Ceftaroline Fosamil—A New Broad-Spectrum Cephalosporin with Significant Activity against Methicillin-Resistant Staphylococci

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Abstract: Ceftaroline fosamil (PPI-0903, TAK-599, Teflaro®, Forest Pharmaceuticals) is the prodrug for ceftaroline (T-91825), a broad-spectrum parenteral (IM/IV) cephalosporin with potent in vitro and in vivo activity against methicillin- and vancomycin-resistant staphylococci as well as other common pathogens of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CAP). Although more active than other cephalosporins against enterococci, the potency of this agent is still modest against E. faecalis (inactive vs. E. faecium). It is also active against Enterobacteriaceae with the exceptions of strains producing extended-spectrum beta-lactamases or carbapenemases. It is also active against anaerobic organisms with the exceptions of Bacteroides and Prevotella species and Clostridium difficile. Ceftaroline fosamil is non-inferior compared with regimens of vancomycin with/without aztreonam (ABSSSI) and ceftriaxone (CAP). The usual dosage regimen is 600 mg every 12 hours, as a 1-hour IV infusion, with dosage adjustment in moderate renal impairment (creatinine clearance [CrCl] of 31–50 mL/min) to 400 mg every 12 hours, in severe renal impairment (CrCl 15–30 mL/min) to 300 mg every 12 hours, and in end-stage renal impairment/hemodialysis (CrCl < 15 mL/min) to 200 mg every 12 hours. Further studies continue with a combination product of ceftaroline fosamil with NXL104 (a beta-lactamase inhibitor). This paper will review the chemistry, mechanism of action, in vitro and in vivo (animal) antibacterial activity, pharmacokinetics, clinical efficacy, tolerability, dosing and administration, and role of this agent. Medline/PubMed, International Pharmaceutical Abstracts, and EMBASE databases were searched for relevant articles using the search terms “ceftaroline”, “PPI-0903”, “TAK-599”, and “T-91825”. All English and French language articles identified in the searches were reviewed for their relevance to this review. In addition, the bibliographies of retrieved articles were reviewed to identify any relevant articles not identified in the initial searches. Also, the proceedings of all Interscience Conferences on Antimicrobial Agents and Chemotherapy (American Society for Microbiology) from 2000 through 2010 were searched for relevant abstracts.

Keywords: cephalosporins, ceftaroline, methicillin resistance, penicillin-binding proteins, beta-lactams
**Chemistry**

Ceftaroline fosamil (also known as PPI-0903, TAK-599) is the prodrug for the active moiety ceftaroline (T-91825). Ceftaroline fosamil decomposes in aqueous solution, following first-order kinetics, into free ceftaroline. Stability of such solutions is greatest at pH 7.0. At 25 °C, pH 7.0, over 95% of ceftaroline fosamil remains in aqueous solution after 24 hours, thus providing adequate stability for usual intermittent IV infusion use. The fosamil salt form is made necessary due to the low degree of solubility of the free acid form (respective solubilities at 25 °C in 2 mol/L phosphate buffer, pH 7.0 are >100 mg/mL and 2.3 mg/mL, respectively).1

Unlike most injectable cephalosporins, ceftaroline fosamil cannot be prepared as an amorphous solid by lyophilization in order to improve solubility since amorphous ceftaroline fosamil is unstable, even stored cold (at 8 °C, after 4 weeks less than 90% remained). Although stable at −20 °C, the lack of −20 °C freezers in most hospitals and other medical facilities makes the amorphous form impractical. Addition of inorganic salts, sugars, and amino acids did not improve the stability of the amorphous form. It was found that ceftaroline fosamil can be prepared as a crystalline salt from acetic acid solution (ie, acetic acid solvate). Two factors were found to be vital in maximizing the stability of the crystalline form: 1) moisture content should be maintained as close to 3% as possible, and 2) ≥60% crystallinity is required for 3-year stability at >95% of baseline.1

The chemical structures of ceftaroline fosamil and free ceftaroline are illustrated in the Figure. The chemical name for ceftaroline fosamil is [(6R,7R)-7-({(Z)-2-(ethoxyimino)-2-[5(phosphonoamino)-1,2,4-thiadiazol-3-yl]-acetyl}amino)-3-{[4-(1-methyl-4-pyridinio)-1,3-thiazol-2-yl]thio}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylatemonoacetate.2 Its molecular weight is 762.75 and empirical formula is $C_{22}H_{21}N_8O_8PS_4 \cdot C_2H_4O_2 \cdot H_2O$.2

**Pharmacodynamics**

**Mechanism of action**

The biological activities of beta-lactam antimicrobials are based on their binding to penicillin-binding proteins (PBPs) in the bacterial cell wall, resulting in inhibition of cell wall growth and even lysis and cell death. Due to the initially unexpected high degree of activity of ceftaroline against methicillin-resistant staphylococci in early *in vitro* studies, the dynamics of the binding interaction of ceftaroline to various PBPs has been extensively studied and explains the mechanism of this activity against methicillin-resistant isolates. In the following discussion, the relative strength of drug to PBP binding will be illustrated using IC$_{50}$ values. The IC$_{50}$ is the concentration of drug needed to block 50% binding of fluorescent Bocillin FL® to PBP sites. The lower the IC$_{50}$ value, the stronger the binding (and vice versa).

For staphylococci, IC$_{50}$ values for ceftaroline are relatively low: PBP 1, 2, and 3 values in MSSA isolates range from 0.03–0.5, 0.03–0.25, and 0.03–0.125 mg/L, respectively while PBP 1, 2, and 3 values in MRSA isolates range from 0.125–8, 0.125–4, and 0.1–0.5 mg/L, respectively. Cephalosporins as a class bind poorly to PBP 4 of MSSA/MRSA, with ceftaroline IC$_{50}$ values >8 mg/L. The binding of ceftaroline to PBP 2a/2x explains the activity of the drug against methicillin-resistant staphylococci. IC$_{50}$ values of ceftaroline for PBP 2a/2x range from 0.01–1 mg/L, up to 512-fold lower than those of penicillin and cephalosporin comparators (eg, ceftriaxone IC$_{50}$ = 677 mg/L, oxacillin IC$_{50}$ = 408 mg/L).3–5 Similarly, ceftaroline potently binds to the PBPs of *S. pneumoniae*, with IC$_{50}$ values of 0.01–0.2 mg/L for PBP 1a, 1b, 2x, 2 a/b and 3. The degree of binding is equal to or greater than those of cefotaxime and ceftriaxone.3,5 For both staphylococci and streptococci, PBP affinity inversely correlates with MIC. That is, the greater the degree of PBP binding, the lower the MIC (ie, the greater the bioactivity).

The mechanism of this potent binding of ceftaroline to PBP 2a/2x is just beginning to be understood. After binding to PBP 2a, ceftaroline is a potent inhibitor of the activity of this enzyme, with a mean ± SD $K_i$ of 330 ± 40 nM and IC$_{50}$ of 300 ± 40 nM.6 The second-order rate constant for the interaction between PBP 2a and ceftaroline ($K_a/K_i$) is (2.4 ± 0.1) × 10$^4$ M$^{-1}$ s$^{-1}$ (ie, represents highly efficient formation of the inhibitory acyl-enzyme intermediate which does not break down easily).6 With other cephalosporins, this process occurs much more slowly. Circular dichroism spectral analysis has demonstrated that ceftaroline can open up the active site of PBP 2a in a manner analogous to the effect of the usual biological “opener” (cell wall
surrogate). Both ceftaroline and cell wall surrogate bind to an allosteric site in order to do this.6

In vitro antimicrobial activity

Table 1 illustrates the in vitro activity of ceftaroline, represented by ranges or single values of MIC90 (ie, the minimum drug concentration inhibiting the growth of 90% of isolates).7–27 Among staphylococci, methicillin-susceptible strains exhibit MIC90 values of 0.12 to 0.25 mg/L while methicillin-resistant strains are 2- to 4-fold less sensitive (MIC90 range of 1–2 mg/L). The susceptibility profiles of community- and hospital-acquired methicillin-resistant staphylococci are similar. Ceftaroline is more active against enterococci than previous cephalosporins but MIC90 values are still high at 4 mg/L for E. faecalis. Vancomycin, ampicillin, linezolid, and quinupristin/dalfopristin resistance traits do not affect E. faecalis susceptibility to ceftaroline. Enterococcus faecium, whether susceptible or resistant to these agents, is resistant to ceftaroline (MIC90 > 16 mg/L). Although MIC90 values rise from penicillin-susceptible to intermediate to resistant pneumococcal isolates (PSSP, PISP, PRSP, respectively), all pneumococci are exquisitely susceptible to ceftaroline, with MIC90 values ≤ 0.25 mg/L.

