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EXPERT REVIEW

Ceftaroline: A Therapeutic Option for Community-Acquired Bacterial Pneumonia

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Abstract: On October 29, 2010, the U.S. FDA approved ceftaroline fosamil, a new cephalosporin with extended Gram positive coverage, for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia (CABP). Unlike the currently available cephalosporins, ceftaroline maintains bactericidal activity against multi-drug resistant Gram positive pathogens like MRSA and drug-resistant *S. pneumoniae* due to its high affinity to PBP-2a and PBP-2x respectively. Its antimicrobial spectrum also includes Gram negative respiratory pathogens like *H. influenzae*, *M. catarrhalis*, and certain non-ESBL producing Enterobacteriaceae. The pharmacokinetic profile of ceftaroline is linear and directly proportional to underlying renal function. Similar to other β-lactams, the pharmacodynamic profile that best determines its antimicrobial activity is %T > MIC. The results from two large randomized double-blind phase III trials (FOCUS 1 and FOCUS 2) for the treatment of adult patients with CABP, demonstrated comparable clinical cure rates between ceftaroline fosamil and ceftriaxone. Finally, ceftaroline fosamil has demonstrated an excellent safety and tolerability profile, making it an attractive option for its approved indications. The following article provides an in-depth, but focused review of the literature as it relates to the use of ceftaroline fosamil for the treatment of CABP.

Keywords: ceftaroline fosamil, community-acquired bacterial pneumonia (CABP), multi-drug resistant (MDR)

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Introduction

Community-acquired bacterial pneumonia (CABP) is among the leading infectious causes of hospitalization, morbidity, and mortality in the U.S. and other developed countries.[1–5] Individuals ≥ 65 years-old, in particular, have experienced an increasing rate of pneumonia-related hospitalizations and attributable mortality.[6,7] One of the important issues regarding the management of CABP is the treatment of multi-drug resistant (MDR) pathogens like community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and drug-resistant *Streptococcus pneumonia*.[8–10] There is a pressing need for new antimicrobials to help treat severe cases of CABP due to these organisms.

On October 29, 2010, the U.S. Food and Drug Administration (FDA) approved ceftaroline fosamil (Teraflo®; Forest Laboratories, Inc.), a new cephalosporin with extended Gram positive coverage, for the treatment of acute bacterial skin and skin structure infections due to methicillin-susceptible *S. aureus* (MSSA), MRSA, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*, and CABP due to *S. pneumonia* (including bacteremic cases), MSSA, *Haemophilus influenzae*, *E. coli*, *K. pneumoniae*, and *K. oxytoca*.[11,12]

The following provides an in-depth, but focused review of published research and selected abstracts from major pharmacology and infectious diseases conferences as they relate to the use of ceftaroline fosamil for the treatment of CABP.

Chemical Structure

Ceftaroline fosamil (TAK-599, PPI-9903) is the ethoxyimino derivative and N-phosphono prodrug of the parent compound ceftaroline (T-91825), which is suitable for parenteral administration in its crystalline form given its excellent water solubility (>100 mg/mL at pH 7) and stability in both liquid and solid state. Ceftaroline fosamil [(6R,7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4 thiadiazol-3-yl]acetamido}-3-{[4-(1-,methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo{4.2.0}oct-2-ene-2-carboxylate monoacetate monohydrate], undergoes rapid enzymatic hydrolysis of the phosphonate group and is converted to its active metabolite, ceftaroline, once infused into the bloodstream (Fig. 1).[12–14]

Mechanism of Action

The mechanism of action is similar to that of other β-lactams. Ceftaroline binds to penicillin-binding proteins (PBP's) and disrupts cell wall synthesis. Coverage of MSSA is mediated by ceftaroline's affinity to PBP-1 (IC_{50} = 0.1–0.5 μg/mL), PBP-2 (IC_{50} = 0.034–0.25 μg/mL), and PBP-3 (IC_{50} = 0.049–0.125 μg/mL). However, unlike other β-lactams, ceftaroline also maintains high affinity to the PBP-2a produced by MRSA (IC_{50} = 0.01–1 μg/mL), forming a stable inhibitory acyl-enzyme intermediate after inducing a conformational change and exposing the allosteric binding site.[15–17] The activity of ceftaroline against penicillin-sensitive and resistant *S. pneumoniae* (PSSP and PRSP) is mediated by its affinity to PBP-2x (IC_{50} = 0.025–0.1 μg/mL and 0.1–1 μg/mL), PBP-2a (IC_{50} = 0.053–0.25 μg/mL and 0.17–0.5 μg/mL), and PBP-2b (IC_{50} = 0.053–4 μg/mL and 0.17–4 μg/mL).[15] Similar to what is seen in *S. aureus*, ceftaroline forms an inhibitory acyl-enzyme intermediate that provides greater bactericidal activity against *S. pneumoniae* compared to penicillin or cefotaxime.[18] Ceftaroline also has demonstrated good affinity to most PBP's present in Gram negative respiratory pathogens like *H. influenzae* and *E. coli*.[19]

Spectrum of in-Vitro Antimicrobial Activity

The in vitro susceptibility to ceftaroline has been determined for a large number of clinical isolates from around the world using reference broth microdilution methods according to the Clinical and Laboratory Standards Institute (CLSI). Comprehensive reviews and analyses of the antimicrobial spectrum of ceftaroline have been published and referenced elsewhere.[20–44] A focused review of the in vitro activity of ceftaroline against pathogens that are associated with CABP is presented below.

In two large randomized, double-blinded, and multicenter phase 3 trials for the treatment of CABP (FOCUS 1 and FOCUS 2), ceftaroline demonstrated excellent in vitro activity against *S. pneumoniae* (MIC_{90} 0.03 μg/mL), including MDR strains (MIC range ≤0.015–0.12 μg/mL). Excellent activity was also demonstrated against MSSA (MIC_{90} 0.25 μg/mL). With regards to Gram negative respiratory pathogens, ceftaroline demonstrated good in vitro activity against *H. influenzae* (MIC_{90} 0.03 μg/mL),

