



## CEFTAROLINE: A NEW CEPHALOSPORIN WITH ACTIVITY AGAINST METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

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According to the CDC, controlling methicillin-resistant *Staphylococcus aureus* (MRSA) infections is a high priority and as such they have dedicated significant resources to this potentially deadly pathogen.<sup>1</sup> Unlike hospital-acquired MRSA, community-acquired MRSA (CA-MRSA) infection rates have not declined over the past decade.<sup>1</sup> Resistance has become an increasing problem across the country and globe.<sup>2</sup> This rampant spread of resistance has led to institutions implementing antibiotic stewardship programs in hopes of preserving the usefulness of available antimicrobials. Even with these efforts, the need for new agents is clear as vancomycin-resistant *S. aureus* infections and other pan-resistant infections have been found in the United States.<sup>18</sup> In October 2010, the FDA approved ceftaroline, a “fifth generation” cephalosporin that is the first beta-lactam approved with activity against MRSA.<sup>3,4</sup> Ceftaroline is made by Forest Laboratories, Inc. under the trade name Teflaro® and has FDA-approved indications for treating acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).<sup>3</sup> The objectives of this article are to discuss the pharmacology, relevant clinical studies, safety and tolerability, and cost of ceftaroline.

### PHARMACOLOGY & PHARMACOKINETICS

Ceftaroline is a beta-lactam cephalosporin with bactericidal activity via inhibition of penicillin binding proteins (PBP).<sup>3</sup> Specifically, it binds to PBP2a on *S.*

*aureus* and PBP2x on *Streptococcus pneumoniae*.<sup>3</sup> It has activity against Gram-positive and some common Gram-negative bacteria but is deactivated by extended spectrum beta-lactamases, carbapenemases, class B metallo-beta-lactamases, and Amp C cephalosporinases.<sup>3</sup> Similar to other beta-lactam antibiotics, ceftaroline is concentration-independent and time-dependent meaning that the efficacy is dependent on the amount of time that the unbound plasma concentration is above the minimum inhibitory concentration (MIC). Specific bacteria that ceftaroline has activity against are listed in **Table 1**.

Ceftaroline has a volume of distribution similar to extracellular fluid volume (20.3 L).<sup>3</sup> The protein binding of ceftaroline (~20%) shows small variability depending on the serum concentration of the drug.<sup>3</sup> Based on its efficacy in clinical studies for ABSSSI and CABP, ceftaroline achieves adequate concentrations in skin and soft tissues long with respiratory tissues. Animal models have shown ceftaroline to be effective in endocarditis, osteomyelitis, infected joint fluid, and meningitis.<sup>5,6,7</sup>

The prodrug ceftaroline fosamil is rapidly converted to ceftaroline by a phosphatase enzyme in the plasma.<sup>3</sup> The prodrug can only be measured during the one hour infusion in which the drug is administered.<sup>3</sup> Following conversion, the beta-lactam ring is hydrolyzed to the ceftaroline M-1 inactive metabolite.<sup>3</sup>

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**Table 1 | Ceftaroline activity against common skin and respiratory pathogens.<sup>3,19</sup>**

Skin Infections	In vitro activity	
	MIC <sub>90</sub> (mcg/cc)	Break Point (mcg/cc)
<b>Gram-positive bacteria</b>		
MSSA	0.25	≤ 1
MRSA	1	≤ 1
<i>Streptococcus pyogenes</i>	≤ 0.008	≤ 0.015
<i>Streptococcus agalactiae</i>	0.03	≤ 0.03
<b>Gram-negative bacteria</b>		
<i>Escherichia coli</i>	0.25	≤ 0.5
<i>Klebsiella pneumonia</i>	0.5	≤ 0.5
<i>Klebsiella oxytoca</i>	-	≤ 0.5
<b>Community-Acquired Bacterial Pneumonia (CABP)</b>		
<b>Gram-positive bacteria</b>		
<i>Streptococcus pneumoniae</i>	0.03 - 0.25 <sup>†</sup>	≤ 0.25
<i>Staphylococcus aureus</i> (methicillin-susceptible isolates only)	0.25	≤ 1
<b>Gram-negative bacteria</b>		
<i>Haemophilus influenza</i>	0.015/0.03*	≤ 0.12
<i>Klebsiella pneumonia</i>	0.5	≤ 0.5
<i>Klebsiella oxytoca</i>	-	≤ 0.5
<i>Escherichia coli</i>	0.25	≤ 0.5