Ceftaroline is active against highly cefotaxime-resistant isolates of pneumococci (MIC90 of 120 isolates = 0.5 mg/L [range, 0.125–2 mg/L]).28 It is also active against laboratory-derived cephalosporin-resistant R6 mutants with known PBP mutations (MIC90 of 18 isolates = 0.03 mg/L [range, ≤0.015–0.25 mg/L]).28 In addition to being active against penicillin-resistant, cephalosporin-resistant, and quinolone-resistant isolates of S. pneumoniae (see Table 1), ceftaroline is also active against trimethoprim/sulfamethoxazole-resistant, tetracycline-resistant, amoxicillin/clavulanate-intermediate, and amoxicillin/clavulanate-resistant isolates, all having an MIC90 of 0.25 mg/L.21,23

There do not appear to be substantial serotype-specific differences in the susceptibilities of pneumococci. For example, MIC90 values range from less than 0.008 mg/L (for 41 serotype 3 isolates) to 0.015 mg/L (for 27 serotype 11A and 18 serotype 7F isolates) to 0.03 mg/L (for 18 serotype 23B isolates) to 0.06 mg/L (for 18, 23, and 16 isolates of serotypes 15A, 6C, and 23A, respectively) to 0.12 mg/L (for 29 serotype 25B and 69 isolates of serotype 9V) to 0.25 mg/L (for 174, 16, 15, 65, and 33 isolates of serotypes 19A, 19F, 22F, 14, and 6B, respectively).18,21,22

Non-enterococcal streptococci are likewise exquisitely susceptible to ceftaroline with MIC90 values as low as ≤0.008 mg/L. Again, the presence of penicillin or macrolide resistance traits does not affect susceptibility to ceftaroline.

The respiratory pathogens Haemophilus influenzae and Moraxella catarrhalis are quite susceptible to ceftaroline, with MIC90 values ranging from ≤0.008 to 0.12 mg/L and 0.25 to 0.5 mg/L, respectively. Beta-lactamase positivity does not alter the susceptibility of either organism to ceftaroline.

Among gram-positive aerobes for which there are few options for therapy, ceftaroline is active against vancomycin-resistant S. aureus (VRSA), with MIC90 ranges of 0.12 to 1 mg/L (N = 8 isolates) and 0.125 to 0.5 mg/L (4 isolates).16,17 Similar susceptibility has been noted with daptomycin non-susceptible S. aureus (MIC90 range for 6 isolates = 0.5–1 mg/L and MIC90 for 10 isolates = 1 mg/L).10,16 Vancomycin-resistant lactobacilli are also susceptible, with an MIC90 of 1 mg/L.25

Among the Enterobacteriaceae, ceftaroline is moderately active against ceftazidime-susceptible isolates of Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter freundii and Enterobacter cloacae (MIC90 range of 0.25–1 mg/L). Ampicillin-resistant strains of E. coli and P. mirabilis and pipercillin-resistant strains of Klebsiella spp. have somewhat higher MIC90 values (about 4-fold increase over that of susceptible isolates). Ceftaroline has poor activity against Providencia spp., Serratia marcescens, Acinetobacter spp., and Pseudomonas aeruginosa (MIC90 range of 16 to >64 mg/L), regardless of their degree of susceptibility to ceftazidime.

Ceftaroline, like earlier third-generation cephalosporins such as ceftazidime and cefotaxime, is susceptible to breakdown by extended-spectrum beta-lactamases (ESBL) and carbapenemases (eg, SHV, TEM, CTX-M, KPC, AmpC, PER, OXA-2, -5, and -7 and combinations thereof).29 Thus, ESBL-producing E. coli, Klebsiella spp., Proteus spp. and Enterobacter spp. will be resistant to ceftaroline.

Although some anaerobes are susceptible to ceftaroline (eg, most Fusobacterium, Veillonella, clinical disease in the community and hospital settings.

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### Table 1. *In vitro* activity of ceftarolinea.

<table>
<thead>
<tr>
<th>Pathogen (# of isolates)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; Range (mg/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (182)</td>
<td>0.5–1</td>
<td>7,8</td>
</tr>
<tr>
<td>Methicillin-susceptible (7786)</td>
<td>0.25–0.5</td>
<td>9–15</td>
</tr>
<tr>
<td>Methicillin-resistant (6936)</td>
<td>1–2</td>
<td>9–15</td>
</tr>
<tr>
<td>VISA (83)</td>
<td>1</td>
<td>16,17</td>
</tr>
<tr>
<td>hVISA (160)</td>
<td>1</td>
<td>10,17</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (1175)</td>
<td>0.12–0.5</td>
<td>7,12,15</td>
</tr>
<tr>
<td><strong>MS S. epidermidis</strong> (284)</td>
<td>0.12–0.25</td>
<td>11,12</td>
</tr>
<tr>
<td><strong>MR S. epidermidis</strong> (316)</td>
<td>0.5</td>
<td>11,12</td>
</tr>
<tr>
<td>Enterococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em> (235)</td>
<td>4</td>
<td>7,12</td>
</tr>
<tr>
<td><strong>VS E. faecalis</strong> (157)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td><strong>VR E. faecalis</strong> (25)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td><em>E. faecium</em> (52)</td>
<td>&gt;32</td>
<td>7</td>
</tr>
<tr>
<td><strong>VR E. faecium</strong> (26)</td>
<td>&gt;16</td>
<td>12</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (1126)</td>
<td>≤0.03–0.12</td>
<td>11,14,18,19</td>
</tr>
<tr>
<td>Penicillin-susceptible (2407)</td>
<td>0.015–0.12</td>
<td>12,13,20,21</td>
</tr>
<tr>
<td>Penicillin-intermediate (319)</td>
<td>0.06–0.12</td>
<td>12,13,20</td>
</tr>
<tr>
<td>Penicillin-nonsusceptible (1059)</td>
<td>0.12–0.25</td>
<td>12,13,19–23</td>
</tr>
<tr>
<td>Macrolide-nonsusceptible (762)</td>
<td>0.12–0.25</td>
<td>19,21–23</td>
</tr>
<tr>
<td>Cephalosporin-nonsusceptible (54)</td>
<td>0.25</td>
<td>21,23</td>
</tr>
<tr>
<td>Quinolone-nonsusceptible (171)</td>
<td>0.12</td>
<td>21,23</td>
</tr>
<tr>
<td>MDRSP (386)</td>
<td>0.12–0.25</td>
<td>19,22,23</td>
</tr>
<tr>
<td><em>Viridans streptococci</em> (198)</td>
<td>0.12–0.25</td>
<td>20</td>
</tr>
<tr>
<td>Penicillin-susceptible (87)</td>
<td>0.03</td>
<td>12</td>
</tr>
<tr>
<td>Penicillin-nonsusceptible (14)</td>
<td>0.5</td>
<td>12</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (141)</td>
<td>≤0.008–≤0.03</td>
<td>11,13</td>
</tr>
<tr>
<td>Macrolide-susceptible (91)</td>
<td>≤0.008</td>
<td>12</td>
</tr>
<tr>
<td>Macrolide-nonsusceptible (10)</td>
<td>0.015</td>
<td>12</td>
</tr>
<tr>
<td>Beta-hemolytic streptococci (687)</td>
<td>≤0.015–0.016</td>
<td>8,9,20</td>
</tr>
<tr>
<td>Macrolide-susceptible Group B (59)</td>
<td>0.015</td>
<td>12</td>
</tr>
<tr>
<td>Macrolide-nonsusceptible Group B (42)</td>
<td>0.015</td>
<td>12</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> (542)</td>
<td>≤0.06–0.12</td>
<td>7,11,12,14</td>
</tr>
<tr>
<td>β-lactamase-positive (126)</td>
<td>0.015–0.03</td>
<td>12,13</td>
</tr>
<tr>
<td>β-lactamase-negative (293)</td>
<td>≤0.008–0.015</td>
<td>12,13</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em> (110)</td>
<td>0.25–0.5</td>
<td>7,13</td>
</tr>
<tr>
<td>β-lactamase-positive (93)</td>
<td>0.25</td>
<td>12</td>
</tr>
<tr>
<td><em>Pasteurella multocida</em> (22)</td>
<td>0.06</td>
<td>12</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em> (404)</td>
<td>0.5</td>
<td>24</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (1097)</td>
<td>0.5</td>
<td>11</td>
</tr>
<tr>
<td>CAZ-S/CAZ-R (345/63)</td>
<td>0.5/≥16</td>
<td>12</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> (357)</td>
<td>0.5</td>
<td>11</td>
</tr>
<tr>
<td>CAZ-S/CAZ-R (210/66)</td>
<td>0.25/≥16</td>
<td>12</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em> (85)</td>
<td>0.25</td>
<td>11</td>
</tr>
<tr>
<td>CAZ-S (58)</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em> (144)</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>CAZ-S/CAZ-R (50/35)</td>
<td>1/≥16</td>
<td>12</td>
</tr>
<tr>
<td><em>Acinetobacter baumanii</em> (23)</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAZ-S/CAZ-R (50/33)</td>
<td>0.25/≥16</td>
<td>12</td>
</tr>
<tr>
<td>CAZ-S Providencia spp. (27)</td>
<td>&gt;16</td>
<td>12</td>
</tr>
<tr>
<td>CAZ-S <em>Serratia marcesens</em> (59)</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> (470)</td>
<td>&gt;64</td>
<td>11</td>
</tr>
</tbody>
</table>