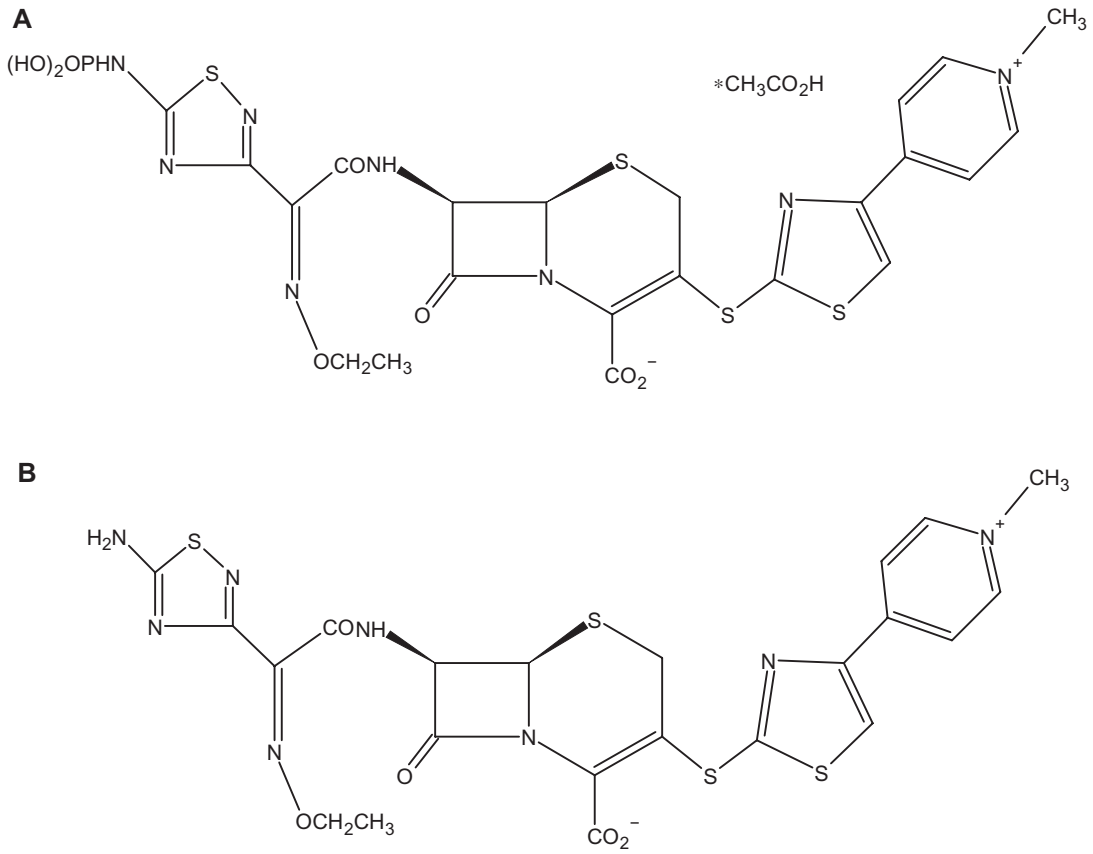

Figure 1. (**A**) ceftaroline-fosamil (TAK-599); (**B**) ceftaroline (T-91825).[13]

H. parainfluenzae (MIC_{90} 0.12 μg/mL), *E. coli* (MIC_{90} 1 μg/mL), and *K. pneumoniae* (MIC_{90} 0.5 μg/mL).[20] The in vitro activity of ceftaroline against common bacterial etiologies of CABP has also been analyzed in an international surveillance study from 2008 to 2009 in the U.S. and Europe that included isolates from the FOCUS 1 and FOCUS 2 trials. The reported MIC_{90} for *S. pneumoniae*, MSSA, and MRSA isolates were 0.12 μg/mL, 0.25 μg/mL, and 1 μg/mL, respectively.[21] Previous in vitro studies have demonstrated that ceftaroline is significantly active not only against PSSP ($MIC_{90} \leq 0.12$ μg/mL), but also against penicillin-intermediate SP (PISP; $MIC_{90} \leq 0.25$ μg/mL), PRSP ($MIC_{90} \leq 0.5$ μg/mL), cefotaxime-resistant SP (MIC_{90} 0.5 μg/mL), levofloxacin non-susceptible SP ($MIC_{90} \leq 0.25$ μg/mL), and MDR-SP (MIC_{90} 0.25 μg/mL).[22–34] In addition, these and other studies have demonstrated that ceftaroline's activity is not just against MSSA ($MIC_{90} \leq 0.5$ μg/mL) and MRSA ($MIC_{90} \leq 2$ μg/mL), but also against vancomycin intermediate and hetero-resistant *S. aureus* (VISA/hVISA; $MIC_{90} \leq 2$ μg/mL), vancomycin resistant *S. aureus* (VRSA; MIC_{90} 0.5 μg/mL), and daptomycin non-susceptible *S. aureus* (MIC_{90} 0.55 μg/mL).[22–26,32,33,35–41]

Results from the international surveillance study demonstrated that ceftaroline had good in vitro activity against common Gram negative respiratory pathogens like *H. influenzae* (MIC_{90} 0.015 μg/mL) and *M. catarrhalis* (MIC_{90} 0.12 μg/mL). The activity of ceftaroline fosamil was not affected by the presence of β-lactamases in *M. catarrhalis*.[21] Similarly, previous in vitro studies have demonstrated that ceftaroline retains significant activity in the presence of β-lactamases produced by both *H. influenzae* and *M. catarrhalis*.[23–26,35] Among enteric Gram negative isolates, ceftaroline has adequate activity against wild-type strains of *E. coli* (MIC_{90} 0.5 μg/mL) and *K. pneumoniae* (MIC_{90} 0.25 μg/mL), but minimal to no activity against extended-spectrum β-lactamase (ESBL)-producing strains (*E. coli*, $MIC_{90} > 16$ μg/mL and *K. pneumoniae*, $MIC_{90} > 16$ μg/mL).[21] Previous in vitro studies have demonstrated similar results in which ceftaroline is not active against enteric Gram negative isolates that produce ESBL's, AmpC β-lactamases, or carbapenemases.[23–25,35,42,45]

In addition, no significant in vitro activity was demonstrated against aerobic, non-fermenting Gram negative pathogens like *Pseudomonas aeruginosa* (MIC_{90} > 32 μg/mL), MDR *Acinetobacter baumanii* (MIC_{90} ≥ 16 μg/mL), *Stenotrophomonas maltophilia* (MIC_{90} > 32 μg/mL), and *Burkholderia cepacia* (MIC_{90} > 32 μg/mL).[22–25,42]

Ceftaroline demonstrated in vitro activity against some anaerobic pathogens that can be implicated in respiratory infection, including *Peptostreptococcus* spp. (MIC_{90} ≤ 4 μg/mL), other anaerobic Gram positive cocci (MIC_{90} ≤ 1 μg/mL), *Actinomyces* spp. (MIC_{90} 0.25 μg/mL), certain *Clostridum* spp. (MIC_{90} ≤ 2 μg/mL), *Fusobacterium nucleatum* and *necrophorum* (MIC_{90}≤ 0.125 μg/mL), *Porphyromonas asaccharolytica* (MIC_{90} 0.03 μg/mL), and *Veionella* spp. (MIC_{90} 0.5 μg/mL). However, no significant activity was demonstrated against *Prevotella* spp. or *Bacteroides* spp. (MIC_{90} ≥ 16 μg/mL and MIC_{90} ≥ 64 μg/mL, respectively).[23,43,44]

