Brand Name: Teflaro

Generic Name: Ceftaroline fosamil

Manufacturer: Forest Pharmaceuticals, Inc[1,2]

Drug Class: Cephalosporin, Fifth Generation[2,3]

Uses:

Labeled Uses: Acute Skin & Skin Structure Infections caused by susceptible bacteria[1,2,4]

Community-acquired Bacterial Pneumonia caused by susceptible bacteria[1,2,4]

Unlabeled Uses: Bacterial endocarditis caused by susceptible bacteria (studied in animal model)[5]

Bacterial osteomyelitis caused by susceptible bacteria (studied in animal model)[6]

Mechanism of Action: Ceftaroline binds to penicillin-binding proteins and prevents the synthesis of peptidoglycan, a major constituent in bacterial cell walls. Ceftaroline has high affinity for PBP2a in resistant *Staphylococcus aureus* strains[1,7,8,9,10] and PBP1A, PBP2B, and PBP2X in resistant *Streptococcus pneumonia* strains.[1,7,8] Beta-lactamases inactivate ceftaroline, rendering it ineffective against ESBL-producing strains, including *Pseudomonas aeruginosa* and *Enterobacteriaceae spp.*[1,11,12]

Pharmacokinetics: Ceftaroline follows a two-compartment pharmacokinetic model with first-order elimination.[9]

Time to Peak (T_{max}):[1,9]	1 hour* IV, 2 hours IM
Volume of Distribution (V_d):[9]	0.31-0.45 L/kg
Half-life ($t_{1/2}$):[1,9,10]	2.3-2.9 hours
Clearance (Cl):[1]	9.6 L/h
Protein binding:[1,9,10]	<20% (binding to albumin unknown)
Bioavailability (F):[9,13]	N/A (not an oral agent)

*Following a 1 hour IV infusion

Metabolism: Ceftaroline fosamil is rapidly converted to its active form upon administration. Serum phosphatases cleave the phosphono group to form

the active metabolite, ceftaroline.[1,4,9,10,13] Only a small fraction of the drug is hydrolyzed to an inactive metabolite, ceftaroline-M-1.[1,4,9,13] Ceftaroline undergoes minimal cytochrome P450 oxidation.[1,13]

Elimination: Ceftaroline is primarily excreted renally. 88% of the total dose is recovered in the urine as either active drug or metabolites.[1] 49.6-75% of the total dose is recovered in the urine as active ceftaroline[1,9,10,13], and 1.8-7.4% of the dose is recovered as ceftaroline-M-1[1,9]. Renal clearance of the drug is 5.20-5.73 L/h, indicating that ceftaroline is primarily eliminated by glomerular filtration.[1,9,13] Only 6% of an administered dose is recovered in the feces, indicating that ceftaroline is undergoes minimal biliary excretion.[1]

Pharmacodynamics: *In vivo* efficacy in clinical trials has only been confirmed for a few organisms. The FDA has approved ceftaroline for infections caused by the following organisms.[1]

Skin and Skin Structure Infections:
Staphylococcus aureus (MSSA and MRSA)
Streptococcus pyogenes
Streptococcus agalactiae
Escherichia coli
Klebsiella pneumonia
Klebsiella oxytoca

Community-acquired Bacterial Pneumonia:
Streptococcus pneumonia
Staphylococcus aureus (MSSA only)
Haemophilus influenza
Klebsiella pneumonia
Klebsiella oxytoca
Escherichia coli

Although MIC breakpoints have not been established, MIC breakpoint estimates have been proposed. The estimated susceptibility breakpoint is 2 – 4 μg/mL and the estimated resistance breakpoint is 8 – 16 μg/mL.[13] *In vitro* susceptibility and resistance patterns can be predicted based on *in vitro* MICs and proposed breakpoints.

