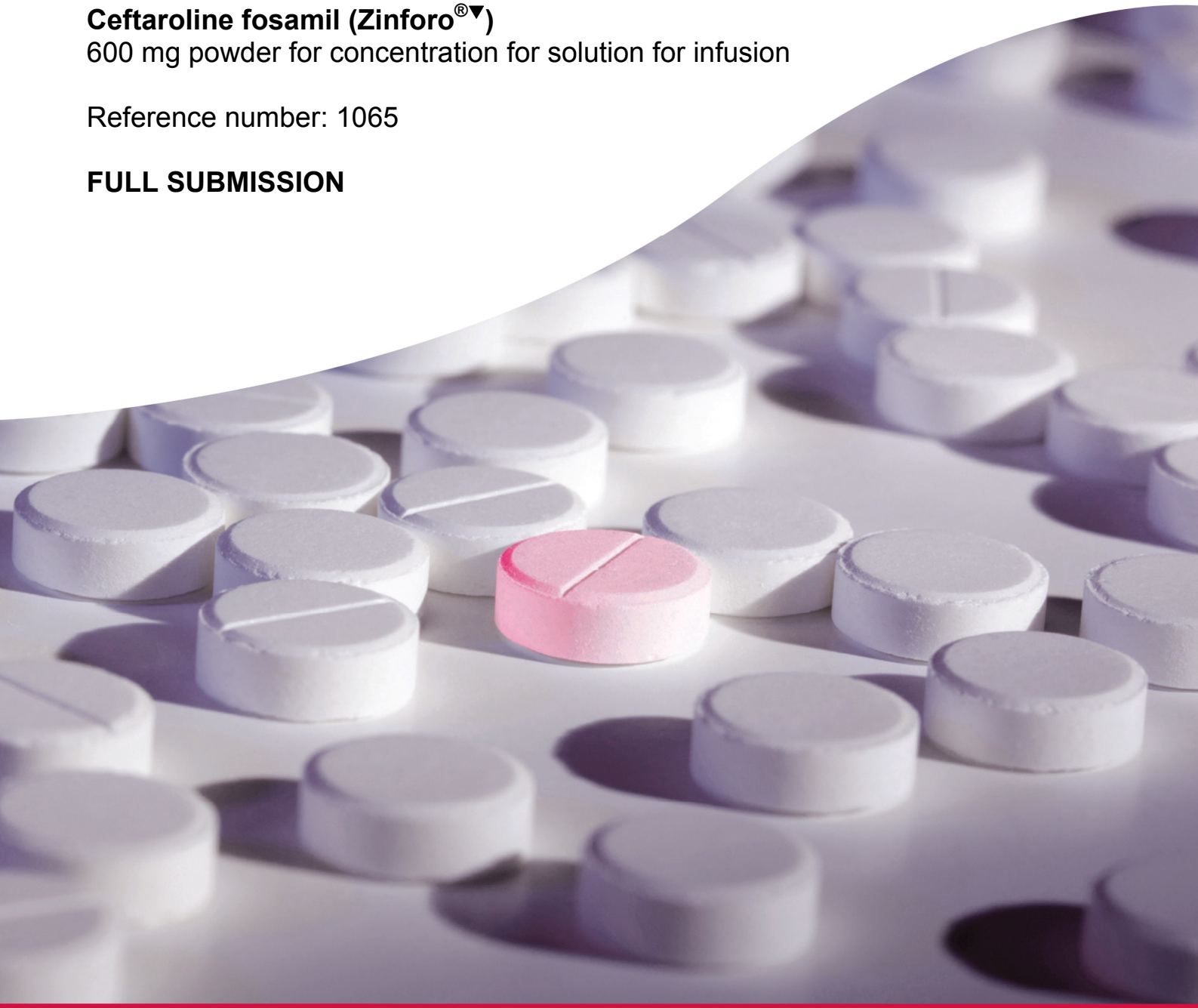
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

# AWMSG SECRETARIAT ASSESSMENT REPORT

**Ceftaroline fosamil (Zinforo®▼)**
600 mg powder for concentration for solution for infusion

Reference number: 1065

**FULL SUBMISSION**



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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# AWMSG Secretariat Assessment Report
# Ceftaroline fosamil (Zinforo®▼) 600 mg powder for concentration for solution for infusion

This assessment report is based on evidence submitted by AstraZeneca UK Ltd on 15 January 2013[1].

## 1.0 PRODUCT DETAILS

| | |
|---|---|
| **Licensed indication under consideration** | Ceftaroline fosamil (Zinforo®▼) is indicated in adults for the treatment of the following infections:<br>• Complicated skin and soft tissue infections (cSSTI)<br>• Community-acquired pneumonia (CAP)[2] |
| **Dosing** | For the treatment of cSSTI and CAP, the recommended dose is 600 mg administered every 12 hours by intravenous infusion over 60 minutes. The recommended treatment duration for cSSTI is 5–14 days and the recommended duration of treatment for CAP is 5–7 days. For patients with renal impairment, the dose should be adjusted where creatinine clearance is ≤ 50 ml/min[2]. |
| **Marketing authorisation date** | 23 August 2012[1]. |

## 2.0 DECISION CONTEXT

### 2.1 Background

Both complicated skin and soft tissue infections (cSSTIs) and community-acquired pneumonia (CAP) are frequently caused by Gram-positive organisms such as *Staphylococcus aureus* and beta-haemolytic streptococci, although other Gram-positive and Gram-negative organisms have also been implicated[3–5]. Owing to the threat posed by antimicrobial resistance, there is a need for new antimicrobial agents to treat and manage serious bacterial infections. Ceftaroline fosamil (Zinforo®▼) is an oxyimino cephalosporin, which has been found to be active *in vitro* against the pathogens frequently associated with the aforementioned conditions[3].

AWMSG appraise a medicine within the whole of its licensed indication. However, the applicant company has requested that the All Wales Medicines Strategy Group (AWMSG) consider ceftaroline fosamil as an alternative intravenous (IV) treatment option for cSSTI patients in Wales where methicillin-resistant *S. aureus* (MRSA) is suspected in the following settings:

- For infections caused by Gram-positive pathogens only where vancomycin IV or teicoplanin IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV or linezolid IV is normally used.
- For mixed infections caused by common Gram-positive and Gram-negative pathogens (excluding extended-spectrum beta-lactamase [ESBL]-producing organisms, AmpC-producing organisms and non-fermenter Gram-negative organisms, such as *Pseudomonas aeruginosa*), where vancomycin IV in combination with co-amoxiclav IV or teicoplanin IV in combination with co-amoxiclav IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV in combination with co-amoxiclav IV or linezolid IV in combination with co-amoxiclav IV is normally used[1].