Recent in vitro and in vivo animal model data is emerging regarding the combination of ceftaroline with the new β-lactamase inhibitor, NXL-104. The combination has demonstrated enhanced activity against ESBL, AmpC β-lactamase, and KPC-enzyme producing Enterobacteriaceae.[46–51] In a recently published study, significant decreases in MIC_{90} were observed between ceftaroline and ceftaroline-NXL104 in *E. coli* strains that expressed CTX-M-14 or CTX-M-2 (MIC_{90} > 256 μg/mL for both vs. MIC_{90} 0.25 and 0.5 μg/mL, respectively), *E. cloacae* strains that expressed AmpC β-lactamases (MIC_{90} 128 μg/mL vs. MIC_{90} 0.5 μg/mL), and in *K. pneumoniae* strains that expressed KPC-2 or KPC-3 enzymes (MIC_{90} > 128 μg/mL for both vs. MIC_{90} 0.25 and 0.5–1 μg/mL, respectively).[51] In addition, enhanced in vitro activity has also been demonstrated against certain anaerobic organisms like *Bacteroides fragilis* (MIC_{90} > 64 μg/mL vs. MIC_{90} 2 μg/mL) and *Prevotella* spp. (MIC_{90} ≥ 8 μg/mL vs. MIC_{90} ≤ 1 μg/mL) with the combination of ceftaroline and NXL-4.[52]

Determination of in Vitro Drug Susceptibility

The Antimicrobial Susceptibility Testing Subcommittee of the CLSI has approved quality control ranges for MIC by broth microdilution and 30 μg disk diffusion-associated zone diameters (ZD) for ceftaroline. The acceptable quality control ranges for susceptibility testing using control organisms from the American Type Culture Collection (ATCC) are as follows: *S. pneumoniae* ATCC 49619 (MIC 0.008–0.03 μg/mL; ZD 31–41 mm), *S. aureus* ATCC 25923 (MIC N/A; ZD 26–35 mm), *S. aureus* ATCC 29213 (MIC 0.12–0.5 μg/mL; ZD N/A), *H. influenzae* ATCC 49247 (MIC 0.03–0.12 μg/mL; ZD 29–39 mm), and *E. coli* ATCC 25922 (MIC 0.03–0.12 μg/mL; ZD 26–34 mm).[12,25,53] The proposed MIC and ZD values associated with "susceptible", "intermediate", or "resistant" phenotypes for pathogens that can be associated with CABP is as follows: *Streptococcoccus* spp. (MIC ≤ 2, 4, and ≥8 μg/mL; ZD ≥ 23, 20–22, and ≤19 mm), *Staphylococcus* spp. (MIC ≤ 4, 8, and ≥16 μg/mL; ZD ≥ 23, 20–22, ≤19 mm), *M. catarrhalis* (MIC ≤ 4, 8, ≥16 μg/mL; ZD ≥ 28, 25–27, ≤24 mm), *H. influenzae* (MIC ≤ 4, 8, ≥16 μg/mL; ZD ≥ 29, 26–28, ≤25 mm), Enterobacteriaceae (MIC ≤ 4, 8, ≥16 μg/mL; ZD ≥ 22, 19–21, ≤18 mm), and *Pseudomonas* spp. (MIC ≤ 4, 8, ≥16 μg/mL; ZD ≥ 21, 18–20, ≤17 mm).[54]

There is an acceptable correlation and agreement between E-test and standard broth microdilution CLSI testing methods to determine MIC.[55] Furthermore, in vitro susceptibility testing does not appear to be adversely affected by variations in the testing and culture conditions.[56,57]

Determination of in Vitro Bactericidal Activity

Time-kill curve assays using ceftaroline concentrations of 2, 4, and 8-times the MIC of the organism demonstrated that among the *S. pneumoniae* isolates tested (75% were penicillin non-susceptible), a ≥3 $\log_{10}$ CFU/mL reduction in the starting inoculum at 24 hours (bactericidal activity) was achieved in 50% of isolates tested, while reductions of 2–3 $\log_{10}$ CFU/mL at 24 hours (bacteriostatic activity) was noted in the remaining 50%. Bactericidal activity was noted in 100% of MSSA and 50% of MRSA isolates at concentrations of 4-times the MIC, while concentrations of the drug of 8-times the MIC, achieved bactericidal activity in 100% of all *S. aureus* isolates. Among the Gram negative isolates tested (including *H. influenzae*, *E. coli*, and *K. pneumoniae*), bactericidal activity was documented in 100% of isolates with ceftaroline concentrations of 2, 4, and 8-times the MIC.[57]

The minimum bactericidal concentration (MBC) required to kill >99.9% of starting bacterial inoculum to MIC ratio of ceftaroline was also determined. The preferred MBC/MIC ratio was ≤4 and results demonstrated MBC/MIC ratios of 1 in 100% and 40% of PSSP and PRSP isolates respectively, while 60% of PRSP isolates had MBC/MIC ratio >4. The MBC/MIC ratios were 1 in 90% and 2 in 10% of MSSA isolates, while 60%, 30%, and 10% of MRSA isolates had MBC/MIC ratios of 1, 2, and >4 respectively. Among and hVISA isolates, 70% had an MBC/MIC ratio of 1, while 20% and 10% had MBC/MIC ratios of 2 and >4 respectively. Among the gram negative isolates tested (including *E. coli* and *K. pneumoniae*), the MBC/MIC ratios were 1, 2, 4, and >4 in 60%, 15%, 15%, and 10% of isolates respectively.[57]

Development of in Vitro Resistance

The in vitro activity of ceftaroline is not affected by β-lactamases produced by Gram positive organisms and common Gram negative respiratory pathogens like *H. influenzae* and *M. catarrhalis*. On the other hand, it is labile in the presence of ESBL, AmpC β-lactamases, and carbapenemases produced by the Enterobacteriaceae.[15,16,20–26,35,42,45]