Susceptible
Staphylococcus aureus (MSSA, MRSA, hVISA, VISA)[9,11,13,14]
Staphylococcus epidermidis (MSSE, MRSE)[9]
Streptococcus pneumoniae[9,11,13,14]

Streptococcus viridans[9,11,13,14]
Streptococcus pyogenes[9,11,13,14]
Streptococcus agalactiae[9,11,13,14]
Clostridium perfringens[15]
Clostridium ramosum[15]
Clostridium innocuum[15]
Clostridium clostridioforme[15]
Lactobacillus casei[15]
Lactobacillus rhamnosus[15]
Anaerococcus prevotii[15]
Anaerococcus tetradius[15]
Finegoldia magna[15]
Parvimonas micra[15]
Peptoniphilus asaccharolyticus[15]
Actinomyces spp. [15]
Propionibacterium acnes[15]
Propionibacterium avidum[15]
"Eubacterium" group[15]
Neisseria meningitides[11]
Neisseria gonorrhoeae[9]
Haemophilus influenzae[9,11,13,14]
Moraxella catarrhalis[9,11,13,14]
Escherichia coli (Non-ESBL producing, Ceftazidime-sensitive)[9,11,13,14]
Klebsiella pneumoniae (Non-ESBL producing, Ceftazidime-sensitive)[9,11,13,14]
Klebsiella oxytoca[9]
Shigella spp.[14]
Citrobacter freundii (Ceftazidime-sensitive)[9,11,13]
Proteus mirabilis (Non-ESBL producing)[11,13]
Porphyromonas asaccharolytica[15]
Fusobacterium nucleatum[15]
Fusobacterium necrophorum[15]
Fusobacterium varium[15]
Veillonella spp. [15]

<u>Intermediate or Conflicting</u>
Enterococcus faecalis[9,11,13,14]
Bacillus sp.[11,13]
Listeria monocytogenes[14]
Clostridium difficile[11]
Peptostreptococcus anaerobius[15]

Peptostreptococcus stomatis[15]
Serratia marcescens[9,11,13,14]
Morganella morganii[11,14]
Salmonella sp.[9,14]
Enterobacter cloacae[9,11,13,14]
Proteus mirabilis (ESBL-producing)[9,14]
Proteus rettgeri[14]
Proteus stuartii[14]

Resistant
Enterococcus faecium[9,11,13,14]
Corynebacterium jeikenum[14]
Eggerthella lenta[15]
Escherichia coli (ESBL-producing, Ceftazidime-nonsensitive)[9,11,13,14]
Klebsiella pneumoniae (ESBL-producing, Ceftazidime-resistant)[9,11,13,14]
Citrobacter freundii (Ceftazidime-nonsensitive)[11,13]
Enterobacter aerogenes (non-ESBL producing)[14]
Acenitobacter sp.[9,11]
Pseudomonas aeruginosa[9,11,14]
Stenotrophomonas maltophilia[9,11,14]
Burkholderia capecia[14]
Proteus vulgaris[11,14]
Providencia sp.[11]
Alcaligenes sp.[11]
Bacteroides fragalis[11,15]
Bacteroides thetaiotaomicron[15]
Prevotella bivia[15]
Prevotella buccae[15]
Prevotella melaninogenica[15]
Prevotella intermedia[15]
Prevotella sp. (other)[11,15]
Fusobacterium mortiferum[15]
Porphyromonas somerae[15]

Similar to other beta-lactam antibiotics, the cytotoxic effect of ceftaroline against microorganisms is time-dependent.[1] A small post-antibiotic effect of 1 – 2 hours has been demonstrated against various Gram-positive organisms.[16]

Efficacy:

Talbot GH, Thye D, Das A, et al. Phase 2 Study of Ceftaroline versus Standard Therapy in Treatment of Complicated Skin and Skin Structure Infections. Antimicrob Agents Chemother. 2007 Oct;51(10):3612-16. [17]

Study Design:

International, multicenter, observer-blinded, parallel, randomized controlled trial of ceftaroline against a standard therapy for complicated skin and skin structure infections.