<sup>†</sup>varies based on strain of *S.pneumoniae*

\* beta-lactamase negative/beta-lactamase positive

As a result of In vitro studies, ceftaroline is not expected to be an inducer or inhibitor of the cytochrome P450 system.<sup>3</sup> As a result, no recommendations related to dosage or use are based on hepatic function; however pharmacokinetic properties have not been established in patients with impaired hepatic function.<sup>3</sup> Renal impairment is not expected to affect the efficacy of ceftaroline, but the majority of ceftaroline is excreted in the urine unchanged.<sup>3</sup> Due to its excretion being renally-dependent, dosing should be adjusted based on creatinine clearance (see Dosing section).<sup>3</sup>

## CLINICAL TRIALS

The safety and efficacy of ceftaroline in ABSSSI and CABP were established through one phase 2 clinical trial and four phase 3 clinical trials (CANVAS 1&2 and FOCUS 1&2).<sup>8-16</sup> The integrated analysis for the CANVAS and FOCUS studies and the phase 2 study are summarized in **Table 2**.

## SKIN INFECTIONS

The phase two study by Talbot was a randomized, observer-blinded study.<sup>8</sup> The study compared ceftaroline (600 mg IV Q12H) versus standard therapy consisting of vancomycin (1 gm IV Q12H) ± aztreonam (1

gm IV Q8H).<sup>8</sup> Treatment periods were 7 to 14 days and the primary outcome was clinical cure rate measured at 8 to 14 days after treatment.<sup>8</sup> Clinical cure was achieved in 96.7% of patients in the ceftaroline group and 88.9% of patients receiving standard therapy, a non-significant difference.<sup>8</sup> Each group had five cases of confirmed MRSA; in the ceftaroline group, four achieved clinical cure and all five in standard therapy group achieved clinical cure.<sup>8</sup> The one patient in the ceftaroline group that did not achieve clinical cure was associated with a diabetic foot ulcer and osteomyelitis that showed marked initial improvement, but upon discontinuation of ceftaroline, required readmission and further treatment.<sup>8</sup>

The investigators acknowledged that a small sample size is the study's major limitation and that it limited further statistical analysis.<sup>8</sup> This limitation is expected in phase two trials.<sup>8</sup> The study's strengths include a strong comparator that, as expected, performed well and a rigorous patient population.<sup>8</sup> The results suggest that ceftaroline can be safe and effective for the management of cSSSI.<sup>8</sup>

The CANVAS trials were phase 3 multicenter, non-inferiority, randomized, double-blind studies that evaluated the safety and efficacy of ceftaroline compared with vancomycin plus aztreonam as the active comparator for skin and skin-structure infections.<sup>11</sup>