In vitro studies analyzing the frequency at which resistance to ceftaroline develops using single-step spontaneous mutant selection methods have demonstrated that among PSSP, PRSP, MSSA, MRSA, VISA, wild-type and β-lactamase producing *H. influenzae*, and *M. catarrhalis*, no spontaneous resistance developed at drug concentrations of 4 to 16-times the MIC of the organism. Furthermore, in vitro studies analyzing the development of resistance by serial passages at sub-inhibitory concentrations of the drug, demonstrated either no change or a ≤2-fold increase in resistance for these same isolates.[35,58] Another study using sub-inhibitory serial passages demonstrated that no resistance (>4-fold increase in MIC or MIC ≥ 32 μg/mL) developed among PSSP, PISP, PRSP, MSSA, MRSA, hVISA/VISA, and VRSA isolates after 50 daily passages.[59] Similarly, the frequency of developing resistance on using sub-inhibitory serial passage is low for *H. influenzae* and *M. catarrhalis*, including β-lactamase producing strains.[60] On the contrary, the frequency at which resistance to ceftaroline develops by single-step mutant selection methods is higher in the Enterobacteriaceae. For example, ceftaroline was able to select for resistant AmpC-derepressed mutants from AmpC-inducible parent strains at concentration of 4-times the MIC of the organism. Furthermore, increases in the baseline MIC ranging from 4 to 256-fold at drug concentrations of 2-times the MIC of the organisms were also noted for the Enterobacteriaceae on sub-inhibitory serial passage methods.[35]

Drug Metabolism and Excretion

Once infused into the bloodstream, the half-life of ceftaroline fosamil is short (range: 0.19–0.43 hr) as it undergoes rapid enzymatic hydrolysis by plasma phosphatase enzymes and converted to its active metabolite, ceftaroline. Additional hydrolysis of ceftaroline's β-lactam ring leads to formation of an open-ring microbiologically inactive metabolite known as ceftaroline M-1. The mean ratio of plasma ceftaroline M-1 to ceftaroline area under the concentration time curve ($AUC_{0-\infty}$) after a single 600 mg intravenous (I.V.) dose of ceftaroline fosamil in adults with normal renal function is ~28%. Less than 20% of the drug is protein bound and most of it (64%), including a small amount of ceftaroline M-1 (2%), is excreted via the kidneys by glomerular filtration (mean renal clearance = 5.56 L/hr). Ceftaroline is not a substrate for hepatic CYP450 enzymes and no effect has been demonstrated by incubating the drug with pooled human liver microsomes.[12–14,61]

Pharmacokinetic Profile

Similar to other cephalosporins that undergo renal clearance, the pharmacokinetics (PK) of ceftaroline are linear and dependent on underlying renal function. The maximum observed serum drug concentration (C_{max}), time of C_{max} (t_{max}), area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$) and over dosing interval (AUC_{0-tau}), elimination half-life ($t½$), and plasma clearance (CL) of ceftaroline have been evaluated in healthy adults with creatinine clearance (CrCl) > 80 mL/min following administration of ceftaroline fosamil 600 mg I.V. over 60 minutes as a single or multiple dose (every 12 hours) regimen. Mean values are presented in Table 1.[12] There appears to be no difference in the C_{max} of ceftaroline after a single 600 mg I.V. dose of ceftaroline-fosamil in patients with CrCl > 80 mL/min, 50–80 mL/min, and 30–50 mL/min, however, the $t½$ and $AUC_{0-\infty}$ display

Table 1. Pharmacokinetic parameters of ceftaroline in healthy adults with normal renal function[§].

A) Ceftaroline-fosamil 600 mg I.V. over 60 minutes as single dose	
C_{max} (µg/mL)	19.0
t_{max} (hr)[¶]	1.0
$AUC_{0-\infty}$ (hr*µg/mL)	56.8
t½ (hr)	1.60
CL (L/hr)	9.58
B) Ceftaroline-fosamil 600 mg I.V. over 60 minutes every 12 hours for 14 days	
C_{max} (µg/mL)	21.3
t_{max} (hr)[¶]	0.92
AUC_{0-tau} (hr*µg/mL)	56.3
t½ (hr)	2.66
CL (L/hr)	9.6

Notes: [§]Mean; [¶]Median; C_{max}, Maximum observed serum drug concentration; t_{max}, Time of maximum observed serum drug concentration (C_{max}); $AUC_{0-\infty}$, Area under the concentration time curve from time 0 to infinity; AUC_{0-tau}, Area under the concentration time curve over dosing interval (0–12 hr); t½, Drug elimination half life; CL, Plasma clearance.

an inverse relationship with the degree of renal impairment (CrCl > 80 mL/min: t½ = 2.84 hr and $AUC_{0-\infty}$=75.1 hr*µg/mL; CrCl 50–80 mL/min: t½=3.61 hr and $AUC_{0-\infty}$ = 89.4 hr*µg/mL; and CrCl 30–50 mL/min: t½ = 4.49 hr and $AUC_{0-\infty}$ = 114 hr*µg/mL).[61] Similarly, the C_{max}, t½, and $AUC_{0-\infty}$ of ceftaroline were significantly greater in patients with CrCl < 30 mL/min after a single 400 mg I.V. infusion of ceftaroline fosamil over 60 minutes (17.9 µg/mL, 5.05 hr, and 113.3 hr*µg/mL) compared to patients with CrCl > 80 mg/mL (14.8 µg/mL, 3.02 hr, and 52.8 hr*µg/mL). In addition, the CL of ceftaroline was significantly less for patients with CrCl < 30 mL/min compared to those with CrCl > 80 mL/min (3.2 L/hr vs. 6.9 L/hr, $P < 0.0001$). No differences were noted however in the median t_{max} between both groups (1.25 hr vs. 1.08 hr, $P = 0.125$).[62]

In patients with end-stage renal disease (ESRD) on intermittent hemodialysis (HD), the C_{max}, t½, and $AUC_{0-\infty}$ were higher compared to patients with CrCl > 80 mL/min (16.5 µg/mL, 2.75 hr, and 48.5 hr*µg/mL) after receiving one dose of ceftaroline fosamil 400 mg I.V. over 60 minutes 4 hours pre-HD and a second dose given post-HD with a seven day washout period in between doses. No significant difference in t_{max} was noted between the two groups. The CL of ceftaroline was significantly less for patients with ESRD on intermittent HD compared to those with CrCl > 80 mL/min (4.9 L/hr pre-HD and 3.1 L/hr post-HD vs. 8.5 L/hr). The concentration of ceftaroline was measured in the dialysate fluid and it was determined that the 4 hour session of HD removed ~21.6% of the pre-HD dose.[63]

Population PK studies of ceftaroline fosamil (dose range: 50–2000 mg I.V. over 60 minutes for up to 14 days or I.M. for up to 5 days) in adults with normal renal function and renal impairment, including HD, have demonstrated a steady-state volume of distribution (Vd) for ceftaroline of 25.8 L and saturable elimination that decreases with decreasing CrCl and increasing age. As opposed to underlying CrCl, age and/or body surface are (BSA) did not appear to play an important role in determining the AUC of ceftaroline.[64] Population PK models have also been performed using data from phase I and II studies of ceftaroline fosamil 600 mg I.V. over 60 minutes every 12 hours in healthy adults, patients with underlying renal impairment, and patients with complicated skin and soft tissue infections. In patients with normal renal function, the C_{max}, t½, and AUC_{0-tau} were 23.53 µg/mL, 2.64 hr, and 124.92 hr*µg/mL, respectively. There was an inverse relationship between CrCl and CL, while the Vd in both central and peripheral compartments appeared to be somewhat proportional to body weight.[65]

The PK parameters of ceftaroline have also been measured after intramuscular (I.M.) administration of ceftaroline fosamil. In patients with normal renal function, there was a direct relationship between dose, C_{max}, t½, and $AUC_{0-\infty}$ after single-dose administration (Table 2). A comparison of PK parameters for ceftaroline was also performed after administration of ceftaroline fosamil 600 mg I.M. or I.V. as a single-dose.