Description of Study:

Methods: One hundred patients who met diagnostic criteria for a complicated skin and skin structure infection were randomized to receive either ceftaroline 600 mg infused over one hour every 12 hours or standard therapy. The standard therapy group had treatment initiated with vancomycin 1 gram every 12 hours and could be de-escalated within 72 hours to a penicillinase-resistant penicillin or augmented with aztreonam 1 gram every 8 hours. Patients were treated for 7 to 14 days and assessed for cure 8 to 14 days after treatment was discontinued. The primary outcome measure was clinical cure rate. Cure was defined as resolution of all signs and symptoms of the infection without need for further antimicrobial therapy. Secondary outcome measures included the clinical cure rate at the end of treatment and the microbiological response 8 to 14 days after completion. Adverse effects and drug safety were also assessed.

Results: Cure rate in the clinical modified intent to treat (cMITT) population was 88.1% in the ceftaroline group (95% CI = 77.8-94.7%) and 81.3% in the standard therapy group (95% CI = 63.6-92.8%). Cure rate in the clinically evaluable (CE) population was 96.7% in the ceftaroline group (95% CI = 88.7-99.6%) and 88.9% in the standard therapy group (95% CI = 70.8-97.6%). Relapse after cure was observed in one patient in each group. Five patients in each group had MRSA infection and were cured at the end of treatment. However, one patient in the ceftaroline group whose infection was associated with a diabetic foot ulcer relapsed eight days later.

Limitations:

Single-blinding in the study is not optimal and may have affected the study results. Also, the range of days when cure and relapse were assessed was relatively large and may have introduced bias. The primary limitation of the study was its small sample size, which limited the power of the study and made it difficult to draw conclusions regarding the comparative efficacy of ceftaroline. In addition, the authors were all

employed by Cerexa, a subsidiary of Forest Laboratories, and Cerexa provided funding for the study.

Conclusion:

Ceftaroline proved to be comparable in efficacy to standard therapy, and trends toward superior efficacy were observed, although statistical significance was not achieved. Adverse effect rates were similar or less common in the ceftaroline group. Further studies with more patients are necessary to be able to reliably compare the efficacy of ceftaroline with standard therapy and to assess its appropriate place in therapy. Additional, higher powered studies will also allow for the determination of *in vivo* efficacy against various different pathogens in complicated skin & skin structure infections.

Corey GR, Wilcox M, Talbot GH, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis. 2010 Sep 15;51(6):641-50. [18]

Study Design:

Two international, multicenter, double-blind, parallel, randomized controlled trials comparing ceftaroline with vancomycin plus aztreonam in the treatment of complicated skin and skin structure infections.

Description of Study:

Methods: The study recruited patients who met diagnostic criteria for a severe complicated skin and skin structure infection. Patients were excluded if they had received antibiotics within the last 96 hours, the suspected causative organism was suspected to be resistant to therapy, or the patient's creatinine clearance was 30 mL/min or less. Patients presenting with decubitus ulcers, diabetic foot ulcers, peripheral vascular disease-associated ulcers, gangrene, osteomyelitis, necrotizing fasciitis, third-degree burns covering >5% of the body, endocarditis, septic arthritis, or human or animal bites were also excluded. One thousand three hundred ninety-six patients were randomized to receive either ceftaroline 600 mg plus normal saline placebo every 12 hours or vancomycin 1 gram plus aztreonam 1 gram every 12 hours. The primary outcome measure was the per-patient clinical cure rate 8 to 14 days after completion of antibiotics Cure was defined as resolution of all signs and symptoms of the infection without need for further antimicrobial therapy. Adverse effects and drug safety were also assessed.

