Ceftaroline:
A new cephalosporin for the treatment of cSSTIs and CAP

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Circular ΕΟΦ 81867/19.11.2012
Conflict of Interest (2013-2018)

• Speakers honoraria, research and travel grants from:
  • Astellas
  • Gilead
  • GSK
  • Janssen
  • MSD
  • Pfizer
By 2050: Antimicrobial resistant infections the leading cause of death

By 2050
- 10 million people will die every year from infections by MDR pathogens
- The infections by MDR pathogens will cost the global economy more than $100 million
“10 x 20” Initiative
New antibiotics

• Eight new antibiotics were approved by the FDA between January 2010 and December 2015:
  • ceftaroline,
  • fidaxomicin,
  • bedaquiline,
  • dalbavancin,
  • tedizolid,
  • oritavancin,
  • ceftolozane-tazobactam
  • ceftazidime-avibactam.

Outline

• Mode of action - Profile
• Spectrum
• Potential for induction of resistance
• Pharmakokinetics
• Safety profile
• Drug-drug interactions
Mode of action - Profile
What is ceftaroline fosamil?

• Parenteral, **bactericidal**, advanced/5\(^{th}\) generation cephalosporin

• High affinity to specific penicillin-binding proteins:
  - PBP-2b and PBP-2x, associated with β-lactam resistance in *Streptococcus pneumoniae*
  - PBP-2a associated with resistant MRSA\(^2\)

• Only available β-lactam with **anti-MRSA activity** for cSSTI, along with activity against other commonly encountered Gram-positive and Gram-negative bacteria\(^1\)

• CLSI designates ceftaroline as a member of a new class of β-lactam antibiotic, ‘**cephalosporin with MRSA activity**’

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**Ceftaroline: Structure activity relationships\(^3\)**

First MRSA-active β-lactam with extended spectrum against Gram-positive and Gram-negative bacteria commonly associated with cSSTI and CAP

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CLSI, Clinical and Laboratory Standards Institute; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *Staphylococcus aureus*

Spectrum

In vitro – Clinical data
In Vitro Activity

<table>
<thead>
<tr>
<th>Bacteria (No. of isolates)</th>
<th>MIC (µg/mL)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus (MS) (1,554)</td>
<td>≤0.008-1</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>S. aureus (MR) (1,237)</td>
<td>0.25-2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus (VISA and hVISA) (100)</td>
<td>0.25-4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus epidermidis (MS) (15)</td>
<td>0.06-0.13</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>S. epidermidis (MR) (26)</td>
<td>0.25-1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus faecalis (613)</td>
<td>0.12 to &gt;16</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Enterococcus faecium (VAN-R) (26)</td>
<td>4-16</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (PS) (202)</td>
<td>≤0.008-0.12</td>
<td>≤0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>S. pneumoniae (PI) (103)</td>
<td>≤0.008-0.5</td>
<td>0.015</td>
<td>0.06</td>
</tr>
<tr>
<td>S. pneumoniae (PR) (296)</td>
<td>≤0.008-0.5</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Viridans group streptococci (PS) (190)</td>
<td>≤0.008-1</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Viridans group streptococci (PR) (42)</td>
<td>≤0.008-1</td>
<td>0.03</td>
<td>0.5</td>
</tr>
<tr>
<td>Streptococcus pyogenes (ERY-S) (91)</td>
<td>≤0.008-0.03</td>
<td>≤0.008</td>
<td>≤0.008</td>
</tr>
<tr>
<td>Streptococcus agalactiae (ERY-S) (59)</td>
<td>≤0.008-0.06</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>S. agalactiae (ERY-NS) (42)</td>
<td>≤0.008-0.12</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>Haemophilus influenzae (BL-) (305)</td>
<td>≤0.008-0.25</td>
<td>≤0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>H. influenzae (BL+) (101)</td>
<td>≤0.008-0.2</td>
<td>0.015</td>
<td>0.03</td>
</tr>
<tr>
<td>Moraxella catarrhalis (BL+) (93)</td>
<td>≤0.008-0.5</td>
<td>0.06</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Active in vitro against common causative pathogens of CAP and cSSTI, including antibiotic-resistant *S. pneumoniae* and MRSA

**NOTE:** In vitro activity does not always correlate with clinical efficacy

In Vitro Activity (Cont.)

<table>
<thead>
<tr>
<th>Bacteria (No. of isolates)</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae (403)</td>
<td>0.002-1</td>
</tr>
<tr>
<td>Escherichia coli (CAZ-S) (345)</td>
<td>≤0.03 to &gt;16</td>
</tr>
<tr>
<td>E. coli (CAZ-NS) (63)</td>
<td>2 to &gt;16</td>
</tr>
<tr>
<td>E. coli (ESBL+) (15)</td>
<td>0.5 to &gt;32</td>
</tr>
<tr>
<td>Klebsiella oxytoca (19)</td>
<td>0.03 to &gt;128</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (210)</td>
<td>≤0.03 to &gt;16</td>
</tr>
<tr>
<td>K. pneumoniae (ESBL+) (15)</td>
<td>32 to &gt;32</td>
</tr>
<tr>
<td>Proteus mirabilis (58)</td>
<td>≤0.03 to &gt;16</td>
</tr>
<tr>
<td>Serratia marcescens (59)</td>
<td>0.12 to &gt;16</td>
</tr>
<tr>
<td>Salmonella spp. (46)</td>
<td>0.13-2</td>
</tr>
<tr>
<td>Citrobacter freundii (CAZ-S) (50)</td>
<td>0.06-16</td>
</tr>
<tr>
<td>C. freundii (CAZ-NS) (33)</td>
<td>4 to &gt;16</td>
</tr>
<tr>
<td>Enterobacter cloacae (CAZ-S) (50)</td>
<td>≤0.03 to &gt;16</td>
</tr>
<tr>
<td>E. cloacaæ (CAZ-NS) (35)</td>
<td>0.12 to &gt;16</td>
</tr>
<tr>
<td>Acinetobacter spp.(47)</td>
<td>≤0.03 to &gt;16</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (58)</td>
<td>1 to &gt;128</td>
</tr>
</tbody>
</table>