Table 2. Pharmacokinetic parameters of ceftaroline in healthy adults with normal renal function after a single intramuscular dose of ceftaroline fosamil[§].

Dose (mg)	400	600	1000
C_{max} (µg/mL)	6.97	8.51	16
t_{max} (hr)[¶]	1.5	2.0	2.0
$AUC_{0-\infty}$ (hr*µg/mL)	35.61	48.11	110.27
t½ (hr)	2.36	2.55	2.68
CL (L/hr)	6.63	6.9	5.4

Notes: [§]Mean; [¶]Median; C_{max}, Maximum observed serum drug concentration; t_{max}, Time of maximum observed serum drug concentration (C_{max}); $AUC_{0-\infty}$, Area under the concentration time curve from time 0 to infinity; AUC_{0-tau}, Area under the concentration time curve over dosing interval (0–12 hr); t½, Drug elimination half life; CL, Plasma clearance.

Results demonstrated that while the C_{max} was lower and the t_{max} was longer for the I.M. formulation (8.51 vs. 19.68 µg/mL and 1.5–2 vs. 0.98 hr, respectively), the t½ and $AUC_{0-\infty}$ were comparable between both groups (2.55 vs. 2.13 hr and 48.11 vs. 44.99 hr*µg/mL, respectively). The absolute bioavailability was 100% following I.M. administration. The PK parameters of ceftaroline following administration of ceftaroline fosamil 600 mg I.M. for 5 days is presented in Table 3. No significant accumulation the active metabolite was noted after 5 days.[66]

The PK parameters of ceftaroline in pediatric patients (ages 12–17) are currently being analyzed following completion of a phase 1 study in 2009. Results from this study were not yet available at the time of this writing.[67]

Pharmacodynamic Profile

The phamacodynamic (PD) parameter that best determines the antimicrobial activity of ceftaroline is the time of free drug in serum above the MIC of the organism (%T > MIC). Higher C_{max} above the MIC or AUC/MIC ratios do not provide enhanced antimicrobial activity compared to %T > MIC. In murine models of thigh and lung infection, the mean %T > MIC required to achieve bacteriostatic, 1-log, and 2-log kill effects against various organisms at 24 hours is presented in Table 4. Minimal post-antibiotic effect was noted against *S. pneumoniae* and *E. coli* isolates regardless of dose, while a longer post-antibioitc effect was noted against *S. aureus* isolates (7.2–8 hr).[68] One study demonstrated that ceftaroline inhibits bacterial re-growth in susceptible isolates even at sub-inhibitory levels that are present in between doses.[69] No significant changes in human intestinal microflora were noted when ceftaroline fosamil 600 mg I.V. every 12 hours was administered to healthy human subjects for 7 days. While minimal and moderate changes were noted in the number of *E. coli* and *Bifidobacteria/Lactobacillus* spp. isolates in fecal matter respectively, no changes in the number of *Enterococcus* spp., *Bacteroides* spp., and *Candida albicans* isolates was appreciated.[70]

Table 3. Pharmacokinetic parameters of ceftaroline in healthy adults with normal renal function after multiple intramuscular doses of ceftaroline fosamil 600 mg for five days§.

C_{max} (µg/mL)	12.96
t_{max} (hr)¶	2.0
AUC_{0-tau} (hr*µg/mL)	65.41
t½ (hr)	2.51
CL (L/hr)	5.7

Notes: §Mean; ¶Median; C_{max}, Maximum observed serum drug concentration; t_{max}, Time of maximum observed serum drug concentration (C_{max}); $AUC_{0-\infty}$, Area under the concentration time curve from time 0 to infinity; AUC_{0-tau}, Area under the concentration time curve over dosing interval (0–12 hr); t½, Drug elimination half life; CL, Plasma clearance.

Animal Pneumonia Models

The clinical efficacy of ceftaroline for the treatment of bacterial pneumonia has been studied in animal models. Ceftaroline (20 mg/kg s.c. t.i.d) was compared to vancomycin and linezolid for the treatment of MRSA pneumonia in a neutropenic murine model. Results demonstrated that ceftaroline was superior to both comparator drugs when started on day 1 post infection with a >99.9% reduction in bacterial cell counts in lung tissue at day 3 post infection ($P \leq 0.01$ vs. both control and comparator drugs). No significant difference in clinical efficacy was between ceftaroline and comparator drugs was observed if treatment was started 2 hours after infection.[22] A more recent study analyzed the clinical efficacy of ceftaroline fosamil (600 mg I.V. every 12 hours) compared to that of ceftriaxone (1 g I.V. every 24 hours) using simulated human dosing regimen for the treatment of pneumonia due to ceftriaxone susceptible PSSP, ceftriaxone susceptible PISP, or ceftriaxone resistant PRSP in a non-neutropenic rabbit model. A subset of animals infected with ceftriaxone resistant PRSP, received ceftaroline fosamil as 5 or 20 mg/kg I.M. every 12 hours. After 2 days of treatment, both ceftaroline fosamil and ceftriaxone eradicated all bacteria to <1 log CFU/g of tissue from the lungs and spleen of infected animals with either ceftriaxone susceptible PSSP or PISP ($P < 0.001$ for both drugs compared to control). For animals infected with ceftriaxone resistant PRSP, ceftaroline fosamil demonstrated superior bactericidal activity after 2 days with a reduction in bacterial load of 8 and 4 log CFU/g of tissue in lungs and spleen respectively ($P < 0.001$ compared to controls). Ceftriaxone achieved a 2 log CFU/g of tissue reduction in bacterial load in the lungs after 2 days of treatment which was not statistically significant when compared to controls. Similar efficacy results were observed in animals infected with ceftriaxone resistant PRSP that were treated with I.M.

Table 4. Mean %T > MIC of free cetaroline in serum required for bacteriostatic, 1 log, and 2 log kill effects against various isolates at 24 hours.