Results: Cure was achieved in 91.6% of clinically evaluable patients in the ceftaroline group and 92.7% of CE patients in the vancomycin plus aztreonam group (Difference = -1.1%, 95% CI = -4.2 to 2.0%). Gram-negative infection cure rates were 85.3% (29/34) in the ceftaroline group and 100% (24/24) in the vancomycin plus aztreonam group (Difference = -15.6%, 95% CI = -31.6 to -1.2%). Cure rates in the microbiologically evaluable (ME- CE patients with a baseline pathogen isolated) population were comparable and above 90% in both groups for MRSA, MSSA, *S. pyogenes*, *S. agalactiae*, *E. coli*, and *K. pneumonia*. Vancomycin plus aztreonam outperformed ceftaroline in infections caused by *E. faecalis* (91.7% vs. 80.0%) and *P. mirabilis* (95.2% vs. 66.7%). Side effects were similar between both groups except for pruritus in the vancomycin plus aztreonam group (8.2% vs. 3.5%). Discontinuation associated with an adverse event was also more common in the vancomycin plus aztreonam group (4.8% vs. 3.0%).

Limitations:

A major limitation to this study is that power was only determined for the primary outcome measure. Therefore, we cannot be sure if the investigators were able to accurately detect a difference in the secondary outcome measures and adverse event rates between groups. The authors also failed to statistically analyze and report p-values for their data, which would have aided in evaluating the differences between treatments. In addition, the follow-up window for evaluation of cure and relapse was large and may have introduced bias. The study also enrolled a relatively low number of African Americans, Asians, and elderly patients. In addition, six of the nine authors were either employees of Cerexa or reported a financial interest in Cerexa, a subsidiary of Forest Laboratories, Inc. Forest Laboratories provided funding for the study.

Conclusion:

Ceftaroline is not inferior to vancomycin plus aztreonam in the empiric treatment of skin and skin structure infections. However, conclusions cannot be drawn about the comparative *in vivo* efficacy of ceftaroline against specific types of infections or organisms. If a gram-negative infection is clinically suspected, however, it may be better to avoid ceftaroline and use vancomycin plus aztreonam. Further research is needed to able to accurately define the role of ceftaroline in clinical practice for the treatment of skin and skin structure infections. Further studies are also needed to evaluate the side effect profile of ceftaroline.

FDA Briefing Document. Ceftaroline Fosamil for the Treatment of Community-acquired Bacterial Pneumonia and Complicated Skin & Skin Structure Infections [updated September 7, 2010]. Anti-Infective Drugs Advisory Committee Meeting. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM224656.pdf. Accessed November 8, 2010. [19]

Study Design:

Two international, multicenter, double-blind, parallel, randomized controlled trials comparing ceftaroline with ceftriaxone in the treatment of community-acquired bacterial pneumonia.

Description of Study:

Methods: Patients were enrolled if they had signs and symptoms of an infectious disease with signs and symptoms of pneumonia lasting up to seven days. Treatment at a hospital or urgent care center was required, and pneumonia PORT score was required to be above 70 but no more than 130. Patients were excluded if outpatient treatment was an option, infection was due to an atypical organism, they received antimicrobial treatment in the last 96 hours, or they had creatinine clearance of 30 mL/min or less. The studies enrolled 614 patients in Study P903-08 and 606 patients in Study P903-09. Patients in each study were randomized to receive ceftriaxone 1 gram IV every 24 hours with placebo infused 12 hours after or ceftaroline 600 mg IV every 12 hours for five to seven days. Patients in both groups in Study P908-08 also received two doses of clarithromycin at the beginning of treatment. The primary endpoint of the study was the clinical cure rate 8 – 15 days after completion of therapy. Cure was defined as resolution of all signs and symptoms of the infection without need for further antimicrobial therapy. Important secondary outcome measures included the per-patient clinical cure rate after the last dose of treatment and the per-pathogen clinical cure rate in patients who had a causative organism identified. Adverse effects and drug safety were also assessed.