The applicant company propose that the use of ceftaroline fosamil would be directed by infectious disease specialists only (microbiologists and infectious disease physicians) and in line with antimicrobial stewardship policies in Wales. The clinical and cost-effectiveness evidence provided in the company submission focuses on the use of ceftaroline fosamil in these settings.

Skin and soft tissue infections (SSTIs) affect the epidermis and subcutaneous tissues leading either to a local or systemic host response[4]. cSSTIs are those which are associated with deep soft tissue, or infections which require surgical intervention, or those in which an underlying disease state complicates the response to treatment[4]. The company estimate that, in Wales, 1,607 patients suffer from cSSTI each year[1] (see Section 5 for further information). MRSA-associated infection is an important healthcare issue; MRSA remains endemic in many UK hospitals, as well as being prevalent in the community[3,6]. New antimicrobial agents have become available in the last decade, but some resistance to these is already evident[3]. At present, there is a lack of licensed beta-lactam antibiotics with a clinically reliable effect against MRSA[3].

### 2.2 Comparators

For cSSTIs where MRSA is suspected, the comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Vancomycin
- Teicoplanin
- Daptomycin
- Linezolid

AWTTC also requested comparators covering the broader uses of ceftaroline fosamil within its full licensed indication (i.e. CAP and cSSTIs without MRSA), but these disease areas are not covered by the company submission.

### 2.3 Guidance and related advice

- Coia et al. Guidelines for the control and prevention of methicillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities (2006)[6].
- Gould et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the United Kingdom (2009)[7].

## 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The evidence provided in the company submission focuses on the use of ceftaroline fosamil for the treatment of cSSTI patients where MRSA is suspected, in the settings described in Section 2.1. This included details from two pivotal phase III trials, CANVAS 1 and CANVAS 2, which described the efficacy and safety of ceftaroline fosamil for the treatment of cSSTIs[8–10]. Due to their identical design, these studies will be described together. A retrospective analysis of the CANVAS trials, conducted in order to assess early clinical response in a subgroup of patients with acute bacterial skin and skin structure infections (ABSSSI, see Glossary for definition) was also included[1,8]. This was a *post-hoc* analysis which (in the context of this appraisal) does not add any clinically relevant evidence beyond that provided by the full results of the CANVAS trials. Therefore the results of this analysis will not be discussed further.

The company have also provided a systematic review and network meta-analysis, which provided information on the efficacy and safety of ceftaroline fosamil versus daptomycin, linezolid and vancomycin in cSSTI[1]. The company also refer to a supportive phase II trial, which will not be further discussed in this report. The applicant company have also provided details of two phase III studies, FOCUS 1 and FOCUS 2, which investigated the effectiveness of ceftaroline fosamil in patients with

CAP. The efficacy results of these trials will not be discussed; however, safety information is included in Section 3.3[1,5,11].

### 3.1 The CANVAS trials

CANVAS 1 and CANVAS 2 were multicentre, randomised, double-blind, active-controlled phase III trials, which investigated the efficacy and safety of ceftaroline fosamil in adult patients (≥ 18 years) with cSSTI. Patients were eligible for these studies if their cSSTI involved deep soft tissue, required significant surgical intervention or involved cellulitis or abscess (of a lower extremity in those patients with diabetes mellitus). Patients (n = 1,378) were randomised 1:1 to receive either ceftaroline fosamil 600 mg followed by 0.9% sodium chloride placebo (n = 693) or vancomycin 1 g followed by aztreonam 1 g (n = 685) administered intravenously over 60 minutes every 12 hours for 5–14 days. In patients with moderate renal impairment (creatinine clearance [CrCl] > 30 and ≤ 50 ml/min, the dose of ceftaroline fosamil was reduced to 400 mg and the dose of vancomycin was adjusted according to local prescribing practices[1,10].

In both studies, the primary objective was to determine non-inferiority in clinical cure rate of ceftaroline fosamil monotherapy compared to vancomycin plus aztreonam combination therapy at the test-of-cure visit (TOC) in the clinically evaluable (CE) and modified intent-to-treat (MITT) populations (refer to Glossary)[1,10]. Clinical cure was defined as a resolution of all signs and symptoms of baseline infection, or improvement such that no further antimicrobial therapy was necessary[1]. A two-sided 95% confidence interval (CI) for the observed difference in the primary outcome measure between ceftaroline fosamil and vancomycin plus aztreonam was calculated. Non-inferiority was concluded if the lower limit of the 95% CI was −10% or higher. According to this criterion, non-inferiority was met in both trials in the CE and MITT populations, and in the integrated analysis (refer to Table 1)[1,10]. Secondary endpoints included microbiological response and clinical cure rates by pathogen at the TOC. For the microbiologically evaluable (ME, refer to Glossary for definition) population, microbiological response was observed in 92.3% (432/468) of patients in the ceftaroline fosamil group compared with 93.7% (418/446) of patients in the vancomycin plus aztreonam group (treatment difference −1.4%; 95% CI: −4.8%, 2.0%). Clinical cure rates were found to be comparable between treatment groups for each pathogen, including MRSA (see Table 2)[1,10].