Organisms	Bacteriostatic effect	1 log kill	2 log kill
S. pneumoniae§	39%	43%	50%
S. aureus¶	26%	33%	45%
Enterobacteriaceae¥	28%	41%	54%

Notes: §PSSP, PISP, and PRSP; ¶MSSA and MRSA; ¥*E. coli* and *K. pneumoniae*.

ceftaroline fosamil. Complete bacterial clearance to <1 log CFU/g of tissue from lung and spleen tissue was observed after 2 days of treatment in the 20 mg/kg arm ($P < 0.01$ and $P < 0.05$ compared to controls respectively), while in the 5 mg/kg arm, a reduction in bacterial load of 6 and 3 log CFU/g of tissue was observed in the lungs and spleen respectively ($P < 0.05$ for both compared to controls).[71]

Human Pneumonia Clinical Trials

Ceftaroline fosamil has been approved by the U.S. FDA for the treatment of CABP in hospitalized patients.[11,12] The decision by the U.S. FDA is based on the efficacy and safety data from two large randomized, double-blinded, and multi-center phase III trials (FOCUS 1; n = 613 and FOCUS 2; n = 627) that compared ceftaroline fosamil 600 mg I.V. every 12 hours to ceftriaxone 1 g I.V. every 24 hours for 5–7 days for the treatment of adults (>18 years) with moderate to severe CABP [Pneumonia Outcomes Research Team (PORT) risk class III or IV] who were hospitalized to a non-intensive care unit setting. The baseline demographic characteristics of patients in the modified intent to treat efficacy population (MITTE) in both FOCUS trials were similar among the treatment groups and most commonly included male sex (63.1%), white race (92.8%), mean age of 61.2 years, and enrollment in an Eastern (45.5%) or Western (35.5%) European study site. The most common underlying co-morbid conditionswerestructural lung disease (26.6%; ie, emphysema, chronic bronchitis, bronchiectasis, or interstitial fibrosis), history of pneumonia in the past (18.6%), and/or asthma (7.5%). Both trials excluded patients with risk factors for MRSA infection or predominance of Gram positive cocci in clusters present on sputum Gram stain given the known lack of efficacy of the comparator arm against this pathogen. The studies also excluded patients with a known or suspected infection caused solely by an atypical pathogen (ie, *Legionella* spp., *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae*). Determining whether clinical cure rates for ceftaroline were non-inferior to ceftriaxone [lower limit of 95% confidence interval (CI) ≥ –10%] in the MITTE and clinically evaluable (CE) patients at the test of cure (TOC) visit 8–15 days post-therapy, was the primary objective of both FOCUS trials.[72–74]

In FOCUS 1, the clinical cure rates at the TOC visit in the MITTE (n = 591) and CE (n = 458) patients, were 83.8% vs. 77.7% (Difference 6.2%; 95% CI, –0.2%–12.6%) and 86.6% vs. 78.2% (Difference 8.4%; 95% CI, 1.4%–15.4%) for ceftaroline fosamil and ceftriaxone, respectively. In the microbiologically modified intent to treat efficacy (mMITTE; n = 155) and microbiologically evaluable (ME; n = 140) patients, the clinical cure rates for ceftaroline fosamil and ceftriaxone were 88% vs. 75% (Difference 13.0%; 95% CI, 0.7%–25.2%) and 89.9% vs. 76.1% (Difference 13.8%; 95% CI, 1.3%–26.4%), respectively. Of note, in patients within the mMITTE population that had documented infection due to *S. pneumoniae*, ceftaroline fosamil demonstrated higher clinical cure rates compared to ceftriaxone (88.9% vs. 66.7%; Difference 22.2%, 95% CI: 0.2%–42.6%). Only two patients had documented infection with MDRSP in the ceftaroline fosamil arm and both were cured (100%), while only one patient in the ceftriaxone arm had documented infection with MDRSP and clinical failure was reported. In patients with documented infection due to *S. aureus*, clinical cure rates were again higher for ceftaroline fosamil than for ceftriaxone (80% vs. 64.3%; Difference 15.7%, 95% CI: –23%–48%). The clinical cure rates for patients with documented infections due to Gram negative pathogens (including *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *E. coli*, and *E. cloacae*) were comparable between the ceftaroline fosamil and ceftriaxone treatment arms (88.6% vs.

84.1%; Difference 4.5%, 95% CI: −10.6%–19.9%). A small number of patients had documented bacteremia (n = 15) and the clinical cure rates were 75.0% and 57.1% for ceftaroline fosamil and ceftriaxone respectively (Difference N/A).[72]

In FOCUS 2, the clinical cure rates at the TOC visit for the MITTE (n = 562) and CE (n = 450) patients were 81.3% vs. 75.5% (Difference 5.9%; 95% CI, −1.0%–12.7%) and 82.1% vs. 77.2% (Difference 4.9%; 95% CI, −2.5%–12.5%) for ceftaroline fosamil compared to ceftriaxone, respectively. In the mMITTE (n = 178) and ME (n = 161) patients, the clinical cure rates for ceftaroline fosamil and ceftriaxone were 80% vs. 75% (Difference 5.0%; 95% CI, −7.4%–17.4%) and 81.2% vs. 75% (Difference 6.2%; 95% CI, −6.7%–19.2%), respectively. In patients within the mMITTE population that had documented infection due to *S. pneumoniae*, clinical cure rates were again higher in the ceftaroline arm (83.3% vs. 70%; Difference 13.3%, 95% CI: −5.2%–31.6%). Two patients in the ceftaroline fosamil arm had documented infection with MDRSP and both were cured (100%). On the other hand, eight patients in the ceftriaxone arm had documented infection with MDRSP and only two (25%) were cured. The clinical cure rates in patients with documented infection due to *S. aureus* were comparable between ceftaroline fosamil and ceftriaxone (66.7% vs. 56.3%; Difference 10.4%, 95% CI: −23.8%–42.2%). The clinical cure rates for patients with documented infections due to gram negative pathogens (including *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *E. coli*, and *E. cloacae*) were comparable between the ceftaroline fosamil and ceftriaxone treatment arms (78.3% vs. 83.0%; Difference −4.7%, 95% CI: −21.2%–11.7%). In patients with documented bacteremia (n = 23), the clinical cure rates were 69.2% and 60.0% for ceftaroline fosamil and ceftriaxone respectively (Difference 9.2%, 95% CI: −29.0%–46.4%).[73]