Results: The clinical cure rate in the CE population 8 – 15 days after the completion of therapy in Study P903-08 was 86.6% in the ceftaroline group versus 78.2% in the ceftriaxone group (Difference = 8.4%, 95% CI = 1.4% to 15.4%). Results were similar in the analysis of patients at the completion of therapy. In study P903-09, the clinical cure rate in the CE population 8 – 15 days after the completion of therapy was 82.1% in the ceftaroline group versus 77.2% in the ceftriaxone group (Difference =

4.9%, 95% CI = -2.5% to 12.4%). Cure rates at the end of treatment were similar to the cure rates at first follow-up. Cure rates were higher in the ceftaroline group for infections caused by *S. pneumoniae* [85.7% (54/63) vs. 69.5% (41/59)], *S. aureus* (MSSA) [72.0% (18/25) VS. 56.0% (14/25)], *E. coli* [83.3% (10/12) vs. 75.0% (9/12)], *E. cloacae* [100.0% (7/7) vs. 75.0% (9/12)], and *K. pneumoniae* [100.0% (13/13) vs. 83.3% (10/12)]. Higher cure rates were observed with ceftriaxone against *H. influenza* [85.0% (17/20) vs. 83.3% (15/18)], *M. catarrhalis* [100.0% (2/2) vs. 66.7% (2/3)], and *K. oxytoca* [87.5% (7/8) vs. 83.3% (5/6)]. Pooled results of adverse events showed that rates were similar for treatment emergent adverse events, serious adverse events, discontinuation due to adverse event, and death.

Limitations:

Power was not reported for any of the outcome measures. Considering that the study objective was to determine noninferiority of ceftaroline, an adequate level of power is essential to ensure that any treatment difference is detected. Study P903-09 did not enroll any patients in North America, and only 4% of the patients in Study P903-08 were enrolled from North America, limiting the applicability of the study results to patients in the United States, especially with differing trends of antibiotic use and resistance. In the majority of patients, a causative organism was not identified, limiting the evaluation of the *in vivo* efficacy against specific organisms. Follow-up assessment at 8 – 15 days was also a wide interval and may have introduced bias. In addition, the study was conducted by the drug manufacturer.

Conclusion:

The study may be underpowered to detect a difference between ceftaroline and ceftriaxone in the treatment of patients with community-acquired bacterial pneumonia. If power was adequate, one would conclude that ceftaroline is not inferior to ceftriaxone in the treatment of community-acquired bacterial pneumonia. Future studies in the United States can confirm its efficacy against resistance patterns in our healthcare systems. Further research is needed to accurately determine its *in vivo* spectrum of activity and its appropriate place in therapy.

Contraindications: **Hypersensitivity:** Ceftaroline is contraindicated in patients who have experienced a hypersensitivity reaction to ceftaroline or other members of the cephalosporin class.[1,20]

Precautions: **Hypersensitivity:** Patients who have experienced a hypersensitivity reaction to any other beta-lactam antibiotic (penicillins, carbapenems)

should be closely monitored for signs of anaphylaxis if ceftaroline is administered, and the drug should be immediately discontinued if a reaction develops.[1,20]

***Clostridium-difficile*-associated diarrhea:** Any antibiotic can permit the overgrowth of *Clostridium difficile* in the gastrointestinal tract and cause infection and severe diarrhea. Although *C. difficile*-associated diarrhea has been reported in clinical trials,[1,18] ceftaroline is likely to have a low level of risk for *C. difficile* infection due to poor penetration into the gastrointestinal tract and only a minor, insignificant effect on the intestinal flora.[21]

Direct Coombs' Test Seroconversion: In phase III trials, patients receiving ceftaroline produced a positive Direct Coombs' test twice as frequently as patients receiving active controls. However, none of the patients developed signs or symptoms of hemolytic anemia. Patients exhibiting signs or symptoms of anemia, drug-induced hemolytic anemia should be considered as a possible etiology.[1,18]

Development of Drug-Resistance: Administration to patients who do not have an active infection increases the risk of developing drug-resistant bacteria.[1]

Adverse Effects:

Greater than 10%

None[1]

2% to 10%

Cardiovascular:

Hypertension (2.3%)[22]

