

## **ceftaroline fosamil, 600mg, powder for concentrate for solution for infusion (Zinforo®)**

**SMC No. (830/12)**

**AstraZeneca UK Ltd**

07 December 2012

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

**ADVICE:** following a full submission

**ceftaroline fosamil (Zinforo®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** treatment of complicated skin and soft tissue infections in adults.

**SMC restriction:** use in patients with known or suspected meticillin resistant *Staphylococcus aureus* (MRSA) infection in the following settings:

- For Gram-positive only infections where vancomycin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv or linezolid iv is normally used.
- For polymicrobial Gram-positive and common Gram-negative pathogens\*, where vancomycin iv in combination with gentamicin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv in combination with gentamicin iv, or linezolid iv in combination with gentamicin iv, or tigecycline iv is normally used.

Ceftaroline should be used only on the advice of local microbiologists or specialists in infectious disease.

In two randomised, controlled clinical studies, intravenous ceftaroline fosamil was non-inferior to intravenous vancomycin plus aztreonam in adult patients with complicated skin and skin structure infections.

Ceftaroline is also licensed for the treatment of community acquired pneumonia. As the company submission related only to the treatment of skin and soft tissue infections, SMC cannot recommend the use of ceftaroline in community acquired pneumonia.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

Published 14 January 2013

## Indication

In adults for the treatment of the following infections:

- complicated skin and soft tissue infections (cSSTI)
- community acquired pneumonia

## Dosing Information

The recommended dose is 600mg administered every 12 hours by intravenous infusion over 60 minutes in patients aged 18 years or older. The recommended treatment duration for cSSTI is 5 to 14 days.

## Product availability date

October 2012

## Summary of evidence on comparative efficacy

Ceftaroline fosamil (subsequently referred to as ceftaroline) is an intravenous (iv) cephalosporin with activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and some common Gram-negative pathogens involved in cSSTI. Ceftaroline has a high affinity for *Staphylococcus aureus* penicillin-binding proteins (PBPs), including PBP 2a, resulting in effective bactericidal activity *in vitro* against MRSA. Ceftaroline fosamil is a prodrug, which is converted to the active ceftaroline by plasma phosphatase enzymes.

Ceftaroline has a marketing authorisation for use in the treatment of complicated skin and soft tissue infections and community acquired pneumonia in adults. The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of ceftaroline in the cSSTI indication only, as an alternative treatment option for patients where MRSA is suspected in the following settings:

- For Gram-positive only infections where vancomycin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv or linezolid iv is normally used.
- For polymicrobial Gram-positive and common Gram-negative pathogens,\* where vancomycin iv in combination with gentamicin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv in combination with gentamicin iv, or linezolid iv in combination with gentamicin iv, or tigecycline iv is normally used.

\* Excluding strains producing extended-spectrum beta-lactamases, AmpC beta-lactamases and non-fermenter Gram-negatives such as *Pseudomonas aeruginosa*.

Both daptomycin and tigecycline have previously been accepted for restricted use within NHS Scotland for the treatment of cSSTI. Daptomycin is restricted to patients with known or suspected MRSA infection and on the advice of local microbiologists or specialists in infectious disease. Tigecycline is restricted to use as a second or third line agent on the advice of local microbiologists or specialists in infectious disease.

The evidence supporting the marketing authorisation is from two identically designed, phase III, double blind, randomised, controlled clinical studies<sup>1,2</sup> in adults with cSSTI that involved deep extensive cellulitis, major abscess requiring surgical drainage, or infected wound, ulcer or burn. (The term complicated skin and skin structure infection [cSSSI] was used in the published studies, but for consistency, the term cSSTI will be used throughout this document.) The cSSTI was required to be severe enough to warrant hospitalisation or treatment in an emergency department and 5 days or more of intravenous antibiotic therapy. Patients must have had three or more clinical signs of infection. Patients with cSSTI caused by *Pseudomonas aeruginosa* or an anaerobic, fungal, parasitic or viral pathogen were excluded, as were patients with decubitus ulcer, diabetic foot ulcer, or ulcer associated with peripheral vascular disease accompanied by osteomyelitis or likely to require amputation or revascularisation within 60 days. Concomitant antimicrobial or high-dose corticosteroid therapy was not permitted.

