total costs	£1,936.60	£309.26	**£1,627.34**	
Scenario analysis: versus 7 days piperacillin/tazobactam					
7 days of treatment with ceftolozane /tazobactam versus 7 days with piperacillin /tazobactam	Medicine acquisition costs	£1,407.63	£43.30	£1,364.33	The dose used is consistent with the SPC[25]
	Administration & monitoring costs	£528.97	£629.98	−£101.01	
	Total costs	£1,936.60	£673.28	**£1,263.22**	
† hospitalisation costs included for scenarios which did not have durations of 7 days					

4.1.3 AWTTC critique

The reliability of the CMA is dependent on the extent to which ceftolozane/tazobactam is considered to be therapeutically equivalent to the comparators. The company justified the use of a CMA, as opposed to a cost-utility analysis (CUA), on the basis that the supporting trials, ASPECT-cIAI and ASPECT-cUTI reported non-inferiority for ceftolozane/tazobactam versus meropenem and non-inferiority for ceftolozane /tazobactam versus levofloxacin respectively[17,18]. NMAs of studies in patients with both cIAIs and cUTIs showed broadly comparable efficacy and safety of ceftolozane/tazobactam versus other antibiotics. The company confirms that the approach used was validated by two UK-based consultants and by 17 Welsh antimicrobial specialists[1].

Strengths and limitations of the economic analysis include:

- The model reflects the correct patient population and adopts an appropriate perspective and time horizon.
- The company's justification for using CMA is not entirely convincing, given that the ASPECT-cIAI study concluded non-inferiority, which does not infer equivalence. Furthermore, although the NMA for cUTIs suggests that ceftolozane/tazobactam is broadly comparable to meropenem; in some instances ceftolozane/tazobactam was found to be non-inferior, in others superior. Given that health outcomes are clearly not equivalent between the two treatments, a CUA would arguably have been a better approach to evaluation in this instance.
- The SPCs for IV formulations of ciprofloxacin[26], metronidazole[27] and levofloxacin[20] all advise on switching to oral treatment as soon as feasible, depending on the clinical situation. These scenarios, which may be associated with reduced costs, have not been considered.
- There is uncertainty around which comparators are most reflective of current practice in Wales; the company has tried to address this by conducting scenario analyses including comparators other than meropenem.

- Use of NMAs introduces uncertainty in determining the relative efficacy and safety of ceftolozane/tazobactam versus the comparators. This uncertainty is further compounded by use of a fixed effects rather than a random effects model [28].

4.2 Review of published evidence on cost-effectiveness

A literature search by AWTTC identified a conference paper detailing a cost-utility analysis comparing ceftolozane/tazobactam with piperacillin/tazobactam at different levels of resistance to four common pathogens in patients with cIAIs[29]. Results showed that at 0% resistance piperacillin/tazobactam was dominant. However, as the resistance to piperacillin/tazobactam was increased the difference in hospital days saved and the difference in quality-adjusted life years (QALYs) for the ceftolozane/tazobactam arm gradually increased: ceftolozane/tazobactam became cost saving at ≥ 4% resistance. Discounted differences in the total QALY gains for ceftolozane/tazobactam versus piperacillin/tazobactam for a cohort of 10,000 patients were 0, 78, 146, 219, 289 and 356 at resistances of 0%, 1%, 2%, 3%, 4% and 5% respectively. These QALY differences reflect varied effects between antibiotics, which suggest that a cost utility analysis may have been a more suitable approach to evaluation than a CMA in this instance. No studies were found comparing ceftolozane/tazobactam with meropenem.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company report that due to recurrent infections and non-uniform coding it was not possible to determine the number of eligible patients using NHS Wales Informatics Service Patient Episode Database for Wales (PEDW) statistics data alone[30]. Due to the possibility of recurrent infections, the company estimated the number of infections rather than the number of infected patients. The company commissioned research using 17 Welsh clinicians, microbiologists and pharmacists to use PEDW data together with their clinical experience to estimate the annual number of infections treated in NHS Wales. The numbers of infections, for which meropenem would be prescribed annually, following a change in antibiotic treatment after susceptibility testing, were estimated as 1,459 cIAIs and 1,426 cUTIs. The company have estimated the uptake of ceftolozane/tazobactam based on market research as a proportion of the meropenem usage ranging from 2% in year one to 8% in year five for both cIAIs and cUTIs.

5.1.2 Results

The budget impact is presented in Table 6. The company estimates that introduction of ceftolozane/tazobactam would lead to an overall cost of £62,246 in year one, increasing to £248,433 in year five. This estimate incorporates cost differences resulting from the displacement of meropenem. The company carried out one sensitivity analysis including the cost of hepatic monitoring for meropenem; this reduced the overall cost slightly to £60,802 in year one, increasing to £242,683 in year five.