Dermatologic:

Rash (1.5-3%)[1,17]

Endocrine and Metabolic:

Hypokalemia (2%)[1]

Gastrointestinal:

Diarrhea (5%)[1]

Nausea (4-6%)[1,17]

Constipation (2%)[1]

Vomiting (2%)[1]

General:

Headache (5.2-6%)[17,18]

Generalized pruritus (2.2%)[18]

Hepatic:

Increased Transaminases (2-6%)[1,17]

Local:

Pruritus (3.5%)[18]

Infusion site pain (3%)[13]

Phlebitis (2%)[1]

Musculoskeletal:

Elevated creatine phosphokinase (0-7.5%)[1,17]

Nervous System:

Insomnia (2.5-6%)[17,18]

Renal:

Crystals in urine (0-9%)[1,17]

Less than 2%

Cardiovascular:

Bradycardia[1]

Palpations[1]

Dermatologic:

Urticaria[1]

Endocrine and Metabolic:

Hyperglycemia[1]

Hyperkalemia[1]

Gastrointestinal:

Abdominal pain[1]

General:

Pyrexia[1]

Hematologic:

Anemia[1]

Eosinophilia[1]

Neutropenia[1]

Thrombocytopenia[1]

Hepatic:

Hepatitis[1]

Immune System:

Hypersensitivity (0.3%)[1]

Anaphylaxis[1]

Infectious:

Clostridium difficile colitis[1]

Local:

Swelling (1.5%)[13]

Thrombosis (1.5%)[13]

Nervous System:

Dizziness[1]

Convulsion[1]

Renal:

Renal failure[1]

Drug Interactions: *No drug interactions have been identified*

Dosing/Administration:

Usual Dose: Skin and Skin-Tissue Infection:

600 mg infused IV over one hour every 12 hours for 5-14 days[1,20]

Community-acquired Pneumonia:

600 mg infused IV over one hour every 12 hours for 5-7 days[1,20]

Geriatric Dose: Same as usual dosage[1,20]

Pediatric Dose: Safety and efficacy in pediatric patients has not been established[1,20]

A dose of 8mg/kg in adolescent patients weighing less than 75 kg produced a 10% lower C_{max} and a 23% lower $AUC_{0\rightarrow\infty}$.[1]

Renal Impairment:

Creatinine Clearance (mL/min)	**Recommended Dose**
> 30 and ≤ 50	400 mg IV over 1 hour Q12H[1,20]
≥ 15 and ≤ 30	300 mg IV over 1 hour Q12H[1,20]
< 15 and hemodialysis	200 mg IV over 1 hour Q12H[1,20]

Ceftaroline is removed by hemodialysis (21.6%) and should be administered after hemodialysis.[1]

Hepatic Impairment: No dosage adjustments necessary.[1,20]

Use in Special Circumstances:

Pregnancy: Category B

No studies in humans have been conducted, but exposure in rats and rabbits have shown no risk to the fetus.[1,20]

Lactation: Excretion into breast milk is unknown, so caution should be exercised if administering to a breast feeding woman.[1,20]

Conclusion:

Ceftaroline shows comparable efficacy against standard treatments in the treatment of skin and skin structure infections and community-acquired bacterial pneumonia. The evidence supporting the use of ceftaroline in community-acquired bacterial pneumonia is not as strong as data supporting its use in skin and skin structure infections. With increasing trends of antimicrobial resistance, ceftaroline may prove useful in the treatment of a wide range of infections as we become more familiar with its pharmacologic activity. However, the clinician should keep in mind that although the drug has broad gram-positive coverage, it lacks consistent efficacy against ESBL-producing gram-negative organisms. Aside from hypersensitivity reactions and *C. difficile* colitis, no serious adverse effects were identified in Phase III trials. Early Phase IV trials will prove crucial in the identification of treatment-related side effects in the general population. With the current data that we have, ceftaroline appears to be a safe and effective alternative for the treatment of SSSI and CABP.

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