Patients were randomised to receive blinded treatment with either iv ceftaroline 600mg followed by iv 0.9% saline placebo, or iv vancomycin 1g followed by iv aztreonam 1g. The dose of ceftaroline was reduced to 400mg in patients with a creatinine clearance of 30 to 50mL/minute and the vancomycin dose was adjusted according to local prescribing protocols. All treatments were administered every 12 hours for between 5 and 14 days.

The primary outcome in both studies was clinical cure rate in the modified intent-to-treat (MITT) population, defined as randomised patients who had received any study medication. A two-sided confidence interval (CI) for the observed difference in the primary outcome between the ceftaroline group and the vancomycin plus aztreonam group was calculated and non-inferiority was concluded if the lower limit of the 95% CI was -10% or higher. A total of 693 patients received ceftaroline (353 in study one<sup>1</sup> and 348 in study two<sup>2</sup>) and 695 patients received vancomycin plus aztreonam (349 in study one and 346 in study two).

The results of the primary outcome in the two studies and from an integrated analysis<sup>3</sup> of both sets of results are shown in the table below. In both studies, non-inferiority of ceftaroline compared with vancomycin plus aztreonam was demonstrated.

**Table 1. Results for the primary outcome in the two studies and the integrated analysis (MITT population).**

	Clinical cure rate n/N (%)		
	Ceftaroline	Vancomycin + aztreonam	Difference, % (95% CI)
<b>Study 1<sup>1</sup></b>	304/351 (87)	297/347 (86)	1.0 (-4.2 to 6.2)
<b>Study 2<sup>2</sup></b>	291/342 (85)	289/338 (86)	-0.4 (-5.8 to 5.0)
<b>Integrated analysis<sup>3</sup></b>	595/693 (86)	586/685 (86)	0.3 (-3.4 to 4.0)

The proportion of patients with known MRSA at baseline was 34% (93/271) and 32% (86/269) in the ceftaroline groups, and 30% (80/263) and 27% (71/259) in the vancomycin plus aztreonam groups, in studies one and two, respectively. In study one the clinical cure rate in the subgroup of patients with MRSA was 95% (78/82) in the ceftaroline group and 95% (59/62) in the vancomycin plus aztreonam group. In study two the clinical cure rate in the subgroup of

patients with MRSA was 91% (64/70) in the ceftaroline group and 93% (56/60) in the vancomycin plus aztreonam group. These results were derived from the microbiologically evaluable (ME) population, which was defined as patients in the MITT population who met the minimal clinical criteria for a cSSTI, who received a prespecified minimum amount of study medication, had a clinical response of cure or failure at the test-of-cure visit, for whom there were no confounding factors that interfered with the assessment of that outcome and from whom at least one bacterial pathogen was isolated from blood or tissue at baseline. Patients (n=482) were excluded from the ME population if culture revealed monomicrobial *Pseudomonas aeruginosa* or only anaerobic infections.

## Summary of evidence on comparative safety

Data from an integrated analysis of the two phase III studies<sup>3</sup> show that the incidence of adverse events (AE) was similar in both treatment groups: 45% (309/692) in the ceftaroline groups and 48% (326/686) in the vancomycin plus aztreonam groups.<sup>3</sup>

AEs occurring in  $\geq 2\%$  of patients (for the ceftaroline group versus the vancomycin plus aztreonam group, respectively) included nausea (5.9% versus 5.1%), headache (5.2% versus 4.5%), diarrhoea (4.9% versus 3.8%), pruritus (3.5% versus 8.2%) and rash (3.2% versus 2.5%).<sup>3</sup>

The incidence of serious adverse events was similar in both treatment groups (4.3% ceftaroline versus 4.1% vancomycin plus aztreonam).<sup>3</sup>

*Clostridium difficile* (*C. difficile*) infection occurred in two patients in the ceftaroline group and one patient in the vancomycin plus aztreonam group (n=1378 in the CANVAS trials).<sup>3</sup>

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

## Summary of clinical effectiveness issues

The submitting company has requested that SMC considers the use of ceftaroline when positioned as an alternative treatment option for patients with cSSTI where MRSA is suspected in the following settings:

- For Gram-positive only infections where vancomycin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv or linezolid iv is normally used.
- For polymicrobial Gram-positive and common Gram-negative pathogens\*, where vancomycin iv in combination with gentamicin iv is inappropriate/has not been tolerated or treatment modification is required; and daptomycin iv in combination with gentamicin iv, or linezolid iv in combination with gentamicin iv, or tigecycline iv is normally used.