**Table 2 | Ceftriaxone Safety and Efficacy Clinical Trial Summaries.**

Enrollment & Design		Inclusion Criteria	Comparator Treatment	Clinical Cure (%)	Conclusion
Phase 2 study of ceftriaxone versus standard therapy in treatment of complicated skin and skin structure infections <sup>8</sup> (cSSSI)	N=100 R, O-B	<ul style="list-style-type: none"> <li>• ≥18 years old</li> <li>• SSSI requiring hospitalization and i.v. antimicrobials</li> <li>• deeper SSSI and/or required surgical intervention</li> <li>• lower extremity infection in diabetes mellitus or PVD</li> <li>• ≥ two local signs of cSSSI</li> <li>• ≥ 1 systemic sign</li> </ul>	<ul style="list-style-type: none"> <li>• i.v. standard therapy for 7 to 14 days.</li> <li>• 21 days was permitted for severe infection</li> <li>• Initially vancomycin (1 g every 12 h)</li> <li>• Culture indication of gram-positive organism susceptible to a penicillinase-resistant penicillin (PRP) therapy with vancomycin could be switched to a PRP within the first 72 h after initiation of therapy.</li> <li>• If Gram-negative pathogen suspected at baseline, concomitant administration of aztreonam (1 g every 8 h) was allowed</li> </ul>	<p>Ceftriaxone 96.7</p> <p>Vancomycin ± Aztreonam 88.9</p>	<p>Ceftriaxone has the potential to be safe and effective for complicated SSSI and other serious community/ hospital acquired infections</p>
Integrated analysis of CANVAS 1 and 2 <sup>11</sup>	N=1378 R, D-B multicenter phase 3 trials	<ul style="list-style-type: none"> <li>• 18 years of age and older</li> <li>• cSSSI requiring hospitalization and i.v. antimicrobials</li> <li>• 3 clinical signs of infection: cSSSI that met either of the following criteria                             <ul style="list-style-type: none"> <li>• (1) involved deep soft tissue or required surgical intervention</li> <li>• (2) cellulitis or abscess of a lower extremity in patients with diabetes mellitus or PVD</li> </ul> </li> <li>• Patients had to provide written informed consent</li> </ul>	<ul style="list-style-type: none"> <li>• 1 g of vancomycin followed by 1 g of aztreonam.</li> <li>• Treatments were administered intravenously in 250 mL of sodium chloride (0.9%) over 60 min every 12 h for 5–14 days.</li> <li>• The vancomycin dose was adjusted according to institutional guidelines or local prescribing practices.</li> </ul>	<p>Ceftriaxone 91.6</p> <p>Vancomycin plus Aztreonam 92.7</p>	<p>Ceftriaxone is non-inferior to Vancomycin plus Aztreonam for ABSSSI</p>
Integrated analysis of FOCUS 1 and FOCUS 2 <sup>15</sup>	N=1228 R, D-B, multicenter phase 3 trials	<ul style="list-style-type: none"> <li>• Adults ≥18 years of age</li> <li>• Radiographically confirmed CAP</li> <li>• Requires hospitalization and i.v. antimicrobial therapy</li> <li>• PORT risk class III or IV only</li> <li>• Acute illness (&gt;7 days duration)</li> <li>• 3 clinical signs or symptoms of lower respiratory tract infection</li> </ul>	<ul style="list-style-type: none"> <li>• Ceftriaxone 1 g IV every 24 h for 5–7 days</li> </ul>	<p>Ceftriaxone 84.3</p> <p>Ceftriaxone 77.7</p>	<p>Ceftriaxone is non-inferior to Ceftriaxone for CAP</p>

Each of the trials individually met the predetermined criteria for non-inferiority and together the ceftaroline group showed a 91.6% clinically evaluable cure rate.<sup>11</sup> The clinically combined evaluable cure rate for the two trials in the vancomycin plus aztreonam group was 92.7%, a statistically insignificant difference of 1.1%.<sup>11</sup> Additionally, ceftaroline showed comparable efficacy to aztreonam against non-ESBL-producing gram negative bacteria with the exception of *Pseudomonas aeruginosa* and *Proteus mirabilis* which is consistent with findings from in vitro studies.<sup>11</sup>

The CANVAS trials showed ceftaroline to be effective across different patient populations, infections with single or multiple pathogens, and different infection types.<sup>11</sup> The study's limitations include its few black, Asian, and elderly patients.<sup>11</sup> The study is further limited by its exclusion criteria that prevented patients with ulcers related to PVD and diabetes from participating.<sup>11</sup> Despite the limitations, the study's size, use of a strong comparator, and high cure rate show ceftaroline's potential as a safe and effective option for monotherapy in ABSSSI.<sup>11</sup>

### COMMUNITY ACQUIRED PNEUMONIA

The FOCUS trials were randomized, non-inferiority, double-blinded, multicenter phase 3 trials that evaluated the safety and efficacy of ceftaroline compared to ceftriaxone in patients with community-acquired pneumonia.<sup>15</sup> The primary outcome was clinical cure rate and was defined as the resolution of all signs and symptoms of pneumonia or improvement to a degree that made stopping antimicrobials possible.<sup>15</sup>

Patients were assigned to treatment with either ceftaroline 600 mg IV every 12 hours for 5-7 days or ceftriaxone 1 gm IV every 24 hours for 5-7 days.<sup>15</sup> The two trials combined enrolled over 1,200 patients, randomly assigned to treatment in a 1:1 ratio, and the integrated analysis showed both groups to be similar with regard to baseline characteristics.<sup>15</sup> Both trials individually showed ceftaroline to be non-inferior to ceftriaxone and that ceftaroline produced a numerically greater cure rate.<sup>15</sup> In the integrated analysis, clinically evaluable patients treated with ceftaroline showed a clinical cure rate of 84.3% compared to 77.7% for ceftriaxone-treated patients; weighted treatment difference 6.7% (95% CI 1.6-11.8).<sup>15</sup> The integrated FOCUS data also showed that ceftaroline had higher clinical cure rates than