Integrated efficacy analyses of both FOCUS trials (n = 1,240) demonstrated that the clinical cure rates at the TOC visit in the MITTE (n = 1,153) and CE (n = 908) patients, were 82.6% vs. 76.6% (Difference 6.0%; 95% CI, 1.4%–10.7%) and 84.3% vs. 77.7% (Difference 6.7%; 95% CI, 1.6%–11.8%) for ceftaroline fosamil compared to ceftriaxone, respectively. Finally, in the mMITTE (n = 333) and ME (n = 301) patients, clinical cure rates were 83.6% vs. 75% (Difference 8.7%; 95% CI, −0.0%–17.4%) and 85.1% vs. 75.5% (Difference 9.7%; 95% CI, 0.7%–18.8%) for the ceftaroline fosamil and ceftriaxone arms, respectively. In patients within the ME populations, the overall microbiological response rate in those infected with *S. pneumoniae* was 87.3% for ceftaroline fosamil and 72.9% for ceftriaxone. In patients infected with MDRSP, the microbiological response rate was 100% for ceftaroline fosamil and 50% for ceftriaxone. Comparable microbiological response rates were observed in patients with documented *S. pneumoniae* bacteremia (cefatroline fosamil, 82.4% vs. ceftriaxone, 72.7%). With regards to patients that had documented *S. aureus* infection, the microbiological response rate was 76% for ceftaroline fosamil (25 MSSA isolates) and 70.4% (25 MSSA and 2 MRSA isolates) for ceftriaxone. The microbiological response rates for isolated Gram negative pathogens were as follows: *H. influenzae* (83.3% vs. 85%), *H. parainfluenzae* (100% vs. 94.1%), *E. coli* (83% vs. 91.7%), and *K. pneumoniae* (100% vs. 83.3%) for ceftaroline fosamil and ceftriaxone respectively. Finally, in patients within the mMITTE population that had documented infection due to *S. pneumoniae*, clinical cure rates at the TOC visit were 85.5% for ceftaroline fosamil and 68.6% for ceftriaxone. In patients with documented infection due to MDRSP, clinical cure rates were higher with ceftaroline fosamil compared to ceftriaxone (100% vs. 22.2%). Patients with documented infection due to *S. aureus* experienced clinical cure rates of 72% and 60.0% in the ceftaroline fosamil and ceftriaxone arms respectively. The clinical cure rates at the TOC visit for patients with documented infection due to Gram negative pathogens were as follows: *H. influenzae* (85% vs. 83.3%), *H. parainfluenzae* (94.1% vs. 83.3%), *E. coli* (83.3% vs. 69.2%), and *K. pneumoniae* (93.3% vs. 76.9%) for ceftaroline fosamil and ceftriaxone, respectively. In patients with documented bacteremia due pathogens like *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *K. pneumoniae*, the overall clinical cure rates were 71.4% and 58.8% for ceftaroline fosamil and ceftriaxone respectively (Difference 12.6%; 95% CI, −17.6%–41.6%).[20,74]

Safety and Tolerability

Ceftaroline fosamil has demonstrated a good safety and tolerability profile that is similar to that of the comparator arm (ceftriaxone) in both trials for the treatment of CABP.[72–75]

The incidence of any adverse event (AE) in FOCUS 1 was comparable between ceftaroline fosamil and ceftriaxone (39.9% vs. 44.2%) in the MITT patient population. The majority of AEs in both arms of the study were mild in nature (19.8% vs. 20.1%). Only 3.7% of patients had to discontinue ceftaroline fosamil due to an AE. The most commonly reported events in the ceftaroline fosamil arm were diarrhea (4.7%), headache (3.4%), insomnia (3.0%), nausea (2.7%), constipation (2.3%), phlebitis (2.3%), and hypertension (2.0%). No infection due to *Clostridium difficile* was documented in either arm of the study. The incidence of any serious AE was reported to be 9.4% for ceftaroline fosamil compared to 10.7% for ceftriaxone. The most common serious events reported in the ceftaroline fosamil arm were worsening pneumonia (0.7%), respiratory failure (0.7%), sudden death (0.7%), and empyema (0.3%). The most common potentially clinically significant hepatic and renal laboratory abnormalities noted in the ceftaroline fosamil arm were elevations ($>3 \times$ upper limit of normal and $>200\%$ increase) in alanine aminotransferases (ALT) (2.2%), aspartate aminotransferase (AST) (0.7%), γ-Glutamyl transferase (1.7%), and/or elevation ($>2.0 \times$ upper limit of normal and $>100\%$ increase) in alkaline phosphatase (ALP) (1.0%). No elevations in total or direct conjugated bilirubin and serum creatinine were noted with ceftaroline fosamil. In patients that had a negative direct Coomb's test result at baseline, 11.8% and 5.2% revealed positive results upon repeat testing at the end-of-therapy, TOC, or both visits in the ceftaroline fosamil and ceftriaxone arms respectively. Nevertheless, no evidence of hemolytic anemia or major changes in baseline hemoglobin were noted in either arm of the study. Prolongation in baseline corrected QT interval was noted in 1.4% of ceftaroline fosamil and 1.0% of ceftriaxone treated patients. No episodes of torsade de pointes were reported. A total of 12 fatalities were reported (ceftaroline fosamil, 2% vs. ceftriaxone, 1.9%), but only 1 fatality per study arm was reported as possibly being directly related to the study drug.[72]

The incidence of any AE in FOCUS 2 was also comparable between ceftaroline fosamil and ceftriaxone (20.3% vs. 16.9%) in the MITT patient population. The majority of AE in the ceftaroline fosamil arm of the study were mild in nature (28.9%), while in the ceftriaxone arm, there were equal number of AE categorized as mild or moderate (19.9% for both). Sixteen patients (5.1%) had to discontinue ceftaroline fosamil due to an AE. The most commonly reported AE in the ceftaroline fosamil arm were diarrhea (3.8%), headache (3.5%), hypokalemia (3.2%), insomnia (3.2%), phlebitis (3.2%), chronic obstructive pulmonary disease (COPD) (2.5%), hypertension (2.5%), and worsening of pneumonia (2.5%). No infection due to *Clostridium difficile* was again documented in either arm of the study. The incidence of any serious AE was reported to be 13% for ceftaroline fosamil compared to 12.7% for ceftriaxone. The most common serious events reported in the ceftaroline fosamil arm were worsening pneumonia (2.2%), COPD (1.3%), pleural effusion (1.3%), pulmonary embolism (1.3%), lung abscess (0.6%), malignant lung neoplasm (1.0%), and empyema (1.0%). The most common hepatic and renal laboratory abnormalities noted in the ceftaroline fosamil arm were elevations in ALT (2.5%), AST (1.5%), γ-Glutamyl transferase (2.3%), and/or elevations in ALP (1.3%) and/or serum creatinine (0.6%). No elevations in total or direct conjugated bilirubin were noted with ceftaroline fosamil. In patients that had a negative direct Coomb's test result at baseline, 8.1% and 3.8% revealed positive results upon repeat testing at the end-of-therapy, TOC, or both visits in the ceftaroline fosamil and ceftriaxone arms respectively. Similar to FOCUS 1, no evidence of hemolytic anemia or major changes in baseline hemoglobin was noted in either arms of the study. Prolongation in baseline QTc interval was reported in 0.6% of ceftaroline fosamil and 1.0% of ceftriaxone treated patients. No episodes of torsade de pointes were reported. A total of 15 fatalities were reported (ceftaroline fosamil, 2.9% vs. ceftriaxone, 2.0%), but none were reported as possibly being directly related to the study drugs.[73]