**Table 1. Primary endpoint results of the CANVAS trials: clinical cure rates at TOC.**

| | Clinical cure rate*, number of patients cured/total number of patients (%) | | |
|---|---|---|---|
| | **Ceftaroline fosamil** | **Vancomycin plus aztreonam** | **Difference, % (95% CI)** |
| | **CE population** | | |
| CANVAS 1 | 288/316 (91.1) | 280/300 (93.3) | −2.2 (−6.6, 2.1) |
| CANVAS 2 | 271/294 (92.2) | 269/292 (92.1) | 0.1 (−4.4, 4.5) |
| Integrated analysis | 559/610 (91.6) | 549/592 (92.7) | −1.1 (−4.2, 2.0) |
| | **MITT population** | | |
| CANVAS 1 | 304/351 (86.6) | 297/347 (85.6) | 1.0 (−4.1, 6.2) |
| CANVAS 2 | 291/342 (85.1) | 289/338 (85.5) | −0.4 (−5.8, 5.0) |
| Integrated analysis | 595/693 (85.9) | 586/685 (85.5) | 0.3 (−3.4, 4.0) |

*clinical cure rates at TOC for the CE population and MITT population were co-primary endpoints.
CE: clinically evaluable; CI: confidence interval; MITT: modified intent-to-treat; TOC: test-of-cure visit

**Table 2. Clinical cure rates by selected baseline pathogen at TOC for the CANVAS trials.**

| | Cure rate, number of patients cured/total number of patients (%) | | | |
|---|---|---|---|---|
| | Ceftaroline fosamil | Vancomycin plus aztreonam | Ceftaroline fosamil | Vancomycin plus aztreonam |
| | ME population | | MITT population | |
| *Staphylococcus aureus* | 352/378 (93.1) | 336/356 (94.4) | 377/425 (88.7) | 356/409 (87.0) |
| MRSA | 142/152 (93.4) | 115/122 (94.3) | 155/179 (86.6) | 124/151 (82.1) |
| MSSA | 212/228 (93.0) | 225/238 (94.5) | 221/245 (90.2) | 233/258 (90.3) |
| *Streptococcus pyogenes* | 56/56 (100) | 56/58 (96.6) | 56/63 (88.9) | 57/62 (91.9) |
| *Streptococcus agalactiae* | 21/22 (95.5) | 18/18 (100) | 25/27 (92.6) | 19/21 (90.5) |
| *Enterococcus facealis* | 20/25 (80.0) | 22/24 (91.7) | 20/28 (71.4) | 23/28 (82.1) |
| *Escherichia coli* | 20/21 (95.2) | 19/21 (90.5) | 21/23 (91.3) | 19/21 (90.5) |
| *Pseudomonas aeruginosa* | NA | NA | 20/25 (80.0) | 22/25 (88.0) |
| *Proteus mirabilis* | 10/15 (66.7) | 20/21 (95.2) | 11/16 (68.8) | 20/23 (87.0) |
| *Klebsiella pneumoniae* | 17/18 (94.4) | 13/14 (92.9) | 17/18 (94.4) | 14/19 (73.7) |

ME: microbiologically evaluable; MITT: modified intent-to-treat; MRSA: methicillin-resistant *Staphylococcus auerus*; MSSA: methicillin-sensitive *Staphylococcus auerus*; NA: not available; TOC: test-of-cure visit

### 3.2 Network meta-analysis

In the absence of any further direct comparative data, the applicant company performed a network meta-analysis to evaluate the efficacy and safety of ceftaroline fosamil compared with daptomycin, linezolid and vancomycin in cSSTI[1]. A systematic review was conducted to identify all relevant clinical trials according to the following criteria:

- Randomised controlled trials (RCTs)
- Conducted in adult patients with cSSTI and suspected or confirmed MRSA treated in hospital
- Involved empiric IV treatment at a licensed dose with ceftaroline fosamil, vancomycin, linezolid, daptomycin, tigecycline or teicoplanin, with or without concomitant Gram-negative antibiotic administration
- Assessed clinical cure rate, clinical response by pathogen, microbiological response (at TOC), and clinical relapse, microbiological recurrence or re-infection, safety, early response (at last follow up [LFU] visit)

A total of nine eligible RCTs were identified, all of which had vancomycin as a common comparator. Study designs and results are summarised in Appendix 1. No suitable studies of teicoplanin were identified for inclusion. A Bayesian network meta-analysis model was used to analyse the data set for ceftaroline fosamil, daptomycin, linezolid and vancomycin. Fixed effects and random effects models were evaluated: the fixed effects model was deemed by the company to provide the best fit to the observed data. Results from the network meta-analysis (fixed effects model) are presented in Table 3, and suggest that ceftaroline fosamil has a comparable expected clinical cure rate to daptomycin, linezolid and vancomycin[1].

**Table 3. Results of the network meta-analysis (fixed effects model): clinical cure rates**

| | Clinical cure at TOC, % (95% CrI) | | |
|---|---|---|---|
| | **ITT population** | **CE population** | **ME population** |
| Ceftaroline | 86.22 (83.02, 89.07) | 92.93 (90.22, 95.27) | 84.64 (81.49, 87.59) |
| Daptomycin | 85.41(80.06, 89.55) | 95.68 (91.59, 97.90) | –* |
| Linezolid | 89.05 (83.83, 92.75) | 96.31 (93.13, 98.14) | 91.02 (85.00, 94.83) |
| Vancomycin | 85.52 (81.94, 88.65) | 93.49 (90.65, 95.80) | 88.02 (83.12, 91.98) |

CE: clinically evaluable; CrI: credible interval; ITT: intention-to-treat; ME: microbiologically evaluable; TOC: test-of-cure visit
*Daptomycin data was taken from a single study in which this endpoint was not measured.

### 3.3 Comparative safety

The safety of ceftaroline fosamil has been investigated in more than 1,700 patients, of which 1,470 were treated for either cSSTI or CAP[3].

In the CANVAS phase III trials, the overall incidence of treatment-emergent adverse events (TEAEs) in patients treated with ceftaroline fosamil was similar to those treated with vancomycin plus aztreonam (44.7% versus 47.5%). Discontinuation due to adverse events (AEs) was reported as 3.0% in patients receiving ceftaroline fosamil compared to 4.8% in patients receiving vancomycin plus aztreonam. The most frequently reported TEAEs in patients treated with ceftaroline fosamil included nausea (5.9%), headache (5.2%), diarrhoea (4.9%), pruritis (3.5%) and rash (3.2%). *Clostridium difficile* infection was reported in two patients in the ceftaroline fosamil group and in one patient in the vancomycin plus aztreonam group. Serious adverse events (SAEs) were found to be comparable between treatment groups (4.3% in the ceftaroline fosamil group versus 4.1% in the vancomycin plus aztreonam group). Three deaths occurred in the ceftaroline fosamil group; however, none of these were found to be related to the study treatment or the cSSTI[1,10].

The FOCUS phase III trials investigated the use of ceftaroline fosamil in patients (n = 1,228) with CAP[5,11]. TEAEs were reported in 47.0% of patients receiving ceftaroline fosamil versus 45.7% of patients receiving the comparator (ceftriaxone). In these trials, frequently associated TEAEs in the ceftaroline fosamil group included diarrhoea (4.2%), headache (3.4%) and insomnia (3.1%); no cases of *C. difficile* were reported in these trials[3].