Table 6. Company-reported costs associated with use of ceftolozane/tazobactam (displacing meropenem) for the treatment of cIAIs and cUTIs

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients***** (Indication covered in this submission)	2,885	2,885	2,885	2,885	2,885
Uptake (%)	2%	4%	6%	7%	8%
Treated patients*	58	115	174	202	231
Net medicine acquisition costs	£64,409	£127,025	£192,211	£223,131	£255,188
Net administration costs[†]	−£1,803	−£3,433	−£5,125	−£5,995	−£6,755
Overall net cost	**£62,246**	**£123,593**	**£187,086**	**£217,136**	**£248,433**
*includes recurrent treatment in some patients; [†]excludes hepatic monitoring for meropenem					

5.1.3 AWTTC critique

- It was not possible to verify the company's annual figures for the number of cIAIs and cUTIs. However, the company has used Welsh experts to estimate the number of infections and the proportion of these for which meropenem would be prescribed, following the results of confirmed susceptibility testing in patients who have failed first line (typically empiric therapy), for the indication under consideration.
- The net cost is highly sensitive to projected uptake, which the company has estimated from market research data.
- The company has included the cost of hepatic monitoring for meropenem treatment as a sensitivity analysis. Since hepatic monitoring is advised in the SPC it is likely that this represents a more realistic scenario[24].
- The budget impact model is limited in terms of the displaced medicines it incorporates (meropenem is the only comparator considered). Further sensitivity analyses would have been beneficial to explore the impact of displacing other possible comparators.

5.2 Comparative unit costs

Acquisition costs for antibiotic treatment of cIAIs and cUTIs are given in Table 7.

Table 7. Examples of medicine acquisition costs for treatment of cIAIs and cUTIs

Regimens	Unit cost	Example doses	Approximate costs per patient
Ceftolozane/tazobactam (Zerbaxa®▼)1 g/0.5 g powder for infusion	£67.03 for 1 g/0.5 g in vial[31]	For cIAIs 1 g/0.5 g every 8 hours for 4–14 days	£804–£2,815
	£67.03 for 1 g/0.5 g in vial[31]	For cUTIs 1 g/0.5 g every 8 hours for 7 days	£1,408
Metronidazole 500 mg/100 ml infusion	£3.10 for 500 mg/ 100ml bag[32]	For anaerobic infections 500 mg every 8 hours for 7 days	£65
Meropenem IV 1 g powder for solution for injection vials	£15.35 for 1 g in vial[32]	For cIAIs and cUTIs 1 g every 8 hours for 7 days	£322
Piperacillin/tazobactam 2 g/0.25 g powder for solution for infusion	£1.03 for 2.25 g vial[32]	For cIAIs and cUTIs 4 g/0.5 g every 8 hours for 4–14 days	£26–£91
Levofloxacin 5 mg/ml solution for infusion	£25.10 for 500 mg in 100ml bag[32]	For cUTIs 500 mg* once daily for 7–14 days	£176–£351
Ciprofloxacin 2 mg/ml solution for infusion	£20.00 for 400 mg/200 ml bag[31]	For cUTIs 400 mg twice or three times daily for 7–21 days	£280–£1,260

Not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details[2,20,24-27].
Costs are based on British National Formulary (BNF) and Monthly Index of Medical Specialities (MIMS) list prices as of April 2016[31,32].
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
*SPC gives dose of 500 mg once daily but ASPECT-cUTI and two other studies used in NMA used 750mg daily

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, ceftolozane/tazobactam (Zerbaxa®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that ceftolozane/tazobactam (Zerbaxa®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 17 March 2016
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Composite cure
The combined microbiological eradication and clinical cure in the ASPECT-cUTI trial. Microbiological eradication was a TOC urine culture with fewer than 10^4 colony-forming units per ml of the baseline uropathogen. Clinical cure was complete resolution, substantial improvement, or return to preinfection signs and symptoms of cLUTIs or pyelonephritis, without the need for additional antibiotic therapy.

Microbiological intent-to-treat (MITT)
All randomised patients of the ASPECT-cIAI trial with at least one baseline pathogen identified in abscess or peritonitis fluid, regardless of susceptibility to study drug. Patients with missing clinical outcome data or indeterminate responses were included in the MITT population and considered to have failed treatment.

Microbial modified intent-to-treat (mMITT)
All randomised patients of the ASPECT-cUTI trial who received at least one dose of the study drug with a positive baseline urine culture. Patients with missing or indeterminate outcome data were included in the mMITT population and classified at treatment failures.

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