(Continued)
Ceftaroline, a new anti-MRSA cephalosporin

Experiments have been performed to determine the effect of varying test conditions on bacterial growth in the presence of ceftaroline. Calcium supplementation, alteration of medium pH to 6 or 8, addition of 10% or 50% human serum or 2.5% laked horse blood, substitution of HTM broth, and incubation in 5% CO² or in anaerobic conditions all exerted non-clinically significant effects. Salt supplementation (5% NaCl) inhibited bacterial growth and/or reduced ceftaroline MIC values for *E. coli* and *K. pneumoniae* and completely inhibited the growth of *M. catarrhalis, H. influenzae*, and all streptococci. Increasing the inoculum from 10⁴ to 10⁶ CFU, the MIC rose 5-fold in one-third each of *E. coli* and *K. pneumoniae* isolates. This also raised the MICs 3- to 5-fold for *M. catarrhalis*. In another study, raising the inoculum from 10⁴ to 10⁶ CFU led to substantial effects in only 5 cases: with ampicillin-resistant, ceftaxime-susceptible *E. coli* (geometric mean 7.3-fold increase in MIC), piperacillin-resistant *K. pneumoniae* (geometric mean 12.5-fold increase in MIC), ampicillin-resistant *P. mirabilis* (geometric mean 64-fold increase in MIC), ampicillin-susceptible *P. mirabilis* (geometric mean 20-fold increase in MIC), and extended-spectrum beta-lactamase producers (geometric mean > 16-fold increase in MICs).

Using an in vitro pharmacokinetic/pharmacodynamic model, simulated regimens of ceftaroline (600–1200 mg every 6 to 12 hours) and vancomycin (1 g every 12 hours) were compared using 2 MRSA and 1 hVISA strain. Ceftaroline and vancomycin were similar in their bioactivity against MRSA (MIC = 0.5 mg/L for both drugs), with regrowth occurring after 32 hours. Ceftaroline was significantly superior compared with vancomycin against the hVISA strain (ceftaroline MIC = 0.125 mg/L, vancomycin MIC = 2 mg/L) and the MRSA 3804 strain (ceftaroline and vancomycin MICs = 0.25 and 0.5 mg/L, respectively). With the hVISA strain, vancomycin resistance emerged after 72 hours of exposure.

In another in vitro pharmacokinetic/pharmacodynamic modeling study, simulated ceftaroline (600 mg

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Table 1. (Continued).

<table>
<thead>
<tr>
<th>Pathogen (slope of isolates)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; Range (mg/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides fragilis</em> (30)</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td><em>Bacteroides</em> group (424)</td>
<td>64–&gt;64</td>
<td>25–27</td>
</tr>
<tr>
<td><em>B. thetaiotaomicron</em> (20)</td>
<td>&gt;64</td>
<td>25</td>
</tr>
<tr>
<td><em>Fusobacterium nucleatum</em> (22)</td>
<td>0.125</td>
<td>25</td>
</tr>
<tr>
<td><em>F. necrophorum</em> (22)</td>
<td>0.06</td>
<td>25</td>
</tr>
<tr>
<td><em>F. mortiferum</em> (10)</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td><em>Veillonella</em> spp. (19)</td>
<td>0.5</td>
<td>25</td>
</tr>
<tr>
<td><em>Prevotella</em> spp. (98)</td>
<td>16–64</td>
<td>25</td>
</tr>
<tr>
<td><em>Porphyromonas sonae</em> (10)</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> spp. (62)</td>
<td>0.5–4</td>
<td>25,27</td>
</tr>
<tr>
<td>“Eubacterium” group (25)</td>
<td>0.25</td>
<td>25</td>
</tr>
<tr>
<td><em>Eggerthalla lenta</em> (17)</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em> (40)</td>
<td>0.12–0.25</td>
<td>25,26</td>
</tr>
<tr>
<td>C. difficile (46)</td>
<td>8–16</td>
<td>26,27</td>
</tr>
<tr>
<td><em>Propionibacterium</em> spp. (46)</td>
<td>0.06</td>
<td>25,27</td>
</tr>
</tbody>
</table>

Notes: *To be included, studies had to be conducted using CLSI-approved MIC methodology, # of isolates >10 per organism, and the inoculum had to range from 10<sup>4</sup>–10<sup>6</sup> CFU.

Abbreviations: MIC, minimum inhibitory concentration; VISA, vancomycin-intermediate *S. aureus*; hVISA, heterogeneous VISA; MS, methicillin-susceptible; MR, methicillin-resistant; VS, vancomycin-susceptible; VR, vancomycin-resistant; MDRSP, multidrug resistant *S. pneumoniae*; CAZ-S, ceftazidime-susceptible; CAZ-R, ceftazidime-resistant; CLSI, Clinical and Laboratory Standards Institute.
isolates, despite having minimum bactericidal isolates. Vancomycin was bacteriostatic against all bacterial counts at 24, 48, and 72 hours with all intervals based on nonsignificant differences in (2 hVISA isolates had values of 58). Ceftaroline was equally active using both 8 and 12 hour dosing 32 37.5 hours and 28.3 and 35 hours with simulated was “temporarily” bactericidal between 25.5 and respectively. With the other MRSA isolate, ceftaroline exhibited bactericidal activity at 6.5, 6.8, and 12 hours for 3 MSSA and 1 hVISA isolate, respectively. With the other MRSA isolate, ceftaroline was “temporarily” bactericidal between 5.05 and 44 hours with both dosing intervals. Regrowth in the latter two cases was not due to tolerance, instability of the drug, or resistance among the entire microbial population. Regrowth was explained by the presence of subpopulations with higher MICs. In summary, ceftaroline in 8 and 12 hour simulated regimens was a superior bactericidal agent compared with vancomycin in 5 of 6 isolates (all $P < 0.05$ for 2 hVISA and 3 MRSA isolates). For only 1 isolate (MRSA), were non-significant differences seen.33

For most susceptible pathogens, the minimum bactericidal concentration (MBC) is equal to or, at most, 2-fold the MIC. This has been noted with community- and hospital-acquired isolates of MRSA as well as isolates of VISA, hVISA, VRSA, daptomycin non-susceptible $S$. aureus, $P$. aeruginosa, $E$. coli and $K$. pneumoniae (both extended-spectrum beta-lactamase-positive and -negative isolates), and $E$. cloacae (including AmpC-positive isolates).16,17,33–35 Bactericidal activity of ceftaroline has also been studied in 50 penicillin-resistant, 11 penicillin-intermediate, and 11 penicillin-sensitive isolates of $S$. pneumoniae. Using broth microdilution methodology, the MBC was ≤2-fold the MIC in 90.3% of the 72 isolates and ≤4-fold in 94.4% of the 72 isolates. Using time-kill methodology, ceftaroline was bactericidal at 4-fold and 8-fold the MIC in all 12 isolates tested. It was also bactericidal at 2-fold the MIC for 11 isolates while 1 penicillin-sensitive isolate regrew.36 Time-kill methodology was also used to assess bactericidal activity of ceftaroline against anaerobes (1 isolate each of beta-lactamase producing $B$. fragilis, $B$. thetaotaomicron, and $P$. intermedia and 1 each of beta-lactamase-negative $F$. nucleatum and Finegoldia magna). The MIC range of these isolates was 0.125 to 16 mg/L. At 6 hours, ceftaroline was bactericidal against 2/5 isolates at 2-fold the MIC and 1/5 isolates at the MIC. At 24 hours, the drug was bactericidal against 3/5 isolates at both 2-fold the MIC and at the MIC. At 48 hours, the drug was bactericidal against 4/5 isolates at both 2-fold the MIC and at the MIC.37

Post-antibiotic effect (PAE) is the time required for bacteria to begin growing after the antimicrobial concentration falls below the MIC. Sub-MIC effect (SME) is the effect on bacterial growth in the presence of sub-MIC antimicrobial concentrations in the absence of previous exposure. PA-SME is the effect of sub-MIC antimicrobial concentrations during the growth period following a reduction in antimicrobial concentration to below the MIC. These parameters were evaluated in 4 isolates of $S$. pneumoniae, 6 of $S$. aureus (4 being methicillin-resistant), and 3 of $E$. faecalis (2 being vancomycin-resistant), and 2 of $E$. faecium (a total of 15 isolates). These 15 isolates had a ceftaroline MIC range of 0.008 to 2 mg/L. The mean PAE duration of all strains was 1.2 hours. Ranges of PAE duration were 0.8 to 1.8 hours (pneumococci), 0.7 to 2.2 hours (staphylococci), and 0.2 to 1.1 hours (enterococci). PA-SME duration increased in the presence of sub-MIC antimicrobial concentrations and were higher than PAE or SME durations. For example, PA-SME duration ranges at 0.4 times the MIC were 2.5 to 6.7 hours (pneumococci), 2.9 to >10 hours (staphylococci), and 7.9 to >10.3 hours (enterococci). By some mechanism, sub-MIC concentrations of ceftaroline extend the PAE period
of aerobic gram-positive cocci to a clinically-important degree.\textsuperscript{38}