The Committee for Medicinal Products for Human Use (CHMP) concluded that the overall safety profile of ceftaroline fosamil does not give rise to any major concerns; however, the risk management plan reflects several issues which need careful follow up. These include *C. difficile* associated diarrhoea, hypersensitivity/anaphylaxis, surveillance of bacterial resistance development, convulsions/seizures, potential treatment induced liver injury, haemolytic anaemia and renal impairment[3].

Safety results from the network meta-analysis focused on the number of withdrawals due to AEs, SAEs and all cause mortality. Ceftaroline fosamil was associated with the lowest expected rate of withdrawals due to AEs (2.7%) compared to linezolid (3.6%) and vancomycin (4.2%), but the differences between groups were not statistically significant. SAEs were found to be comparable across each treatment group (4.4% ceftaroline fosamil versus 4.3% linezolid and 4.2% vancomycin). Results for all cause mortality showed that fewer deaths were associated with ceftaroline fosamil treatment than with the comparators; however, it should be noted that a lack of events prohibited

a formal quantitative comparison. No data were available for daptomycin for any of the safety endpoints[1].

### 3.4 AWTTC critique

- In their submission, the applicant company has proposed ceftaroline fosamil as an alternative IV treatment option for cSSTI patients in Wales where methicillin-resistant *S. aureus* (MRSA) is suspected in the following settings:
  - For infections caused by Gram-positive pathogens only where vancomycin IV or teicoplanin IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV or linezolid IV is normally used
  - For mixed infections caused by common Gram-positive and Gram-negative pathogens (excluding extended-spectrum beta-lactamases [ESBLs]-producing organisms, AmpC-producing organisms and non-fermenter Gram-negative organisms, such as *Pseudomonas aeruginosa*), where vancomycin IV in combination with co-amoxiclav IV or teicoplanin IV in combination with co-amoxiclav IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV in combination with co-amoxiclav IV or linezolid IV in combination with co-amoxiclav IV is normally used

  No evidence for the clinical effectiveness of ceftaroline fosamil in the treatment of CAP or in the broader treatment of cSSTI (i.e. cSSTI which may not necessarily be associated with MRSA) was provided by the company, and therefore the clinical effectiveness of ceftaroline fosamil in these disease areas cannot be assessed.
- Direct evidence of comparative clinical effectiveness included in the company submission compares ceftaroline fosamil with vancomycin. However, the company has proposed the use of ceftaroline fosamil after vancomycin failure/intolerance or where it is not appropriate[1].
- In the absence of any other direct evidence of comparative clinical effectiveness, the company submission included a systematic review and network meta-analysis in which the efficacy of ceftaroline fosamil was compared to daptomycin, linezolid and vancomycin[1]. Whilst this appears to have been well-conducted, the data identified for inclusion have limitations. A number of trials of linezolid were identified, but not all were blinded[1]. Only one suitable daptomycin RCT was identified, the design of which meant that not all patients in the comparator arm received vancomycin (the reference comparator for the purpose of the meta-analysis)[1]. A limited range of sensitivity analyses have been conducted, including exclusion of the daptomycin RCT from the network. This appears not to change the results of the network meta-analysis significantly.
- In the CANVAS phase III trials, and in the network meta-analysis, ceftaroline fosamil was evaluated in a broader study population than specified by the company in their submission. Suspected MRSA was not listed in the inclusion criteria for either CANVAS trial. Clinical cure rates were found to be comparable between treatment groups in the MRSA subgroup (see Table 2); however, the studies may not be sufficiently powered to detect non-inferiority for this subgroup.
- Patients were excluded from participating in the CANVAS trials if they had a decubitis ulcer, diabetic foot ulcer, ulcer associated with PVD, severe infection, were immunocompromised or had severe sepsis[1,3,10]. Therefore the efficacy of ceftaroline fosamil cannot be determined for these population groups.
- Ceftaroline fosamil may offer advantages over existing therapies. Ceftaroline fosamil would not require additional renal function monitoring, therapeutic drug monitoring, regular full blood counts or dose adjustment according to weight[12–15]. In addition, ceftaroline fosamil could be used as monotherapy in polymicrobial infections[1,2].

- The aztreonam dose administered in the CANVAS trials (1 g every 12 hours; the licensed dose in the US) is lower than the recommended administered dose of 1 g every 8 hours or 2 g every 12 hours (licensed dose in the EU)[3,15]. The use of aztreonam does not reflect current practice in Wales where co-amoxiclav is reported to be the most widely used treatment option. However, the company state (based on expert advice) that Gram-negative coverage of aztreonam and co-amoxiclav are comparable for treatment of MRSA suspected cSSTIs within the settings included in their submission[1].
- CHMP noted that a higher dose and/or longer infusion time of ceftaroline fosamil may be required in patients with very severe systemic disturbances. In addition, they state that this regimen is not predicted to cover MRSA infections that require > 1 mg/l ceftaroline fosamil for inhibition. Therefore, a comparative study investigating ceftaroline fosamil 600 mg three times daily in patients with comorbidities associated with poor outcomes is included in the risk management plan[3].

## 4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submission describes cost minimisation analyses (CMA) of ceftaroline fosamil 600 mg as an alternative IV treatment option for cSSTI patients in Wales where methicillin-resistant *S. aureus* (MRSA) is suspected in the following settings:

- For infections caused by Gram-positive pathogens only where vancomycin IV or teicoplanin IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV or linezolid IV is normally used.
- For mixed infections caused by common Gram-positive and Gram-negative pathogens (excluding extended-spectrum beta-lactamase [ESBL]-producing organisms, AmpC-producing organisms and non-fermenter Gram-negative organisms, such as *Pseudomonas aeruginosa*), where vancomycin IV in combination with co-amoxiclav IV or teicoplanin IV in combination with co-amoxiclav IV is inappropriate/has not been tolerated or treatment modification is required; and daptomycin IV in combination with co-amoxiclav IV or linezolid IV in combination with co-amoxiclav IV is normally used[1].