Integrated safety analyses of both FOCUS trials, demonstrate that the incidence of any AE in the MITT patient population was 47% for ceftaroline fosamil and 45.7% for ceftriaxone. The majority of AE were mild in nature in both arms of the study (24.5% vs. 20.0%). Only 4.4% of patients had to prematurely discontinue ceftaroline fosamil due to a AE. The most commonly reported AE ($\geq 2\%$ of patients) in the ceftaroline fosamil arms were diarrhea (4.2%), headache (3.4%), insomnia (3.1%), phlebitis (2.8%),

hypertension (2.3%), hypokalemia (2.3%), and nausea (2.3%). The only AE that was classified as study-drug related and that occurred in ≥3% of patients was diarrhea (ceftaroline fosamil, 3.1% vs. ceftriaxone, 1.5%). The incidence of at least one serious AE was 11.3% for ceftaroline fosamil and 11.7% for ceftriaxone. The most commonly reported serious events that occurred in ≥2 patients in the ceftaroline fosamil arms were worsening of pneumonia (1.5%), COPD (0.7%), pleural effusion (0.8%), pulmonary embolism (0.8%), empyema (0.7%), respiratory failure (0.7%), and malignant lung neoplasm (0.5%). The incidence of any renal event (serum Cr > 1.5 mg/dL and >50% increase from baseline, or >50% decrease in CrCl, or a renal AE) was 2.9% for ceftaroline fosamil and 2.4% for ceftriaxone. The majority of reported renal events in the ceftaroline fosamil arm involved a serum Cr > 1.5 mg/dL and >50% increase from baseline (2.0%), while a >50% decrease in CrCl was noted in 1% of patients. At least one renal AE was reported in 1.6% of patients treated with ceftaroline fosamil and 0.8% of those treated with ceftriaxone. Similarly, the incidence of at least one AE that indicated liver abnormalities was 2.3% for ceftaroline fosamil and 2.9% for ceftriaxone. Furthermore, using Hy's Law laboratory criteria to determine the likelihood of drug induced hepatocellular toxicity, simultaneous elevations in ALT or AST, ALP and total bilirubin were noted in none of ceftaroline fosamil and 0.2% of ceftriaxone treated patients.[74–76] Only 9.8% of ceftaroline fosamil and 4.5% of ceftriaxone treated patients had a negative direct Coomb's test result at baseline followed by a positive result at the end-of-therapy, TOC, or both visits. However, no cases of hemolytic anemia were reported in either arm of the study. No major differences were noted between ceftaroline fosamil and ceftriaxone with regards to serious hepatobiliary (0.3% vs. 0.8%), renal (0.3% vs. 0.3%), or hematological (0.3% vs. 0.0%) laboratory abnormalities. A low and comparable number of patients in the ceftaroline fosamil (n = 6) and ceftriaxone (n = 5) arms had documented prolongation in baseline QTc interval. No episodes of torsade de pointes were reported. A combined total of 27 fatalities were reported between the ceftaroline fosamil (n = 15, 2.4%) and ceftriaxone (n = 12, 2.0%) arms of both studies, but only one fatality was reported to be possibly associated with the study drug in each of the two combined treatment arms.[74,75]

The integrated safety analysis of the FOCUS 1 and FOCUS 2 trials also revealed that patients treated with ceftaroline fosamil developed allergic skin reactions to the drug at rates that were similar to those reported by other cephalosporins (≤3%).[75,77,78] Nevertheless, as with other cephalosporins, caution must be ensured in patients who give a history of β-lactam allergy and ceftaroline fosamil should be avoided in those with documented type I (immediate) hypersensitivity reactions to this class of antimicrobials.

Based on limited data, ceftaroline fosamil is a pregnancy category B drug. Developmental toxicity studies in rats did not show maternal or fetal toxicity, but no controlled studies in pregnant women have been performed. Therefore, the drug should only be used in pregnancy if the benefit to the mother justifies any potential risk to the fetus. At this time, it is not known if ceftaroline is excreted in human breastmilk, therefore, the manufacturer recommends caution if the drug is administered to nursing mothers.[12]

Recommended Dosage and Duration of Therapy

The current recommended dose of ceftaroline fosamil for the treatment of CABP due to susceptible pathogens is 600 mg infused over 60 minutes (I.V.) every 12 hours in adult patients with CrCl > 50 mL/min. Reduction in dose to 400 mg (I.V.) every 12 hours and 300 mg (I.V.) every 12 hours is required for patients with CrCl of 30–50 mL/min and 15–30 mL/min, respectively. In patients with ESRD (CrCl < 15 mL/min) that are on intermittent HD, the recommended dose is 200 mg over 60 minutes every 12 hours given after HD on HD days. No dosing recommendations are presently available for patients undergoing renal replacement therapy. No dose modification is required for patients with underlying hepatic dysfunction. The current recommended duration of treatment of CABP using ceftaroline fosamil is 5–7 days. However, duration of therapy should be based on severity, site, and individual microbiological and clinical response.[12]

Place in Therapy and Conclusions

The approval of ceftaroline fosamil by the U.S. FDA for the treatment of CABP has opened the doors for a new era in antimicrobial therapy in which β-lactams may once again come to forefront in the treatment of serious respiratory infections caused by PRSP, and

MDR-SP.[11,12] In addition to its documented clinical efficacy, ceftaroline fosamil has a favorable safety and tolerability profile which can makes it an attractive option for patients with CABP.[72–75] Nevertheless, the results from both FOCUS trials failed to demonstrate a clear superiority of ceftaroline fosamil over ceftriaxone for the treatment of CABP.[72–74] Furthermore,despite having in vitro activity against MRSA, no clinical trials evaluating its efficacy in MRSA-related pneumonia have been completed to date. Its lack of activity against MDR Gram negative pathogens may also limit its empiric use for treatment of health-care associated pneumonia (HCAP). The results from the FOCUS trials, however, should serve as stepping stones for further studies looking at the treatment of serious CAPB and HCAP caused by MRSA.[72–74] The ongoing evaluation of Ceftaroline with the new β-lactamase inhibitor NXL104 is of great interest as well, and the authors eagerly await any emerging clinical data regarding this combination and the treatment of respiratory infections caused by some MDR Enterobacteriaceae.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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