The \textit{in vitro} antimicrobial effects of combination therapy with ceftaroline have been extensively evaluated. In one study, combinations of ceftaroline with vancomycin, linezolid, levofloxacin, azithromycin, daptomycin, amikacin, aztreonam, tigecycline, and meropenem were evaluated against a wide range of aerobic pathogens using a broth microdilution checkerboard methodology. The only "positive" results were synergy against \textit{S. aureus} isolates and \textit{K. pneumoniae} isolates when ceftaroline was combined with meropenem and synergy against \textit{P. aeruginosa} isolates and extended-spectrum beta-lactamase-producing \textit{E. coli} isolates when ceftaroline was combined with amikacin. With no combination was antagonism found.\textsuperscript{39}

In another study, combinations of ceftaroline with meropenem, tazobactam, cefepime, amikacin, levofloxacin, aztreonam, and tigecycline were evaluated against 26 isolates of \textit{P. aeruginosa} and 10 isolates each of extended-spectrum beta-lactamase-producing \textit{E. coli} and \textit{K. pneumoniae} and AmpC derepressed \textit{E. cloacae} using time-kill methodology. When tazobactam at a fixed concentration of 4 mg/L was combined with ceftaroline, the MICs of \textit{E. coli} and \textit{K. pneumoniae} isolates fell 2- to 572-fold. Ceftaroline plus amikacin was synergistic against 90% of all tested isolates (was indifferent for 1 \textit{P. aeruginosa} isolate). Ceftaroline plus tazobactam was synergistic against 100% of \textit{E. coli} and \textit{K. pneumoniae} isolates and indifferent against \textit{E. cloacae} and \textit{P. aeruginosa} isolates. Ceftaroline plus meropenem was synergistic against 100% of \textit{E. coli} isolates while ceftaroline plus aztreonam was synergistic against 100% of \textit{E. cloacae} isolates. These two combinations were indifferent against the remainder of isolates. Combinations with levofloxacin, tigecycline, and cefepime were indifferent against all isolates. No antagonism was found. Of tested combinations, ceftaroline plus amikacin was the most active and synergistic against most isolates.\textsuperscript{34}

Time-kill experiments were conducted using 2 isolates of MRSA and 1 isolate each of VISA and hVISA. Ceftaroline MICs ranged from 0.125 to 0.5 mg/L and MBCs from 0.25 to 0.5 mg/L. Vancomycin with/without tobramycin was compared with ceftaroline with/without tobramycin. In studies of the 3 agents individually, at 0.25 or 0.5 times the MIC, no bactericidal activity was found against all 4 isolates. For vancomycin and ceftaroline combination therapy at 0.25 times the MIC, no synergy or antagonism was noted with the 4 isolates. However, at 0.5 times the MIC, ceftaroline plus tobramycin was synergistic against the two MRSA isolates (bactericidal effects beginning at 6.1 and 4.8 hours) and the hVISA isolate (bactericidal effect beginning at 4.5 hours). In contrast, vancomycin plus tobramycin at 0.5 times the MIC was indifferent against the two MRSA isolates. Like ceftaroline plus tobramycin, vancomycin plus tobramycin at 0.5 times the MIC was synergistic against the hVISA isolate (bactericidal effects beginning at 5.1 hours). The bactericidal activities of ceftaroline plus tobramycin were significantly greater than those of vancomycin plus tobramycin (both at 0.5 times the MIC) against the 2 MRSA isolates (\(P = 0.006, P = 0.01\)). No mono or combination therapies were bactericidal or synergistic against the VISA isolate. In summary, at sub-MIC concentrations, ceftaroline plus tobramycin was significantly more active than vancomycin plus tobramycin against MRSA isolates (\(P \leq 0.01\)).\textsuperscript{35}

Based upon these and additional studies, a combination product containing ceftaroline fosamil plus the beta-lactamase inhibitor NXL104 is currently being investigated, with a goal of extending the antimicrobial spectrum of ceftaroline to include extended-spectrum beta-lactamase-producing \textit{Enterobacteriaceae} and anaerobes.\textsuperscript{26,29,37,40–48}

Susceptibility breakpoints for MIC and disk diffusion testing (latter using a 30 mcg disk) are presented in Table 2.\textsuperscript{2} In addition, quality control limits for these testing methods were approved by the Antimicrobial Sensitivity Testing subcommittee of the Clinical Laboratory Standards Institute (USA) in June, 2006. These limits were established for 2 strains of \textit{S. aureus} and 1 strain each of \textit{E. coli}, \textit{S. pneumoniae}, and \textit{H. influenzae}.\textsuperscript{39} The results of ceftaroline susceptibility testing with the E-test MIC and the reference broth microdilution MIC methodology (CLSI) were compared using 39 bacterial isolates (\textit{E. coli}, \textit{Enterobacter} spp., \textit{K. pneumoniae}, \textit{P. mirabilis}, \textit{Serratia} spp., \textit{Citrobacter} spp., \textit{E. faecalis}, \textit{MSSA}, \textit{MRSA}, \textit{VISA}, \textit{hVISA}, and \textit{MR coagulase-negative staphylococci}). Excellent agreement was noted, even over a 10\textsuperscript{2} range in inoculum size (100%
of E-test results were within 1 tube dilution of the reference standard).50

In vitro resistance
Spontaneous mutation frequencies were determined in 11 different gram-positive and -negative isolates exposed to ceftaroline. For MSSA, MRSA, community-acquired MRSA, VISA, PRSP, PSSP, and beta-lactamase-negative H. influenzae isolates, the spontaneous mutation frequencies were zero. No spontaneous resistance was noted with the vancomycin-resistant E. faecalis isolate as well. However, for the vancomycin-susceptible E. faecalis isolate, a spontaneous mutation frequency of $1.25 \times 10^7$ was found.51

Single-step mutant selection has not occurred in experiments with MSSA, MRSA, VISA, pneumococci, and H. influenzae.31 However, single-step mutant selection was possible with AmpC-inducible E. cloacae and TEM-positive E. coli.31

Multistep mutant selection has not occurred in experiments with MSSA, MRSA, and VISA but was seen with TEM-positive strains of E. coli (where MICs rose 16- and 512-fold in 2 strains).31,51 It has also not occurred with CA-MRSA, PSSP, PRSP, and beta-lactamase-negative H. influenzae.51 However, ceftaroline MIC values have been increased 4-fold with serial passaging of vancomycin-susceptible and -resistant isolates of E. faecalis.51 In studies with pneumococcal and S. pyogenes isolates, no selection of resistant clones has occurred upon serial passaging in the presence of ceftaroline, even with penicillin- and macrolide-resistant isolates. This was similar to the results with amoxicillin/clavulanate, ceftriaxone, and linezolid. In contrast, resistant clones did develop to azithromycin (in 4/5 and 3/4 isolates), moxifloxacin (in 5/8), and tigecycline (in 2 pneumococcal isolates).52,53 In another study utilizing H. influenzae (4 isolates) and M. catarrhalis (1 isolate), serial passaging in the presence of ceftaroline selected out a resistant clone in only 1 isolate, a quinolone-resistant, beta-lactamase-positive strain of H. influenzae (MIC rose 16-fold, from 0.06 to 1 mg/L). Comparators developed no clones (ceftriaxone, amoxicillin/clavulanate), 1 clone (azithromycin, tigecycline), 3 clones (linezolid), or 4 clones (moxifloxacin).54

Four MRSA isolates with a ceftaroline MIC of 4 mg/L were investigated to determine the mechanism(s) of reduced susceptibility to the drug. Three amino acid mutations were found in the non-penicillin binding domain of mecA (N → K146/204; E → K150). All were related to the ST-239/spa t037 clone and had no mecI (repressor).15

The induction of AmpC production by ceftaroline was studied using two strains each of E. cloacae, C. freundii, M. morganii, S. marcescens, and P. vulgaris. Mean induction ratios at 1 times the MIC were 1.8-fold, 1.8-fold, and 3.0-fold for ceftaroline, cefotaxime, and ceftriaxone, respectively. All agents were low AmpC producers compared with the reference standard cefoxitin (mean 116-fold, ranged up to 417-fold). Ceftaroline was a significant inducer (up to 146-fold) at 4 to 16 times the MIC but still was weaker than cefoxitin. Thus, like other oxyimino cephalosporins, ceftaroline is a relatively weak inducer of AmpC production. Increased AmpC production was shown to be the mechanism of resistance in the single isolate which developed reduced susceptibility to ceftaroline during the acute bacterial skin and skin structure infection trials (N = 1,396 patients). This E. cloacae isolate exhibited a 5.4-fold increase in AmpC production without

<table>
<thead>
<tr>
<th>Pathogen (Source)</th>
<th>MICs (mg/L)</th>
<th>Disk zone diameters (mm)a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>S. aureus (skin only)</td>
<td>≤1</td>
<td>–</td>
</tr>
<tr>
<td>S. agalactiae (skin only)</td>
<td>≤0.03</td>
<td>–</td>
</tr>
<tr>
<td>S. pyogenes (skin only)</td>
<td>≤0.015</td>
<td>–</td>
</tr>
<tr>
<td>S. pneumoniae (CAP isolates only)</td>
<td>≤0.25</td>
<td>–</td>
</tr>
<tr>
<td>H. influenzae (CAP isolates only)</td>
<td>≤0.12</td>
<td>–</td>
</tr>
<tr>
<td>Enterobacteriaceae (CAP and skin)</td>
<td>≤0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: aUsing a 30 mcg disk. Adapted from reference 2.
Abbreviations: MIC, minimum inhibitory concentration; S, sensitive; I, intermediate; R, resistant; CAP, community-acquired bacterial pneumonia.