\* Excluding strains producing extended-spectrum beta-lactamases, AmpC beta-lactamases and non-fermenter Gram-negatives such as *Pseudomonas aeruginosa*.

The use of ceftaroline would be directed by infectious disease specialists only (microbiologists and infectious disease physicians) and would be in line with antimicrobial stewardship policies in Scotland.

The company submitted two identically designed, phase III, randomised, controlled clinical studies<sup>1,2</sup> that demonstrated non-inferiority of iv ceftaroline compared with an iv tricyclic glycopeptide plus an iv beta-lactam with bactericidal activity against Gram-negative infections in adult patients with cSSTI. An integrated analysis of the results from both studies was also presented. Safety data from the integrated analysis showed that ceftaroline had a similar safety profile to the comparator treatment.

A key limitation of the clinical evidence is that the study population is much broader than the population that reflects the company's proposed positioning for ceftaroline, i.e. patients with cSSTI and suspected MRSA infection. The study inclusion criterion was a defined cSSTI; however, there was no requirement for patients to have suspected MRSA infection. In both studies, approximately 30% of patients had MRSA at baseline, and sub-group analysis showed that the clinical cure rates in these patients were similar for the ceftaroline groups and the comparator groups. However the studies were not powered to determine non-inferiority of ceftaroline in the MRSA population.

The comparator treatment was iv vancomycin plus aztreonam, which is not the most relevant comparator for the company's proposed positioning, which is second-line to vancomycin. In addition, the dose of aztreonam used in the studies (1g every 12 hours) was lower than that recommended in the UK (1g every 8 hours or 2 g every 12 hours). Current treatment guidance for severe cSSTI with MRSA infection recommends treatment with a glycopeptide (e.g. vancomycin), daptomycin, linezolid or tigecycline.<sup>4</sup>

Since its assessment by SMC in 2006 the use of tigecycline has been restricted due to safety concerns. The Medicines and Healthcare products Regulatory Agency advised in April 2011 that in an analysis of pooled results from comparative clinical trials of tigecycline in a range of infections the mortality rates were numerically higher in patients receiving tigecycline. Therefore, prescribers have been advised to use tigecycline only when other antibiotics are unsuitable.

There is uncertainty about the generalisability of the study results to Scottish patients. The study centres were mostly in America and Eastern Europe; there was only one UK study centre and none in Scotland. In addition, some of the exclusion criteria, such as decubitus ulcer and diabetic foot ulcer may limit the generalisability to patients in Scotland.

The prescribing of cephalosporins is restricted in Scotland because of the potential for *C. difficile* infection. In the pivotal studies, *C. difficile* infection was reported in two patients in the ceftaroline groups and one in the control group but the risk of *C. difficile* during clinical use of the drug remains uncertain.

Ceftaroline may offer an advantage over alternative antibacterials, since its use does not require additional monitoring of renal function or therapeutic drug monitoring, unlike vancomycin and gentamicin. Ceftaroline may offer an advantage over linezolid, which requires weekly full blood counts and, as a monoamine oxidase inhibitor (MAOI), is subject to dietary restrictions and has the potential for drug interaction with other MAOIs, antidepressants and sympathomimetic drugs. Ceftaroline may offer an advantage over daptomycin which requires dose adjustment according to patient weight as well as monitoring in patients who are at risk of developing

myopathy. Ceftaroline also provides a monotherapy option in infections caused by mixed Gram-positive and common Gram-negative pathogens which are otherwise treated with combination antimicrobial therapy.

To support the economic case, the company presented a Bayesian network meta-analysis (NMA) in which ceftaroline was indirectly compared with linezolid, daptomycin and tigecycline, using vancomycin as a common comparator. The network was comprised of 13 randomised, controlled studies in adults with cSSTI and suspected or confirmed MRSA treated in hospital. Three outcomes were compared: clinical cure rate (assessed in the intention-to-treat [ITT], clinically evaluable and microbiologically evaluable populations), withdrawal due to adverse events, and incidence of serious adverse events. The primary analysis was conducted using a fixed-effects model and the results suggest that ceftaroline is similar in efficacy and safety to the other anti-microbial agents compared. Sources of clinical and methodological heterogeneity between the studies were identified and several sensitivity analyses were performed to assess the resultant potential modification of the relative treatment effect. The results of these sensitivity analyses did not materially alter the conclusion.