The CMA approach assumes equivalent efficacy and safety for ceftaroline fosamil and its comparators (daptomycin and linezolid). There are no direct comparative data; therefore this assumption is based on a systematic review and a network meta-analysis in which ceftaroline fosamil was compared with daptomycin and linezolid, using vancomycin as the common comparator (see Section 3.2). The time horizon used in the base case analysis is 10 days, representing the minimum common licensed treatment duration for ceftaroline fosamil, daptomycin and linezolid. Treatment duration and length of hospital stay are assumed to be the same for all comparators. Data from the NHS Wales Informatics Service for year 2010–2011 are used to estimate the length of stay[16]. The dose used for both ceftaroline fosamil and linezolid is based on their Summaries of Product Characteristics (SPCs); the dose of daptomycin, which is weight dependent, is conservatively assumed to be 4 mg/kg (the lowest recommended dose).

The costs used in the model include acquisition costs of treatment, cost of administration and cost of monitoring. Treatment costs are taken from the British National Formulary (BNF)[15] while costs of monitoring tests and staff time are based on the National Schedule of Reference Costs (2010-11)[17] and Personal Social Services Research Unit (PSSRU)[18] costs.

### 4.1.2 Results of the company's analyses

The results of the base case analyses are presented in Tables 4 and 5. These show that for polymicrobial infections caused by mixed Gram-positive and common Gram-negative pathogens, ceftaroline fosamil is cost saving versus all the comparators for a ten-day course of treatment. For the monomicrobial (Gram-positive only) infections, ceftaroline fosamil is cost saving versus linezolid, while daptomycin 4 mg/kg is less costly than ceftaroline fosamil.

**Table 4. Monomicrobial base case analysis results**

| Base case comparison | Total costs per course of treatment | | | | | Plausibility |
|---|---|---|---|---|---|---|
| | Ceftaroline fosamil | Linezolid | Difference | Daptomycin | Difference | |
| **Treatment costs** | £750.00 | £890.00 | **−£140** | £736.60 | **£13.40** | Assumption of equivalence in efficacy and safety based on a network meta-analysis that used vancomycin as comparator |
| **Administration costs** | £78.00 | £78.00 | **£0.00** | £39.00 | **£39.00** | |
| **Monitoring costs** | £0.00 | £6.72 | **−£6.72** | £6.33 | **−£6.33** | |
| **Total cost** | £828.00 | £974.72 | **−£146.72** | £781.93 | **+£46.07** | |

**Table 5. Polymicrobial base case analysis results**

| Base case comparison | Total costs per course of treatment | | | | | Plausibility |
|---|---|---|---|---|---|---|
| | Ceftaroline fosamil | Linezolid + co-amoxiclav | Difference | Daptomycin + co-amoxiclav | Difference | |
| **Treatment costs** | £750.00 | £968.06 | **−£218.06** | £814.66 | **−£64.66** | Assumption of equivalence in efficacy and safety based on a network meta-analysis that used vancomycin as comparator |
| **Administration costs** | £78.00 | £195.00 | **−£117.00** | £156.00 | **−£78.00** | |
| **Monitoring costs** | £0.00 | £10.53 | **−£10.53** | £8.24 | **−£8.24** | |
| **Total cost** | £828.00 | £1,173.59 | **−£345.59** | £978.90 | **−£150.90** | |

One way sensitivity analyses explored variations in drug acquisition, administration and monitoring costs in the range ±25%, and treatment duration of 8 days instead of 10 days in the base case analysis. The results were generally similar to the base case analyses: ceftaroline fosamil remained cost saving versus all the comparators for the polymicrobial infections while daptomycin remained the least costly option in the treatment of monomicrobial infections.

Scenario analyses explored the impact of assuming higher doses of daptomycin: at daptomycin doses of 6 mg/kg or higher in all patients, ceftaroline fosamil is the least costly option. Threshold analyses indicate that ceftaroline fosamil becomes cost saving versus daptomycin when the proportion of patients receiving daptomycin 6 mg/kg, 8 mg/kg or 10 mg/kg approaches 16%, 8% or 5% of patients, respectively, while the remaining patients receive 4 mg/kg.

### 4.1.3 AWTTC critique of the economic evidence

The reliability of the company's CMA is dependent on the extent to which ceftaroline fosamil is considered to be therapeutically equivalent to the comparator treatments. There are no direct comparative data available and hence the company conducted a network meta-analysis. Vancomycin is the common comparator of the included trials, which differ in several ways (see Appendix 1 for details of the trials), and the extent to which they reflect the use of ceftaroline in the company-proposed patient group is questionable. The results of the CMA suggest that ceftaroline fosamil is cost saving in polymicrobial infections but may not be cost saving compared to daptomycin in monomicrobial infections.

Strengths of the economic evidence include:

- In the absence of direct comparative evidence, the company based its analysis on a well-conducted systematic review and network meta-analysis.
- The base case analysis conservatively uses the least costly dose of daptomycin.
- A range of sensitivity and scenario analyses has been conducted to explore the impact of changing key assumptions and parameter values.

Limitations of the economic evidence include:

- AWMSG appraises medicines within the whole of their licensed indication. For treatment of cSSTI suspected to involve MRSA, AWTTC requested comparison against vancomycin, teicoplanin, daptomycin and linezolid. However, the company has only submitted evidence relating to use of ceftaroline fosamil after vancomycin failure/intolerance or where it is not appropriate, and so the CMA submitted by the company considered daptomycin and linezolid as the only comparators. No evidence is provided in support of the use of ceftaroline fosamil in any of its wider licensed indications.
- The company based its analysis on the assumption of equivalent efficacy and safety, based on a network meta-analysis. However, the trials included in the network meta-analysis used vancomycin as the common comparator and hence, the trial populations comprised patients who were eligible for treatment with vancomycin. Additionally, the results of the network meta-analysis were based on the total trial population, regardless of MRSA status and whether comparator treatments were administered with or without concomitant Gram-negative cover. Therefore, the trial populations considered in the network meta-analysis do not reflect the proposed patient population covered by the company submission. A limited range of sensitivity analyses have been conducted, involving exclusion of selected trials to explore the impact of heterogeneity. These appear not to change the results of the network meta-analysis significantly.
- The Gram-negative coverage used in the trials included in the network meta-analysis is aztreonam, which does not reflect current practice in Wales where co-amoxiclav is reported to be the most widely used treatment option. However, the company state (based on expert advice) that Gram negative coverage of aztreonam and co-amoxiclav are comparable for treatment of MRSA suspected cSSTIs within the settings included in their submission. The dose of aztreonam used in the vancomycin arm of the ceftaroline fosamil trials (1g every 12 hours) was lower than the recommended dose of 1g every 8 hours or 2 g every 12 hours[15].
- The length of treatment in the base case is considered to be 10 days, with a scenario analysis exploring 8 days. However, shorter treatment durations are plausible based on the SPCs of ceftaroline fosamil and comparator treatments. The greater the treatment duration assumed, the greater the additional costs associated with monitoring required for comparators.