### Table 2. Susceptibility breakpoints for MIC and disk diffusion testing of ceftaroline.
induction and 12.8-fold increase when induced (at 1 times the MIC).\textsuperscript{55} Thus, ceftaroline, like other cephalosporins, can select for AmpC-derepressed or hyperinducible mutants which can potentially lead to widespread resistance. This has led to interest in a combination product of ceftaroline fosamil plus a beta-lactamase inhibitor (NXL104) as previously discussed.

**In vivo antimicrobial activity (Animals)**

Ceftaroline has also been tested using in vivo animal models of infection. In the rabbit endocarditis model using one strain each of MSSA, MRSA, and GISA, ceftaroline, daptomycin, and tigecycline significantly reduced vegetation bacterial counts compared with no treatment controls ($P$ range $< 0.05$–$< 0.001$) in all 3 strains. In addition, the effects of ceftaroline and daptomycin significantly exceeded those of tigecycline in all 3 strains ($P$ range $< 0.05$–$< 0.001$). Daptomycin-resistant mutants emerged from the MSSA and MRSA strains.\textsuperscript{56} Similar findings occurred in a study comparing ceftaroline and teicoplanin with no treatment controls using a susceptible strain of MRSA. Both active treatments significantly reduced vegetation bacterial counts and increased the proportions having sterile vegetations compared with controls (all $P < 0.001$).\textsuperscript{57} In a model of enterococcal endocarditis, two *E. faecalis* strains were used, one vancomycin-sensitive (VSEF) and one vancomycin-resistant (VREF). For the VSEF strain, ceftaroline had a numerically greater effect on vegetation counts than did vancomycin or linezolid (all 3 being superior to controls, all $P < 0.001$). For the VREF strain, ceftaroline was superior to both active comparators ($P < 0.001$).\textsuperscript{58}

Ceftaroline was compared with vancomycin and linezolid in the rabbit endocarditis model using 1 strain each of MRSA and hGISA (respective MICs were 1 and 2 mg/L, 1 and 4 mg/L, and 2 and 1 mg/L). Ceftaroline and linezolid were administered as human-equivalent IV doses while vancomycin was administered as a continuous IV infusion (no data were provided with respect to the presence/absence of a loading dose and targeted/achieved serum concentrations). All 3 active agents were superior to no drug controls in terms of reducing vegetation bacterial counts for both strains (all $P < 0.001$). In addition, vegetation counts were significantly lower in ceftaroline-treated animals compared with linezolid-treated animals (means 2.5 vs. 7.1 log CFU/g, $P < 0.001$) and in vancomycin-treated animals compared with linezolid-treated animals (mean 2.7 log CFU/g with vancomycin, $P < 0.001$) for the MRSA strain. For the hGISA strain, ceftaroline was superior to both linezolid and vancomycin (mean log CFUs/g of 3.0, 6.9, and 6.7, respectively; all $P < 0.001$).\textsuperscript{59}

Ceftaroline, daptomycin, and vancomycin were compared in the rat endocarditis model using a bioengineered bioluminescent, biofilm-positive strain of *S. aureus*. Results were similar for tissue bacterial counts quantitated using traditional methods or bioluminescent signals. Only vancomycin and ceftaroline significantly reduced vegetation bacterial counts compared with no drug controls (respective mean log CFU/g values of 6.8, 4.9, and 9.9; vancomycin $P < 0.05$; ceftaroline $P < 0.0005$). Similar findings were noted for kidney and spleen tissue counts (respective mean log CFU/g values of 4.2, 4.1, and 7.3 in kidney and 4.3, 3.6, and 6.5 in spleen; all vancomycin, $P < 0.05$; all ceftaroline, $P < 0.0005$).\textsuperscript{60}

In a rabbit osteomyelitis model, ceftaroline and linezolid were superior to vancomycin in reducing bacterial counts in joint fluid, bone marrow, and bone (for 1 strain each of MRSA and GISA, all $P < 0.05$).\textsuperscript{61} Ceftaroline was compared with ceftriaxone and ceftriaxone plus vancomycin in the penicillin-susceptible and penicillin-resistant *S. pneumoniae* meningitis model in rabbits, respectively. For the penicillin-susceptible strain, at 1 hour the reductions in cerebrospinal fluid (CSF) bacterial counts were similar but at 8 hours, ceftaroline had a significantly greater effect ($−6.35$ vs. $−5.54$ log CFU/mL, $P < 0.03$). For the penicillin-resistant strain, ceftaroline was associated with significantly greater effects than the combination at both 1 hour ($−0.71$ vs. $−0.59$ log CFU/mL, $P < 0.009$) and 8 hours ($−5.54$ vs. $−4.65$ log CFU/mL, $P < 0.003$).\textsuperscript{62} In two *in vivo* animal studies (murine sepsis model and neutropenic thigh mouse model) using *Enterobacteriaceae* producing extended-spectrum $\beta$-lactamase or carbapenemases, ceftaroline, as expected, performed poorly.\textsuperscript{37,41}

In a study of the effect of ceftaroline on intestinal microflora, 12 healthy volunteers received a seven day regimen of 600 mg IV every 12 hours. Fecal counts of
E. coli were minimally impacted while counts of enterococci and Candida albicans were within normal variation. Bifidobacteria and Lactobacilli counts fell moderately (by 2.1 and 1.7 log CFU/g feces) over the initial 9 days while clostridial counts concurrently rose approximately 2.0 log CFU/g feces. There was no important effect on Bacteroides species counts. No new colonizing aerobic or anaerobic bacteria resistant to ceftaroline were found. Two subjects had C. difficile strains isolated on study days 5, 7, and 9. All were toxin B positive and positive for the ToxA and ToxB genes. However, in the absence of the binary toxin gene and symptoms, these findings were considered to have no clinical relevance. Overall, ceftaroline was found to have no significant ecological impact on human intestinal microflora.

Pharmacokinetics

Table 3 illustrates single- and multiple-dose pharmacokinetic parameters for ceftaroline after IV infusion and IM administration. The conversion of the prodrug ceftaroline fosamil to ceftaroline proceeds rapidly, such that concentrations of the prodrug are below assay limits within a short time following the end of infusion. Pharmacokinetics appear to be linear in nature, with dose-proportional changes in peak serum concentrations (Cmax) and areas under the serum concentration-versus-time curve (AUC) occurring for single IV doses ranging from 50 to 1000 mg, single IM doses ranging from 400 to 600 mg, and multiple IV doses ranging from 300 to 600 mg every 12 hours. This linearity also applies to pharmacokinetics of the prodrug and a ceftaroline metabolite (M-1). In multiple dose studies, no accumulation was noted, whether administered by the IV or IM routes.

Intramuscular dosing studies were initially conducted in rats, rabbits, and monkeys in order to examine the feasibility of this route in humans. Using human-equivalent single IM and IV doses, absolute bioavailability of the IM preparation was excellent, with AUCIM exceeding AUCIV for equivalent doses in all species. The mean absolute bioavailabilities were 229%, 107.3%, and 112.7% in rabbits, rats, and monkeys, respectively. No explanation for the unusual result in rabbits was available. Mean Cmax values were reduced in rabbits and monkeys by 62% and 63%, respectively, compared to values after IV dosing. Since the microbiological activity of beta-lactams is related to time over which the drug concentration exceeds the MIC and is not related to peak drug concentrations, this route was acceptable as long as drug concentrations still exceeded the MICs of most pathogens over at least 50%–60% of the dosing interval. In addition, IM dosing was well-tolerated and supported investigation of the IM route in humans. Mean absolute bioavailability of ceftaroline in humans is approximately 100%. On day 5 of a dosage regimen of 600 mg IM every 12 hours, the mean percentage of time wherein the serum concentration exceeded an MIC value of 2 mg/L was 64.7% of the dosing interval. In a double-blind trial, healthy volunteers were randomized to receive either ceftaroline 600 mg IM every 12 hours or cefepime 1000 mg IM every 12 hours, both for 5 days. Although the frequency/severity of adverse events (AEs) overall were similar for the two drugs, injection site pain was noted by 2 of 6 cefepime recipients (33%) compared with none of 12 ceftaroline recipients. More relevant comparators for IM tolerability studies would be ceftiraxone and ertapenem, both being agents frequently used to treat serious lower respiratory tract infections in long-term care facility (LTCF) residents. 