ceftriaxone on all common pathogens including multi-drug resistant *Streptococcus pneumoniae* and in all patient subgroups.<sup>15</sup> A possible explanation for the advantage of ceftaroline over ceftriaxone is its greater affinity for penicillin binding proteins in the most common pneumonia pathogen, *Streptococcus pneumoniae*.<sup>20</sup> Affinities of the two cephalosporins are similar for non-beta-lactam resistant strains, but in strains that contained PBP 2x/2a/2b, ceftaroline showed almost a 2-fold higher binding affinity than ceftriaxone which resulted in lower MICs.<sup>20</sup> However, this cannot be stated conclusively as the FOCUS trials documented zero cases of penicillin resistant *Streptococcus pneumoniae*.<sup>15</sup>

This study is limited by its exclusion of patients with known or suspected atypical pathogens, which are a common cause of CAP.<sup>15</sup> These patients were excluded to reduce confounding by eliminating the need for concomitant macrolide therapy.<sup>15</sup> Patients with risk factors for MRSA were also excluded because it is not a common community-acquired respiratory pathogen.<sup>15</sup> The study shows ceftaroline's potential as safe and effective treatment for CABP, but its use as monotherapy is limited just as ceftriaxone is by the potential for pathogens not covered by beta-lactams.<sup>15</sup>

### DOSING

For patients 18 years of age and older without renal impairment ceftaroline is dosed at 600 mg IV, given as a one-hour infusion every 12 hours for both ABSSSI and CABP.<sup>3</sup> The recommended duration of treatment is 5-14 days for ABSSSI and 5-7 days for CABP.<sup>3</sup> Dosage adjustments for patients with renal impairment are summarized in **Table 3**.

Although data are lacking, EC may decrease the effectiveness of other hormonal contraceptives. In addition, patients should be reminded that ulipristal only works to prevent pregnancy and does not protect against sexually-transmitted infections (STIs).<sup>4</sup>

### SAFETY AND TOLERABILITY

In general, ceftaroline is well tolerated with a similar side effect profile to its comparators.<sup>12, 16</sup> In the integrated safety summary for the CANVAS trials, 4.3% of patients discontinued therapy due to adverse events compared to 4.1% in the vancomycin plus aztreonam group.<sup>12</sup> Hypersensitivity

**Table 3 | Recommended Dosage of Ceftaroline in Patients with Renal Impairment.<sup>3</sup>**

Estimated CrCl <sup>a</sup> (mL/min)	Recommended Dosage Regimen for Ceftaroline
> 50	No dosage adjustment necessary
> 30 to ≤ 50	400 mg IV (over 1 hour) every 12 hours
≥ 15 to ≤ 30	300 mg IV (over 1 hour) every 12 hours
End-stage renal disease, including hemodialysis <sup>b</sup>	200 mg IV (over 1 hour) every 12 hours <sup>c</sup>

a Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.

b End-stage renal disease is defined as CrCl < 15 mL/min.

c Ceftaroline is hemodialyzable (~21% recovered after 4hr HD session); thus ceftaroline should be administered after hemodialysis on hemodialysis days.

**Table 4 | CANVAS Comparison of specific side effects occurring with a frequency of  $\geq 1\%$  (with  $\geq 0.5\%$  difference between regimens).<sup>12</sup>**

	Ceftaroline fosamil, n (%) (n=692)	Vancomycin plus aztreonam, n (%) (n=686)
Nausea	41 (5.9)	35 (5.1)
Headache	36 (5.2)	31 (4.5)
Diarrhea	34 (4.9)	26 (3.8)
Pruritus	24 (3.5)	56 (8.2)
Rash	22 (3.2)	17 (2.5)
Generalized pruritus	15 (2.2)	19 (2.8)
Dizziness	14 (2.0)	8 (1.2)
Hypokalemia	10 (1.4)	15 (2.2)
Anemia	9 (1.3)	13 (1.9)
Pain	9 (1.3)	4 (0.6)
Pyrexia	9 (1.3)	16 (2.3)
Chest pain	8 (1.2)	5 (0.7)
ALT increase	8 (1.2)	12 (1.7)
AST increase	7 (1.0)	13 (1.9)
Infusion site erythema	7 (1.0)	2 (0.3)

was the leading cause of discontinuation in both groups.<sup>12</sup> The most frequent adverse events found in the ceftaroline group were nausea (5.9%), headache (5.2%), and diarrhea (4.9%).<sup>12</sup> The ceftaroline group had 24 incidents of pruritus compared to the vancomycin plus aztreonam group that had 56, representing an absolute difference of 4.7% (**Table 4**).<sup>12</sup>