### 4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified a published conference abstract describing a budget impact analysis of the use of ceftaroline fosamil in cSSTI in the USA[19]. The comparator was vancomycin plus aztreonam, as per the phase III clinical trials. Given the different positioning of the use of ceftaroline fosamil, and differences in health care systems compared with Wales, this abstract is of little informative value for the current decision problem.

## 5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

### 5.1 Budget impact evidence

#### 5.1.1 Context and methods

The company reported that in 2010–2011, the total number of admissions to hospital for SSTI in Wales was 6,709[16]. The company estimated the annual number of patients treated for cSSTI in Wales to be 1,607 (24%), based on extrapolating from data on the point prevalence of antibiotic prescribing in Welsh hospitals[20] and data from the literature to estimate the proportion of patients (5%) who fail on their first line treatment with vancomycin or teicoplanin. The company estimated 185 patients with cSSTI would be eligible for treatment with ceftaroline annually, and that this annual number of patients will remain constant in the five years 2013–2017 inclusive. The company expected its market share to increase from 11% in year one to 54% in year five; hence the number of patients to receive ceftaroline fosamil was estimated to be 20 in year one, increasing to 100 in year five.

#### 5.1.2 Results of company's budget impact analysis

The company anticipates an overall net cost saving from switching to ceftaroline fosamil from the comparator regimens, assuming cSSTI is treated by equal proportions of each regimen (linezolid and daptomycin for monomicrobial infections and their combinations with co-amoxiclav for polymicrobial infections). The results of the base case are summarised in Table 6.

The company also reported alternative assumptions relating to treatment duration and proportion of patients who fail treatment with vancomycin or teicoplanin. These suggest that the annual number of patients eligible for treatment with ceftaroline fosamil may vary between 129 and 268.

**Table 6. Company-reported costs with the use of ceftaroline fosamil for cSSTIs in Wales**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Number of eligible patients*** | 185 | 185 | 185 | 185 | 185 |
| **Uptake (%)** | 11% | 16% | 27% | 41% | 54% |
| **Treated patients** | 20 | 30 | 50 | 75 | 100 |
| **Net costs versus weighted average of comparators** | | | | | |
| **Medication** | −£2,047 | −£3,070 | −£5,117 | −£7,675 | −£10,233 |
| **Administration and monitoring** | −£4,068 | −£6,103 | −£10,171 | −£15,257 | −£20,342 |
| **Primary care** | NA | NA | NA | NA | NA |
| **Secondary & tertiary care** | NA | NA | NA | NA | NA |
| **Staffing** | NA | NA | NA | NA | NA |
| **Infrastructure** | NA | NA | NA | NA | NA |
| **Personal social services** | NA | NA | NA | NA | NA |
| **Overall net cost** | **−£6,115** | **−£9,173** | **−£15,288** | **−£22,931** | **−£30,575** |

*Only the subsets of patients included in the company submission are considered.
NA: not available

### 5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable efforts to characterise the epidemiology of cSSTIs in Wales and used Wales-specific data to do so.
- The validity of the anticipated savings is dependent on the validity of the usage levels of the different comparators, given that comparator costs are calculated as weighted average cost based on these estimates.
- The cost estimates are derived from the company's CMA, therefore the limitations and uncertainties associated with the costs assumed in the CMA also apply to the budget impact analysis.

### 5.2 Table of comparative unit costs

Examples of acquisition costs for ceftaroline fosamil and other agents for the treatment of cSSTI are shown in Table 7. In contrast to other agents, ceftaroline fosamil does not require Gram-negative cover (e.g. co-amxoiclav) in polymicrobial infections.

**Table 7. Examples of acquisition costs for antibiotics used for the treatment of cSSTIs**

| Treatment | Example dose* | Example cost per treatment course** |
|---|---|---|
| **Zinforo®▼ (Ceftaroline fosamil)** IV infusion, powder for reconstitution in vials, 600 mg | 600 mg every 12 hours | **£750** |
| **Cubicin® (Daptomycin)** IV infusion, powder for reconstitution in vials, 350 and 500 mg | 4 mg/kg once daily; increased to 6 mg/kg once daily | **£620–£859.13**† |
| **Zyvox® (Linezolid)** IV infusion, bags, 2 mg/ml in 300 ml bags | 600 mg every 12 hours | **£890**† |
| **Vancomycin (non proprietary)** IV infusion, powder for reconstitution, 500 mg and 1 g vials | 1–1.5 g every 12 hours | **£290–£435**† |
| **Targocid® (teicoplanin)** IV infusion, powder for reconstitution, 200 mg and 400 mg vials | 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily | **£82.47**† |
| *Doses based on SPCs<br>**Costs are based on current MIMS and BNF list prices as of 24 February 2013, assuming 10 days of treatment and average adult body weight of 70kg[15,21].<br>†Excludes costs of Gram-negative cover in mixed infections (e.g. co-amoxiclav at approx. £78–£104).<br>This table does not imply therapeutic equivalence of drugs or the stated doses.<br>See relevant SPCs for full dosing details[2,12–14,22]. | | |

## 6.0 ADDITIONAL INFORMATION

### 6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, ceftaroline fosamil (Zinforo®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

### 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 Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

### 6.4 Evidence search

**Date of evidence search:** 21 February 2013
**Date range of evidence search:** No date limits were applied to database searches.

## GLOSSARY

**Acute bacterial skin and skin structure infections (ABSSSI)**
ABSSSI refers to both uncomplicated and complicated skin and skin structure infections. These infections should have a minimum surface area of measurable erythema, oedema, and/or induration (i.e., ≥75 $cm^2$ of cellulitis)[8].