Ceftaroline plasma protein binding is approximately 20% and decreases slightly over a concentration range of 1 to 50 mg/L (range, 14.5%–28.0%). Few data exist regarding penetration of the drug into various body fluid and tissue compartments. Penetration across inflamed meninges in the rabbit S. pneumoniae meningitis model was approximately 14%. Lung tissue penetration in rabbits after single human-equivalent doses administered IV was characterized by mean lung/plasma concentration ratios of 36 to 46 (mean 42), with mean lung tissue concentrations falling from 19 mg/kg down to 0.6 mg/kg over the course of 1 hour. The median (range) steady-state volume of distribution in healthy adults was 20.3 L (18.3–21.6 L), similar to extracellular fluid volume. Ceftaroline was not metabolized by the cytochrome P450 enzyme system in in vitro human liver microsome studies. However, the presence of a metabolite found in phase I human studies (M-1) still requires an explanation in terms of the mechanism of its production and its chemical structure. It is known that it is an open-ring, biologically inactive metabolite.
Ceftaroline, a new anti-MRSA cephalosporin

Table 3. Pharmacokinetic parameters of ceftaroline in humans (data are expressed as means, unless otherwise noted).

<table>
<thead>
<tr>
<th>Subject population</th>
<th>Dose and frequency (N)</th>
<th>Route</th>
<th>C\textsubscript{max} (mg/L)</th>
<th>AUC (mg/L·hr.)\textsuperscript{a}</th>
<th>t 1/2 (hr.)</th>
<th>CL (mL/min)</th>
<th>CL\textsubscript{R} (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects\textsuperscript{d64}</td>
<td>50 mg × 1 dose (6)</td>
<td>IV over 1 hr.</td>
<td>1.5</td>
<td>3.9</td>
<td>2.0</td>
<td>–</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>100 mg × 1 dose (6)</td>
<td></td>
<td>2.9</td>
<td>6.6</td>
<td>2.2</td>
<td>–</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>250 mg × 1 dose (6)</td>
<td></td>
<td>9.9</td>
<td>22.9</td>
<td>2.3</td>
<td>–</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>500 mg × 1 dose (6)</td>
<td></td>
<td>16.5</td>
<td>44.7</td>
<td>2.5</td>
<td>–</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>750 mg × 1 dose (6)</td>
<td></td>
<td>23.0</td>
<td>56.9</td>
<td>2.6</td>
<td>–</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>1000 mg × 1 dose (6)</td>
<td></td>
<td>30.2</td>
<td>80.5</td>
<td>2.9</td>
<td>–</td>
<td>129</td>
</tr>
<tr>
<td>Healthy subjects\textsuperscript{d65}</td>
<td>300 mg q 12 hr. × 14 days (6)</td>
<td>IV over 1 hr.</td>
<td>day 1 10</td>
<td>26</td>
<td>2.5</td>
<td>173</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>600 mg q 12 hr. × 14 days (6)</td>
<td></td>
<td>day 1 8.4</td>
<td>24</td>
<td>2.6</td>
<td>183</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>800 mg q 24 hr. × 7 days (6)</td>
<td></td>
<td>day 1 29</td>
<td>72</td>
<td>2.2</td>
<td>164</td>
<td>–</td>
</tr>
<tr>
<td>Healthy subjects,\textsuperscript{d66} mild and moderate renal impairment</td>
<td>600 mg × 1 (N = 6 in each group)</td>
<td>IV over 1 hr.</td>
<td>27 ± 7</td>
<td>68 ± 18</td>
<td>2.8 ± 0.4</td>
<td>126 ± 34</td>
<td>–</td>
</tr>
<tr>
<td>Healthy subjects,\textsuperscript{d66} severe renal impairment</td>
<td>400 mg × 1 (N = 6 in each group)</td>
<td>IV over 1 hr.</td>
<td>15 ± 1.8</td>
<td>53 ± 11</td>
<td>3.0 ± 0.4</td>
<td>115 ± 24</td>
<td>–</td>
</tr>
<tr>
<td>Healthy subjects\textsuperscript{d68}</td>
<td>400 mg × 1 (6)</td>
<td>IM</td>
<td>7.0 ± 1.6</td>
<td>36 ± 6.1</td>
<td>2.4 ± 0.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>600 mg × 1 (6)</td>
<td></td>
<td>8.5 ± 1.7</td>
<td>48 ± 3.9</td>
<td>2.6 ± 0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1000 mg × 1 (6)</td>
<td></td>
<td>16 ± 3.7</td>
<td>110 ± 31</td>
<td>2.7 ± 0.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>600 mg × 1 (6)</td>
<td>IV over 1 hr.</td>
<td>Day 1 12 ± 3.4</td>
<td>55 ± 11</td>
<td>2.5 ± 0.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Healthy subjects\textsuperscript{d68}</td>
<td>600 mg q 12 hr. × 5 days (12)</td>
<td>IM</td>
<td>Day 5 13 ± 1.4</td>
<td>65 ± 12</td>
<td>2.5 ± 0.5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: \textsuperscript{a}For single-dose data, used AUC\textsubscript{∞}; for multiple-dose data, used AUC\textsubscript{τ}; \textsuperscript{b}ascribed to “sample processing problem”; \textsuperscript{c}CrCl > 80 mL/min (mean ± SD, 108 ± 13 in ref. 66, mean ± SD data NA in ref. 67); \textsuperscript{d}CrCl 51–80 mL/min (mean ± SD, 64 ± 11); \textsuperscript{e}CrCl 31–50 mL/min (mean ± SD, 38 ± 10); \textsuperscript{f}data expressed as mean ± SD; \textsuperscript{g}CrCl ≤ 30 mL/min (mean ± SD data NA); \textsuperscript{h}Same subjects received 600 mg single doses by IM and IV routes, with a 7-day washout period between doses.

Abbreviations: N, number of subjects; C\textsubscript{max}, peak plasma concentration; AUC, area under the plasma concentration-versus-time curve; t 1/2, terminal disposition half-life; CL, total body clearance; CL\textsubscript{R}, renal clearance; IV, intravenous; IM, intramuscular; NA, not available.

Ceftaroline and the M-1 metabolite appear to be eliminated primarily via renal excretion.\textsuperscript{d64} The M-1 metabolite/ceftaroline AUC\textsubscript{∞} ratio following a single 600 mg IV dose in healthy volunteers was 28% ± 3.1% (mean ± SD).\textsuperscript{2} Ceftaroline was not eliminated via the fecal route as evidenced by no measurable fecal drug concentrations on days 2, 5, and 7 of a seven day regimen of 600 mg IV every 12 hours.\textsuperscript{d63} However, following administration of a single 600 mg IV dose of radiolabelled compound to healthy subjects, approximately 88% of the radioactivity was recovered in urine and 6% in feces within 48 hours.\textsuperscript{2} Taking the results of these two data sources together, apparently only metabolite(s) is/are excreted...
in feces. In urine, 64% and 2% of the radioactivity was excreted as ceftaroline and the M-1 metabolite, respectively. Renal clearance of ceftaroline was 5.56 ± 0.20 L/hr (mean ± SD), suggesting that clearance occurs predominantly via glomerular filtration.

The pharmacokinetics of ceftaroline are altered in the presence of renal impairment (Table 3). Terminal disposition half-life increases and total body clearance (CL) decreases as renal function falls. In mild renal impairment (creatinine clearance [CrCl] of 31–50 mL/min), AUCs rose by means of 19% and 51–80 mL/min) and moderate renal impairment (CrCl of mild renal impairment (CrCl < 30 mL/min), mean AUC and C max rose 115% and 21%, respectively, while CL, renal clearance, and amount excreted as parent drug fell 53%, 66%, and 84%, respectively, compared with subjects with normal renal function. In patients undergoing hemodialysis, post-hemodialysis administration led to a mean 167% increase in AUC compared with subjects with normal renal function. Mean dialysate recovery of ceftaroline was 22% of the administered dose over a 4-hour hemodialysis session. Although formal studies have not been conducted, it does not appear that hepatic impairment would have a significant impact on ceftaroline pharmacokinetics. In elderly patients (≥65 years old), the geometric mean AUC∞ of ceftaroline was approximately 33% higher than the AUC∞ in 18–45 year old subjects. This effect could be explained by age-related reductions in renal function. Thus, age by itself has no significant effect on ceftaroline pharmacokinetics. In a 4-way study involving healthy young males/females and healthy elderly males/females, there was a nonsignificant trend towards a higher C max (mean 17%) and AUC∞ (means of 6%, 15%) in female subjects. This could be explained by differences in weight between the genders.

The population pharmacokinetics of ceftaroline have been determined using serum concentration-versus-time data from 127 subjects completing phase I and II clinical trials. The subject population comprised 54 healthy subjects, 23 subjects with renal impairment, and 50 subjects with acute bacterial skin and skin structure infections (ABSSSI). Using a commercially-available modeling (NONMEM) program, data fit a two-compartment open model with zero-order input and first-order output. Renal function was the primary factor predicting CL. Mean renal clearance was 63 mL/min with a between-subject coefficient of variation (CV, a measure of variability) of 21%. Volume parameters V1 and V2 were mean 17.3 L (26% CV) and 4.89 L (40% CV), respectively, while the intercompartment flow rate was mean 30.5 mL/min (58% CV). A mean non-renal clearance value of 74.5 mL/min (no CV data provided) was calculated. The model created was said to be robust in predicting actual serum concentration-versus-time profiles in subjects with differing levels of renal function.