In the analysis of clinical cure rates in the ITT population, the use of outcome data from a different patient population (microbiologically-modified ITT) was used from a tigecycline study. A sensitivity analysis which excluded this study did not alter the results of the NMA. A limitation of the network meta-analysis, acknowledged by the company, was that the included studies recruited a broader population of patients than the one that would be eligible for ceftaroline under the company's proposed positioning. Due to the variable reporting of sub-group outcomes and the methodology of empiric therapy study design it was not possible to formulate a network of evidence focused on this position.

SMC clinical experts were generally supportive of ceftaroline as a potential treatment option for the management of cSSTI. The national policy to restrict cephalosporin use was noted, however, and it was acknowledged that it would be appropriate to restrict its use such that ceftaroline may be prescribed only on the recommendation of local microbiologists or infectious diseases specialists.

## **Summary of comparative health economic evidence**

The submitting company presented a cost-minimisation analysis comparing ceftaroline with daptomycin and linezolid in patients with monomicrobial (Gram-positive only) infections. In patients with polymicrobial infections caused by mixed Gram-positive and common Gram-negative pathogens, ceftaroline was compared with daptomycin plus gentamicin, linezolid plus gentamicin, and tigecycline. The company requested ceftaroline be considered as an alternative treatment option for cSSTI patients in Scotland where MRSA is suspected and where vancomycin is inappropriate, has not been tolerated or treatment modification is required.

To support the assumption of comparable efficacy which underpins the cost-minimisation analysis, the company conducted a Bayesian NMA in which ceftaroline was indirectly compared with linezolid, daptomycin and tigecycline, using vancomycin as a common comparator. Based on the results of the NMA the company concluded that the efficacy of ceftaroline is similar to the other treatments.

The cost-minimisation analysis included drug acquisition, monitoring and administration costs. No adverse event costs were included on the basis that the safety profiles are similar. The time horizon used was one course of treatment, which was estimated to be 7 days. The company justified the short time horizon on the basis that cSSTIs are acute conditions and the clinical studies cover the patient pathway from hospital admission to the condition resolving and therefore no extrapolation was required.

The results of the base case analysis are presented below. It should be noted that the pattern of the results was unchanged when only drug acquisition costs were included.

<b>Infection subgroup</b>	<b>Treatment</b>	<b>Total cost per course</b>	<b>Result (ceftaroline vs comparator)</b>
<b>Mono- or polymicrobial</b>	ceftaroline	£653	-
<b>Monomicrobial (Gram- positive only)</b>	Daptomycin*	£575	£78
	linezolid	£759	-£106
<b>Polymicrobial (Mixed- Gram positive and common Gram - negative)</b>	daptomycin + gentamicin	£695	-£42
	linezolid + gentamicin	£880	-£227
	tigecycline	£613	£40

\*Assumes 33% of patients are obese and therefore require a larger or additional vial of daptomycin.

The following limitations were noted:

- Ceftaroline is cost-saving in comparison with some, but not all the comparators. In the monomicrobial (Gram-positive only) infection subgroup, ceftaroline is associated with an incremental cost of £78 versus daptomycin. In the polymicrobial (infections caused by mixed Gram-positive and common Gram-negative pathogens) subgroup, ceftaroline treatment is £40 more expensive than tigecycline. The submitting company suggested higher doses of daptomycin may be used in practice. If daptomycin is used at a higher dose (8mg/kg instead of 4mg/kg assumed in the base case) ceftaroline becomes cost-saving.
- The analysis also included some monitoring tests for comparator therapies which NDC members felt would not always be relevant, for example, INR and prothrombin tests for daptomycin treated patients as these would only be used for patients who were on warfarin. There were also concerns expressed about the tests included for renal monitoring for gentamicin. The submitting company provided revised analysis to show the impact of excluding these costs from the comparator regimens.

Despite these limitations, the economic case was demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was received from National Concern for Healthcare Infections.