**Clinically evaluable (CE)**
The CE population was a subset of the cMITT population that included subjects who received at least the prespecified minimum amount of the intended dose and duration of study treatment, for whom sufficient information regarding the cSSTI site was available to determine the subject's outcome, and for whom there were no confounding factors that interfered with the assessment of that outcome[3].

**Clinical MITT (cMITT**)
The cMITT population comprised all subjects in the MITT population with a confirmed cSSTI[1].

**Microbiologically evaluable (ME)**
The ME population was a subset of the CE population that included subjects from whom at least one bacterial pathogen was isolated from an appropriate microbiologic specimen (blood or tissue obtained from the cSSTI site) at baseline[3]. At least one of the pathogens isolated at baseline must have had susceptibility testing performed. Patients were excluded from the ME population if baseline culture revealed monomicrobial *P. aeruginosa* or anaerobic infection[1].

**Modified intent-to-treat (MITT) population**
The MITT population is defined as all randomised subjects who received any dose of study treatment[3].

**Test-of-cure visit (TOC)**
Assessments conducted 8 to 14 days after administration of the last dose of the study treatment[1].

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## Appendix 1. Additional clinical information

### Table 1. Studies included in the network meta-analysis.

| Study | Study design | Inclusion criteria | Treatment groups | Concomitant medicines | Treatment duration | Primary endpoint |
|---|---|---|---|---|---|---|
| CANVAS 1 and CANVAS 2[9,10,23] | Randomised, multicentre, multinational, double-blind, multicentre phase III trial. | ≥ 18 years; cSSSI that warranted ≥ 5 days of antibacterial therapy, purulent drainage or ≥ 3 of the following signs or symptoms: erythema, heat and/or localised warmth, fluctuance, pain and/or tenderness to palpation, fever or hypothermia, WBC count > 10,000/mm$^3$, or > 10% immature neutrophils. | Ceftaroline fosamil 600 mg/12 hours IV n = 693<br><br>Vancomycin 1 g/12 hours IV plus aztreonam 1 g/12 hours IV n = 685 | NA | 5–14 days. | Non-inferiority in clinical cure rate of ceftaroline treatment compared to vancomycin plus aztreonam treatment at the test-of-cure visit in the clinically evaluable and modified intent-to-treat populations.<br><br>Non-inferiority was met. Refer to Section 3.0 for results. |
| Talbot et al[24] | Randomised, multicentre, multinational, observer-blinded, phase II trial. | ≥ 18 years; SSSI involved deeper soft tissue and/or required significant surgical intervention or had developed on a lower extremity in a subject with diabetes mellitus or well-documented peripheral vascular disease; ≥ 2 local signs of cSSSI plus ≥ 1 systemic sign. | Ceftaroline fosamil 600 mg/12 hours IV n = 67<br><br>Vancomycin 1 g/12 hours IV n = 32 | NA<br><br>If Gram-positive and susceptible to penicillinase-resistant penicillin, therapy with vancomycin could be switched to penicillinase-resistant penicillins within the first 72 hours after initiation of therapy. If Gram-negative, concomitant administration of aztreonam (1 g every 8 hours) was allowed. | 7–14 days, up to 21 days for severe infections. | Clinical cure rate at TOC in the CE and cMITT populations.<br><br><u>CE population</u><br>Ceftaroline fosamil 96.7%<br>Standard therapy 88.9%<br><br><u>mITT population</u><br>Ceftaroline fosamil 88.1%<br>Standard therapy 81.3% |
| DAP-SST-98-01 and DAP-SST-99-01[25] | Two randomised, multicentre, multinational, evaluator-blinded, phase III trials. | Aged 18–85 years; with cSSSI associated with Gram-positive organisms, required hospitalisation and parenteral antimicrobial therapy for ≥ 96 hours. Appropriate diagnoses included wound infections, major abscesses, infected diabetic ulcers of the lower extremity, and infected ulcers due to other causes. | Daptomycin 4 mg/kg/day IV n = 534<br><br>Penicillinase-resistant penicillins 4–12 g per day IV or vancomycin 1 g/12 hours IV (assigned by unblinded investigator) n = 558 | Concomitant aztreonam or metronidazole therapy was allowed. | 7–14 days. | Non-inferiority in success rates of daptomycin versus comparator therapy.<br><br><u>ITT population</u><br>Daptomycin 71.5%<br>Comparator therapy 71.1% (95% CI, −5.8 to 5.0).<br>Non-inferiority was met.<br><br><u>CE population</u><br>Daptomycin 83.4%<br>Standard therapy 84.2% (95% CI, −4.0 to 5.6).<br>Non-inferiority was met. |

**Table 1. Continued. Studies included in the network meta-analysis.**

| Study | Study design | Inclusion criteria | Treatment groups | Concomitant medicines | Treatment duration | Primary endpoint |
|---|---|---|---|---|---|---|
| Weigelt et al 2005[26] Weigelt 2004[27] | Randomised, open-label, multicentre, multinational, comparator controlled trial. | SSSI that required hospitalisation with suspected or proven MRSA infection that involved substantial areas of skin or deeper soft tissues. Required physical findings included erythema, fluctuation, heat/localised warmth, pain/tenderness and drainage/discharge with ≥ 1 of the following: fever, hypothermia, hypotension, a WBC count > 10,000/$mm^3$, or > 15% immature neutrophils. | Linezolid 600 mg/12 hours IV or orally<br>n = 592<br><br>Vancomycin 1 g/12 hours IV<br>n = 588 | If Gram-negative organism, concomitant use of aztreonam or other antibiotics was permitted.<br><br>After initial vancomycin therapy, MSSA infected patients were to be switched to oxacillin sodium, nafcillin, or flucloxacillin (1 to 2 g) IV every 6 hours, or to dicloxacillin sodium (500 mg) orally every 6 hours.<br><br>If Gram-negative organism, concomitant use of aztreonam or other antibiotics was permitted. | 7–14 days, not longer than 21 days. | Clinical cure rates for the ITT population.<br><br><u>ITT population</u><br>Linezolid 92.2%<br>Vancomycin 88.5% (p = 0.057)<br><br>Clinical response to treatment at the TOC (subgroup analysis)<br><br><u>ITT population</u><br>Linezolid 93%<br>Vancomycin 87% (95% CI: −5.32 to 16.73) |
| Stevens et al[28] | Randomised, open-label, multicentre, multinational trial. | Patient hospitalised or institutionalised; ≥ 13 years; weight ≥ 40 kg; with presumed MRSA infection; laboratory findings consistent with *S. aureus* infection; signs and symptoms consistent with pneumonia, SSTI, urinary tract infection, right-side endocarditis, other infection, or bacteraemia of unknown source. | Linezolid 600 mg/12 hours IV<br>n = 240<br><br>Vancomycin 1 g/12 hours IV<br>n = 220 | Concomitant administration of aztreonam or gentamicin was allowed.<br><br>Use of topical antiseptics and topical steroids was permitted. | 7–28 days (7–14 days for SSTI). | Primary endpoints included clinical cure rates and microbiological success rates.<br><br><u>Clinical cure rates</u><br>Linezolid 73.2%<br>Vancomycin 73.1%<br><br><u>Microbiological success rates</u><br>Linezolid 58.9%<br>Vancomycin 63.2 |