This model was utilized to simulate 600 mg every 12 hour IV regimens of ceftaroline in subjects with normal renal function and mild and moderate renal impairment, with a view to providing dose adjustment recommendations for the renally-impaired. With predicted mean AUC∞ values of 129, 163, and 187 mg·L⁻¹·h and C max values of 23.1, 24.7, and 25.7 mg/L, respectively, dosage adjustment was only recommended in those with moderate renal impairment (ie, reduce dose from 600 to 400 mg/dose).

Another group has evaluated the population pharmacokinetics of ceftaroline, using serum concentration-versus-time data from 185 subjects in seven phase I clinical trials. This study included data from subjects with severe renal impairment, including those on hemodialysis. The pharmacokinetics of both the prodrug and ceftaroline were modeled. The prodrug pharmacokinetics were best described by a three-compartment open model with zero-order input (or dual-phase first-order input after IM dosing) and first-order elimination. Mean prodrug CL was 3933 mL/min. Mean intramuscular bioavailability was 129%. For ceftaroline, its pharmacokinetics were best described by a two-compartment open model with first-order prodrug conversion (k met = mean 22.4 hr⁻¹) and parallel first-order (k lin = mean 0.342 hr⁻¹) and saturable elimination (V max = mean 386 mg/hr, K i = mean 40.4 mg/L). The mean steady-state volume of distribution was 25.8 L. Volume of distribution of the central compartment rose with increasing body surface area (BSA). V max and K i fell as CrCl fell. V max also fell as age rose. Creatinine clearance was the pri-
mary determinant of ceftaroline systemic exposure while age and BSA had clinically-insignificant effects. Despite the presence of nonlinear pharmacokinetics, the AUCₚ for 250 to 1000 mg doses varied by less than 10% (normalized to a 600 mg dose). This latter fact probably accounts for the technically incorrect findings of linearity found in earlier small investigations.

**Clinical Efficacy**

CANVAS-1 was a randomized, double-blind study comparing IV ceftaroline fosamil with the combination of IV vancomycin plus IV aztreonam in the treatment of acute bacterial skin and skin structure infections in adults. Subjects were randomized (1:1) to receive either ceftaroline fosamil 600 mg every 12 hours or vancomycin 1 g plus aztreonam 1 g, each every 12 hours, both regimens for a duration of 5–14 days. The primary goal of this study was to determine whether or not ceftaroline fosamil was noninferior to the combination therapy in clinical cure rates determined at 8–15 days following the end of treatment in clinically-evaluable (CE) and modified intent-to-treat (mITT) populations. Noninferiority was defined as occurring when the lower limit of the 95% confidence interval (CI) of the difference in cure rates was greater than −10%. Of 702 subjects enrolled, 353 and 349 were randomized to receive ceftaroline fosamil and the combination, respectively. In the CE population (definition not provided), clinical cure rates were 91.1% (288/316) with ceftaroline fosamil therapy and 93.3% (280/300) with combination therapy. Ceftaroline fosamil was noninferior to the combination since the lower limit of the 95% CI was −6.6%. In the mITT population (definition not provided), corresponding clinical cure rates were 86.6% (304/351) and 85.6% (297/347). Again, ceftaroline fosamil was noninferior to the combination since the lower limit of the 95% CI was −4.2%. Overall microbiological success rates (definition not provided) were 91.8% (224/244) with ceftaroline fosamil and 92.5% (210/227) with the combination. Microbiological success rates for MRSA were 94.9% (75/79) with ceftaroline fosamil and 95.1% (58/61) with the combination. Clinical cure rates in this MRSA subset were identical to the microbiological success rates previously noted. Both study groups experienced similar rates of adverse events, serious adverse events, deaths, and discontinuations due to adverse events. The most common adverse events (ceftaroline fosamil/combination) were nausea (5.7%/4.6%), headache (5.1%/3.7%), and pruritus (3.1%/8.4%). No results of statistical analyses (with the exception of noninferiority) were provided. Using data and *S. aureus* isolates from this study, it has been suggested that the presence of Panton-Valentine Leukocidin (pvl) does not alter clinical response in acute bacterial SSSI.

Results of a phase II trial conducted in sites in the US, South America, South Africa, and Russia, evaluating the comparative efficacy of IV ceftaroline fosamil and IV vancomycin with/without aztreonam in acute bacterial skin and skin structure infections, have been published. Acute bacterial infections were defined as those in deeper soft tissues and/or those requiring significant surgical intervention and/or those on a lower extremity in patients with diabetes or peripheral vascular disease. Subjects had to exhibit at least 1 marker of systemic inflammation (1 or more of oral temperature >38 °C, white blood cell count >10,000/cu.mm., and >10% band forms of polymorphonuclear leukocytes). They also had to exhibit 2 or more local signs (purulent/serosanguinous drainage, erythema, fluctuance, heat/local warmth, induration, swelling, and pain). In this observer-blinded study, subjects were randomized (2:1) to receive either ceftaroline fosamil 600 mg IV every 12 hours or vancomycin 1 g IV every 12 hours, both regimens for a duration of 7–14 days. Aztreonam 1 g IV every 8 hours could be added to the vancomycin regimen if gram-negative bacilli were suspected at baseline (this occurred in 7 subjects [26%] and continued for a mean of 5.1 days [range 1.0–12.1 days]). The mean (range) durations of the ceftaroline fosamil and vancomycin therapies were 7.8 days (0.4–9.5 days) and 8.0 days (2–20.5 days), respectively. A parenteral penicillinase-resistant penicillin could be substituted for vancomycin within the initial 72 hours of therapy if allowable on the basis of culture and susceptibility test results (this occurred in 1 subject [4%]). No oral “switch therapy” was allowed. The primary outcome was clinical cure rate at the test-of-cure visit 8 to 14 days after the end of therapy. Secondary outcomes include microbiological success rate (defined as eradication or presumed eradication if the site could no longer be sampled) at the test-of-cure visit and clinical relapse rate at 21 to 28 days after the end of therapy.
Of 100 subjects enrolled, 88 were clinically-evaluable (61 on ceftaroline fosamil, 27 on vancomycin with/without aztreonam). Clinical cure rates were 96.7% (ceftaroline fosamil) and 88.9% (vancomycin with/without aztreonam). In the clinically modified intent to treat population, corresponding clinical cure rates were 88.1% and 81.3%. In the 63 microbiologically-evaluable subjects (defined as clinically-evaluable plus had ≥1 susceptible pathogen cultured at baseline), microbiological success rates were 95.2% (ceftaroline fosamil, N = 42) and 85.7% (vancomycin with/without aztreonam, N = 21). Clinical relapse occurred in 1 subject in each group. Microbiological eradication rates (by pathogen) were 93.1% (ceftaroline fosamil, 58 organisms) and 90.9% (vancomycin with/without aztreonam, 22 organisms). The most common adverse events (ceftaroline fosamil/vancomycin with/without aztreonam) included insomnia (6%/6.3%), nausea (6%/0), and rash (1.5%/6.3%). With ceftaroline fosamil therapy, 3%, 1.5%, and 1.5% of subjects experienced infusion site pain, swelling, and thrombosis, respectively. Overall, 6% of ceftaroline fosamil recipients experienced infusion-associated local or systemic adverse events (3% were considered to be treatment-related). With vancomycin with/without aztreonam therapy, 9.4%, 3.1%, and 3.1% of subjects experienced infusion site phlebitis, pruritus and erythema, and swelling and erythema, respectively. Overall, 25% of vancomycin with/without aztreonam recipients experienced infusion-associated local or systemic adverse events. All were considered treatment-related and 9.4% had symptoms suggestive of histamine release, ie, “Red Man Syndrome”.78

FOCUS 1 and 2 were two randomized, double-blind studies of the treatment of hospitalized patients with community-acquired bacterial pneumonia (CAP) with IV ceftaroline fosamil and IV ceftriaxone. Adult patients of Pneumonia Outcomes Research Trial (PORT) risk classes 3 and 479 who required IV therapy were randomized (1:1) to receive 5 to 7 days of ceftaroline fosamil 600 mg every 12 hours or ceftriaxone 1 g every 12 hours. The primary goal of these studies was to determine whether or not ceftaroline fosamil was noninferior to ceftriaxone in terms of clinical cure rates at 8 to 15 days after the end of treatment. The definition of noninferiority was the same as previously described. Pooled results only were provided. Of 1228 treated subjects, 614 received each drug. Clinical cure rates in the CE population were 84.3% (ceftaroline fosamil, N = 459) and 77.7% (ceftriaxone, N = 449). Noninferiority of ceftaroline fosamil was confirmed since the lower limit of the 95% CI was +1.6%. In the mITT population, corresponding clinical cure rates were 82.6% (N = 580) and 76.6% (N = 573). Again, noninferiority was confirmed by a lower limit of the 95% CI of +1.4%. For the separate trials, noninferiority was confirmed in the mITT populations by lower limits of the 95% CI of +1.4% (FOCUS-1) and −2.5% (FOCUS-2). In the microbiologically mITT population, clinical cure rates in subjects with documented pneumococcal infection were 85.5% (ceftaroline fosamil, N = 69) and 68.6% (ceftriaxone, N = 70). Corresponding clinical cure rates in S. aureus infections were 72.0% (N = 25) and 60.0% (N = 30). The 3 most common adverse events (ceftaroline fosamil/ceftriaxone) were diarrhea (4.2%/2.6%), headache (3.4%/1.5%), and insomnia (3.1%/2.3%).80