Serious adverse events were comparable between ceftaroline and vancomycin plus aztreonam groups, and worsening of cellulitis was the only serious adverse event that occurred in the ceftaroline group more than once.<sup>12</sup>

The most frequently-occurring side effects in the FOCUS trials are shown in **Table 5**.<sup>16</sup> The rate of serious adverse events were comparable between the ceftaroline and ceftriaxone groups, 11.3% and 11.7% respectively.<sup>16</sup> Discontinuation rates were also similar between groups: 4.4% for

ceftaroline and 4.1% for ceftriaxone.<sup>16</sup> Twice the number of patients in the ceftaroline group compared to the ceftriaxone group experienced a direct antiglobulin seroconversion (51 versus 24 patients), but the statistical significance of this difference was not reported.<sup>16</sup> A thorough evaluation of all patients with potential anemia or hemolysis showed no patients presenting with hemolytic anemia.<sup>16</sup>

### COST

The average wholesale price for Teflaro® is \$41 per vial for either the 400 mg or 600 mg vial.<sup>17</sup> This equates to a wholesale cost of \$82 per day and \$410 to \$1148 for a typical treatment (5-14 days). The average treatment duration in the CANVAS and FOCUS studies were ~8 and ~6.5 days,

**Table 5 | FOCUS Comparison of specific side effects occurring with a frequency of  $\geq 1\%$  (with  $\geq 0.5\%$  difference between regimens).<sup>16</sup>**

	Ceftaroline fosamil, n (%) (n=613)	Ceftriaxone, n (%) (n=615)
Diarrhea	26 (4.2)	16 (2.6)
Headache	21 (3.4)	9 (1.5)
Insomnia	19 (3.1)	14 (2.3)
Phlebitis	17 (2.8)	13 (2.1)
Constipation	9 (1.5)	6 (1.0)
Urinary tract infection	9 (1.5)	5 (0.8)
Vomiting	7 (1.1)	2 (0.3)
Pleural effusion	5 (0.8)	8 (1.3)
Chest pain	8 (1.2)	5 (0.7)
ALT increase	8 (1.2)	12 (1.7)
AST increase	7 (1.0)	13 (1.9)
Infusion site erythema	7 (1.0)	2 (0.3)



respectively, resulting in an estimated average medication cost of \$656 and \$533, respectively.<sup>11, 15, 17</sup>

## SUMMARY

Ceftaroline is a bactericidal fifth generation cephalosporin dosed 600 mg every 12 hours IV in patients without renal impairment. Ceftaroline is indicated for ABSSSI and CABP.<sup>3</sup> Ceftaroline has the additional benefit of being effective against MRSA in ABSSSI.<sup>3</sup> Ceftaroline is not active against *Pseudomonas aeruginosa* or organisms producing extended spectrum beta-lactamase.<sup>3</sup> Ceftaroline has an adverse event profile similar to other cephalosporins.<sup>16</sup>



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## DRUG UPDATES

### Fentanyl nasal spray (Lazanda®) - Archimedes Pharma

On June 30, 2011, the FDA approved Lazanda® (fentanyl nasal spray), for breakthrough cancer pain in adults who are already receiving opioid therapy but have developed resistance to their current regimen. Lazanda® is the first available nasal spray formulation of fentanyl available in the US, but it has been previously available in 5 European countries under the name *PecFent* (fentanyl pectin nasal spray). According to the manufacturer, Lazanda®, which will use the same delivery mechanism as *PecFent*, delivers fentanyl in a fine mist that forms a gel when it comes into contact with the nasal mucosa. The nasal formulation is not considered equivalent to other forms of fentanyl due to differences in pharmacokinetics. Therefore, dose comparisons cannot be made directly to other formulations of fentanyl such as buccal tablets, lozenges, or transdermal patches. The most common adverse events associated with its use included nausea, vomiting, constipation, and pyrexia. Lazanda® is expected to be released later this year with an accompanying Risk Evaluation and Mitigation Strategy (REMS) program that will require pharmacies, distributors, and prescribers to enroll in the program in order to prescribe, dispense, or distribute Lazanda®.

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