**Table 1. Continued. Studies included in the network meta-analysis.**

| Study | Study design | Inclusion criteria | Treatment groups | Concomitant medicines | Treatment duration | Primary endpoint |
|---|---|---|---|---|---|---|
| Wilcox et al[29] | Randomised, open-label, multicentre, multinational study. | Patients were ≥ 13 years; had a central venous, pulmonary artery, or arterial catheter in place for > 3 days; suspected catheter-related infection. | Linezolid 600 mg/12 hours IV<br>n = 363<br><br>Vancomycin 1 g/12 hours IV<br>n = 363 | If suspected Gram-negative, aztreonam or amikacin was recommended.<br><br>If Gram-negative anaerobic, fungal, and viral infections, concomitant therapy was allowed.<br><br>If methicillin-susceptible organisms, patients could be switched to oxacillin 2 g every 6 hours IV or dicloxacillin 500 mg every 6 hours orally.<br><br>If suspected Gram-negative organism, aztreonam or amikacin was recommended.<br><br>If Gram-negative anaerobic, fungal, and viral infections, concomitant therapy was allowed. | 7–28 days. | The primary end point was the microbiologic outcome in MME and ME populations at TOC.<br><br>In the subset with cSSSI (MME)<br>Linezolid 89.6%<br>Control 89.9% (95% CI, −7.1 to 6.4)<br><br>In the subset with CRBSI (ME) Linezolid 86.3%<br>Control 90.5% (95% CI, −13.8 to 5.4) |

**Table 1. Continued. Studies included in the network meta-analysis.**

| Study | Study design | Inclusion criteria | Treatment groups | Concomitant medicines | Treatment duration | Primary endpoint |
|---|---|---|---|---|---|---|
| Lin et al[30] | Phase III, randomised, double-blind, multicentre study conducted in China. | For a known or suspected cSSTI, ≥ 2 of physical symptoms: drainage/discharge; erythema; fluctuance; heat/localised warmth; pain/tenderness to palpation; or swelling/Induration; ≥ 1 of infection-related symptoms: fever; tachypnoea; hypotension; tachycardia; altered mental status; requirement for mechanical ventilation; WBC count > 10,000/mm$^3$; or neutrophils > 75%. | Linezolid 600 mg/12 hours IV n = 71<br><br>Vancomycin 1 g/12 hours if aged ≤ 60 years or 0.75 g/12 hours if aged > 60 years IV n = 71<br><br>Vancomycin 2 g/day IV (n value not specified) | If mixed Gram-positive and Gram-negative organisms, concomitant use of aztreonam was permitted.<br><br>If mixed Gram-positive and Gram-negative organism, concomitant use of aztreonam was permitted.<br><br>Aztreonam 4 g/day IV. | 7–21 days for cSSTI. | The primary efficacy endpoint was clinical outcome as measured by the effective treatment rate at the end-of treatment visit (defined as within 72 hours after the last dose of study medication) and the follow up visit 7–28 days post treatment.<br><br><u>At the end-of treatment visit</u><br>Linezolid 86.9%<br>Vancomycin 61.7% (p = 0.0015, 95% CI 10.3–40.2)<br><br><u>At the follow up visit</u><br>Linezolid 83.1%<br>Vancomycin 64.9% (p = 0.0300, 95% CI 2.5–33.8). |

**Table 1. Continued. Studies included in the network meta-analysis.**

| Study | Study design | Inclusion criteria | Treatment groups | Concomitant medicines | Treatment duration | Primary endpoint |
|---|---|---|---|---|---|---|
| Itani et al[31] | Randomised, open-label, phase IV trial. | cSSTI involving deep tissues and ≥ 2 of the following: purulent drainage, erythema, swelling or in duration, tenderness or pain, and local warmth. ≥ 1 sign of systemic infection: fever, hypotension, increased WBC count (≥ 10,000/mm$^3$), or more than 15% immature neutrophils. | Linezolid 600 mg/12 hours oral or IV<br>n = 537 | If Gram-negative organisms, aztreonam (or other antibiotic known to be inactive against Gram-positive organisms/MRSA) was allowed.<br><br>If anaerobic organisms, metronidazole was permitted. | 7–14 days. | Clinical outcome at the end of treatment and at the end of the study in the per-protocol population.<br><br><u>Success rates at the end of treatment</u><br>Linezolid 92%<br>Vancomycin 88% (95% CI −1.7 to 9.5)<br><br><u>Success rates at the end of the study</u><br>Linezolid 84%<br>Vancomycin 80% (95% CI −3 to 11.5) |
| | | | Vancomycin 15 mg/kg/12 hours IV<br>n = 515 | If Gram-negative organisms, aztreonam (or other antibiotic known to be inactive against Gram-positive/MRSA) was allowed.<br><br>If anaerobic organisms, metronidazole was permitted. | | |
| | | | Vancomycin 1 g/12 hours IV<br>(n value not specified) | Aztreonam 2 g/12 hours IV. | | |

CE: clinically evaluable; CI: confidence interval; cMITT: clinical modified intention-to-treat; cSSTI: complicated skin and soft tissue infection; cSSSI: complicated skin and skin structure infection; CRBSI: catheter-related bloodstream infection; (IV: intravenous; ME: microbiologically evaluable; MME: modified microbiologically evaluable; MRSA: methicillin-resistant *Staphylococcus aureus*; NA: not available; SSSI: skin and skin structure infection ; SSTI: skin and soft tissue infection; TOC: test-of-cure visit; WBC: white blood cells