Medical resource utilization in the FOCUS 1 and 2 trials was evaluated in a pooled retrospective analysis. For a subset of the study population (how this subset was selected was not described), data were collected pertaining to hospital admission and discharge dates, times in various inpatient units, and times on mechanical ventilation. Patients from a given country could only be included if that country had a hospital reimbursement policy similar to that of the US (ie, diagnosis-related group- or DRG-based). Of 317 patients whose data were selected for analysis, 157 and 160 had received ceftaroline fosamil and ceftriaxone, respectively. Documented pneumococcal infection had occurred in 8% and 10% of patients, respectively. The analysis was conducted on all 317 datasets as well as the 29 datasets with subjects having confirmed pneumococcal disease. The mean length of stay was 0.8 days shorter in ceftaroline fosamil recipients compared with ceftriaxone recipients (P = NS). The groups were also similar for rates of mechanical ventilator use (ceftaroline fosamil, 4.5%; ceftriaxone, 5%; P = NS) and mean durations of stay in the intensive care unit (ceftaroline fosamil, 0.1 day; ceftriaxone, 0.2 day; P = NS). In the population with documented pneumococcal infection, the mean difference in the lengths of stay (3.5 days in favor of ceftaroline fosamil) was greater than that in the overall
population (0.8 days) but was still nonsignificant. This study suffered from small numbers of datasets, leading to a lack of statistical power.81

**Tolerability**

Similar to most beta-lactams, ceftaroline fosamil is well-tolerated after IV administration, with mild to moderate nausea, insomnia, headache, rash, and diarrhea being the most common although infrequent (≤6%), adverse effects. Infusion site reactions are uncommon (≤3%). Table 4 illustrates adverse event data for 1300 recipients of IV ceftaroline fosamil and 1297 recipients of IV comparator agents (vancomycin plus aztreonam or ceftriaxone) in four phase 3 randomized, controlled trials in ABSSSI (N = 2 trials) and CAP (N = 2 trials). Serious adverse events occurred in 7.5% and 7.7% of ceftaroline fosamil and comparator drug recipients, respectively, most being in the respiratory and infection system organ classes. Treatment discontinuation due to adverse events occurred in 2.7% and 3.7%, respectively (most common were hypersensitivity reactions in 0.3% and 0.5%, respectively). Seroconversion from a negative to a positive direct Coombs’ test result occurred in 10.8% and 4.4%, respectively. However, drug-induced hemolytic anemia was not reported.2 Tolerability of the IM route was good, as well, although the database for this route was much smaller than that for the IV route.

Ceftaroline fosamil is rated as category B in pregnancy and it is not known whether or not it is excreted in human breast milk.2 Safety and effectiveness have not been established in pediatric patients.2 Almost one-third (30.5%) of patients enrolled in the four phase 3 trials were at least 65 years old. Adverse event profiles were similar in these patients compared with younger patients.2 Ceftaroline fosamil, administered as a single 1500 mg IV infusion over 1 hour, had no significant effect on the QTc interval of the electrocardiogram.2

### FDA-Approved Indications

Ceftaroline fosamil is indicated for the treatment of acute bacterial skin and skin structure infections (caused by susceptible strains of methicillin-sensitive and -resistant*S. aureus*, *S. pyogenes*, *S. agalactiae*, *E. coli*, *K. pneumoniae*, and *K. oxytoca*) and community-acquired bacterial pneumonia (caused by susceptible strains of *S. pneumoniae*, *S. aureus* [methicillin-susceptible strains only], *H. influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*).2

### Dosage and Administration

Ceftaroline fosamil is available in 400 and 600 mg vials for reconstitution with sterile water. The ceftaroline fosamil dosage regimen in the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia is 600 mg, administered via IV infusion over 1 hour, given every 12 hours. Durations of therapy are 5 to 14 days (ABSSSI) and 5 to 7 days (CAP). Dosage adjustment is necessary in moderate, severe, and end-stage renal impairment/hemodialysis. In moderate renal impairment (CrCl 31–50 mL/min), the dosage should be reduced to 400 mg (from the usual 600 mg) while the dosing interval remains at 12 hours. For severe renal impairment (CrCl 15–30 mL/min), the dosage should be reduced to 300 mg administered at the usual 12-hour interval. For end-stage renal impairment and patients on hemodialysis, the dosage should be reduced to 200 mg administered at the usual 12-hour interval. In addition, in patients on hemodialysis therapy, the dose should be administered at the end of...
the dialysis session since the drug is dialyzable (22% removal over 4 hours). The author is unaware of whether or not any drug-drug interaction studies have been performed with ceftaroline fosamil. Certainly, at a minimum, the interaction with probenecid, a blocker of renal tubular secretion of other beta-lactams, should be investigated. Investigation of the interaction of ceftaroline fosamil with warfarin would also be desirable. In addition, the compatibility of ceftaroline fosamil with a variety of large volume parenteral (LVP) solutions and admixed/Y-connector-exposed drugs needs to be assessed. Until then, ceftaroline fosamil should only be admixed into the following LVP solutions: normal and one-half normal saline, 2.5% and 5% dextrose in water, and lactated Ringer’s. It should not be admixed with or administered via Y-connector concurrently with any other drug. Information regarding the reconstitution of the product for IM use and specific indications for IM use are pending.

**Place in Therapy**

Ceftaroline fosamil appears to be a potentially valuable addition to the therapeutic armamentarium for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, especially in geographic areas where community- and/or hospital-acquired MRSA is a concern and in post-influenzal bacterial pneumonia where *S. aureus* as a secondary invader is a significant issue. Its use in acute bacterial skin and skin structure infections may be somewhat compromised by the presence of resistant *Enterobacteriaceae, Pseudomonas aeruginosa*, and anaerobes, especially in the context of infected diabetic ulcers in the lower extremities and pressure ulcers overlying the sacrum. Local infection control reports will need to be consulted regarding the beta-lactamase-producing status of gram-negative aerobic and anaerobic dermatologic pathogens as a guide to deciding whether or not to use empiric ceftaroline fosamil therapy. Should the current investigation of ceftaroline fosamil in combination with a broad-spectrum beta-lactamase inhibitor (NXL104) lead to marketing of a combination product analogous to other beta-lactam/beta-lactamase inhibitor combinations, these preceding fears will largely be allayed. In addition, the types of bacterial infections treatable with ceftaroline fosamil will be expanded beyond the current limited spectrum with ceftaroline fosamil alone (ie, ABSSSI and CAP). Ceftaroline fosamil plus NXL104 will, in all likelihood, expand the indications to include the management of a variety of intra-abdominal and genitourinary tract infections. In the interim, ceftaroline fosamil should be investigated for the management of staphylococcal bloodstream infections and endocarditis, indications for which it may become the treatment-of-choice, based on the *in vivo* animal data to date.

**Conclusions**

Ceftaroline fosamil (PPI-0903, TAK-599) is the prodrug for ceftaroline (T-91825), a broad-spectrum parenteral (IM/IV) cephalosporin with potent *in vitro* and *in vivo* activity against methicillin- and vancomycin-resistant *Staphylococcus* as well as other common pathogens of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CAP). Although more active than other cephalosporins against enterococci, the potency of this agent is still modest against *E. faecalis* (inactive vs. *E. faecium*). It is also active against *Enterobacteriaceae* with the exceptions of strains producing extended-spectrum beta-lactamases or carbapenemases. It is also active against anaerobic organisms with the exceptions of *Bacteroides* and *Prevotella* species and *Clostridium difficile*. Ceftaroline fosamil is non-inferior compared with regimens of vancomycin with/without aztreonam (ABSSSI) and ceftriaxone (CAP). The usual dosage regimen is 600 mg every 12 hours, as a 1-hour IV infusion, with dosage adjustment in moderate renal impairment (creatinine clearance [CrCl] of 31–50 mL/min) to 400 mg every 12 hours, in severe renal impairment (CrCl 15–30 mL/min) to 300 mg every 12 hours, and in end-stage renal impairment/hemodialysis (CrCl < 15 mL/min) to 200 mg every 12 hours. Further studies continue with a combination product of ceftaroline fosamil with NXL104 (a beta-lactamase inhibitor).

Availability of a combination ceftaroline fosamil-NXL104 product would expand the indications for this valuable new agent considerably. In the interim, it would be of considerable potential value to investigate ceftaroline fosamil in the therapy of serious staphylococcal infections including bacteraemia and endocarditis. Ceftaroline monotherapy of the latter conditions may be an important advance.
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Disclosures
This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that he has permission to reproduce any copyrighted material.

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