## Additional information: guidelines and protocols

Guidelines for the prophylaxis and treatment of MRSA infections in the UK were developed in 2006 by a joint working party of the British Society for Antimicrobial Chemotherapy, Hospital Infection Society and Infection Control Nurses Association<sup>5</sup>, and updated in 2008.<sup>4</sup> In non-hospitalised patients with SSTIs, the guidelines<sup>4</sup> recommend use of doxycycline or clindamycin, or, with strains resistant to these drugs, glycopeptides or linezolid. Co-trimoxazole could also be considered. Outpatient parenteral therapy with glycopeptides or daptomycin is a cost-effective option in moderately severe infections where continuing intravenous therapy is deemed necessary.<sup>4</sup> In hospitalised patients with severe SSTI and/or where the risk of bacteraemia is high, glycopeptides, linezolid or daptomycin should be considered. The guidelines state that linezolid may provide marginally greater effectiveness compared with glycopeptides in this patient population. In polymicrobial infections (e.g. diabetic foot infections) where MRSA is considered an important pathogen, monotherapy with tigecycline may be considered an alternative. The guidelines do not make recommendations on the use of combination therapy, due to the lack of clinical trial data and the risk of additive toxicity.<sup>4</sup> Where there has been treatment failure with glycopeptide monotherapy, the guidelines do not make a clear recommendation between addition of a second agent (such as doxycycline, rifampicin or fusidate) or switching to monotherapy with either linezolid or daptomycin.<sup>4</sup>

Guidance developed by the Scottish Antimicrobial Prescribing Group in collaboration with the Scottish Microbiology Forum recommends treatment with a local vancomycin protocol for suspected MRSA infection. If intolerance, vancomycin allergy, treatment failure or clinical concerns, then alternative therapy should be discussed with an infection specialist.<sup>6</sup>

## Additional information: comparators

The current edition of the British National Formulary (no. 64, September 2012) recommends that a tetracycline or clindamycin alone, or a combination of rifampicin and sodium fusidate can be used for skin and soft tissue infections caused by MRSA. A glycopeptide (e.g. vancomycin) can be used for severe skin and soft tissue infections associated with MRSA; if a glycopeptide is unsuitable, then linezolid may be used on expert advice; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. Tigecycline and daptomycin are both licensed for the treatment of cSSTI involving MRSA.



## Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Ceftaroline	600mg every 12 hours	£525 to £1050
Linezolid	600mg every 12 hours	£623 to £1246
Tigecycline	100mg initially, then 50mg every 12 hours	£485 to £937
Daptomycin	4mg/kg to 6mg/kg every 24 hours	£434 to £1240
Clindamycin	600mg three times a day	£259 to £519
Vancomycin	1g every 12 hours	£226 to £451

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 04 October 2012. If costs were not available on eVadis, then costs from the BNF, no. 62, September 2012 were used. All costs were based on a 7 to 14 day course; all drugs given intravenously. Adding gentamicin 210mg to 420mg daily would increase the cost of a course by £21 to £84.

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 524 in year 1 rising to 531 in year five with an estimated uptake rate of 5.71% in year 1 and 67.24% in year 5. The gross impact on the medicines budget was estimated to be £15k in year 1 and £182k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £3k in year 1 and £39k in year 5. SMC clinical expert responses suggest that the company may have over-estimated uptake so the predicted cost savings may not be realised in practice.

## References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Corey GR, Wilcox MH, Talbot GH et al. CANVAS 1: the first phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J. Antimicrob. Chemother. 2010; 65 Suppl. 4: iv41-51.
2. Wilcox MH, Corey GR, Talbot GH et al. CANVAS 2: the second phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob. Chemother 2010; 65 Supple 4: iv53-65.
3. Corey GR, Wilcox M, Talbot GH et al. Integrated analysis of CANVAS 1 and 2: Phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clinical Infectious Diseases 2010; 51 (6): 641-50.
4. Gould FK, Brindle R, Chadwick PR et al. Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the United Kingdom. Journal of Antimicrobial Chemotherapy 2009; 63: 849-61.
5. Gemmell CG, Edwards DI, Fraise AP et al. Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK. Journal of Antimicrobial Chemotherapy 2006; 57 (4): 589-608.
6. Scottish Medicines Consortium. Guidance on management of proven or suspected *Staphylococcus aureus* bacteraemia.  
[http://www.scottishmedicines.org.uk/files/sapg/SAB\\_algorithm\\_final\\_white.pdf](http://www.scottishmedicines.org.uk/files/sapg/SAB_algorithm_final_white.pdf)

This assessment is based on data submitted by the applicant company up to and including 16 November 2012.

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

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Advice context:**

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

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