Extended spectrum of activity against commonly encountered Gram-negative and Gram-positive pathogens in CAP and cSSTI

**NOTE:** In vitro activity does not always correlate with clinical efficacy
Ceftaroline Susceptible Pathogens

- In cSSTIs, Ceftaroline efficacy has been demonstrated in clinical studies against the following pathogens, which were also susceptible to Ceftaroline in vitro:
  - **Gram-positive**
    - *Staphylococcus aureus* (including MRSA)
    - *Streptococcus pyogenes*
    - *Streptococcus agalactiae*
    - *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)
    - *Streptococcus dysgalactiae*
  - **Gram-negative**
    - *Escherichia coli*
    - *Klebsiella pneumoniae*
    - *Klebsiella oxytoca*
    - *Morganella morganii*

- In CAP, Ceftaroline efficacy has been demonstrated in clinical studies against the following pathogens, which were also susceptible to Ceftaroline in vitro:
  - **Gram-positive**
    - *Streptococcus pneumoniae*
    - *Staphylococcus aureus* (methicillin-susceptible strains only)
  - **Gram-negative**
    - *Escherichia coli*
    - *Haemophilus influenzae*
    - *Haemophilus parainfluenzae*
    - *Klebsiella pneumoniae*

**NOTE:** Ceftaroline is not active against strains of Enterobacteriaceae producing ESBLs or *P. aeruginosa*. In vitro data indicate that the following atypical species are not susceptible to Ceftaroline: *Chlamydia phila* spp., *Legionella* spp., and *Mycoplasma* spp.

CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infections; ESBL, extended-spectrum beta-lactamases; MRSA, methicillin-resistant *Staphylococcus aureus*
## Ceftaroline Susceptibility

The European Committee on Antimicrobial Susceptibility Testing breakpoints for susceptibility

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC breakpoint (mg/mL)</th>
<th>Susceptible (≤S)</th>
<th>Resistant (R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td></td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Streptococcus groups A, B, C, G</strong></td>
<td></td>
<td>Note&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Note&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td></td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Refers to dosing of adults or adolescents (from 12 years and 33kg) with ceftaroline fosamil every 12 hours using 1-hour infusions (see section 4.2). Note that: There are no clinical trial data regarding the use of ceftaroline fosamil to treat CAP due to *S. aureus* with ceftaroline fosamil MICs >1mg/L; <sup>b</sup>Refers to dosing of adults or adolescents (from 12 years and 33kg) with ceftaroline fosamil every 8 hours using 2-hour infusions to treat cSSTI (see section 4.2). *S. aureus* with ceftaroline fosamil MICs ≥4mg/L are rare. PK-PD analyses suggest that dosing of adults or adolescents (from 12 years and 33kg) with ceftaroline fosamil every 8 hours using 2-hour infusions may treat cSSTI due to *S. aureus*, for which the ceftaroline fosamil MIC is 4mg/L; <sup>c</sup>Infer susceptibility from susceptibility to benzylpenicillin.

CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infection; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetics

ZINFORO® SmPC, 2017
Potential for induction of resistance

Ceftaroline
Potential for induction of resistance

- **Multistep studies** (multi-passage resistance selection for ceftaroline).

- Daily passages of *Staphylococcus aureus* were performed until a significant increase in MIC (>4-fold or MICs ≥ 32 μg/ml) was obtained or until 50 consecutive passages were completed. The minimum number of passages was 20 passages.

- No mutations associated with resistance have been detected

- *No in vitro automatic selection of mutations have been reported* (strains with MICs ≥ 4X in vitro, typical frequencies <10^{-10})

  - *No strains with MICs ≥ 4X, even after 50 passages to ceftaroline concentrations lower than MIC*

Pharmakokinetics

Ceftaroline
Tissue Penetration of Ceftaroline—CAP

Epithelial lining fluid\(^1\)

- Two dosages of **Ceftaroline** were compared in healthy adult subjects (IV 600mg q12h versus q8h)
- Plasma and ELF **Ceftaroline** concentration profiles were similar for both dosages, with the q8h regimen showing ~10-20% higher concentrations
- The ratio of the **Ceftaroline** area under the time-concentration curve in bronchial ELF to AUC in plasma was ~23%

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**Ceftaroline** has been found to have rapid and deep tissue penetration in lung tissue\(^2\)

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AUC, area under the curve; CAP, community-acquired pneumonia; ELF, epithelial lining fluid; IV, intravenous; q8h, every 8 hours; q12h, every 12 hours
# Tissue Penetration of Ceftaroline—cSSTI

Antibiotics for MRSA infections have different pharmacokinetic profiles and tissue penetration.  

<table>
<thead>
<tr>
<th></th>
<th>Ratio of SSTI: Plasma penetration (%)</th>
<th>Volume of distribution</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>104</td>
<td>40-50L</td>
<td>31</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>74</td>
<td>7-9 L/kg</td>
<td>71-89</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>24-77</td>
<td>0.7-1.4 L/kg after 3-6mg/kg</td>
<td>88-91 (with weak affinity)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>68</td>
<td>0.1 L/kg</td>
<td>90-93</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>10-30</td>
<td>0.43-0.9 L/kg</td>
<td>30-55</td>
</tr>
<tr>
<td>Ceftaroline fosamil</td>
<td>Not available</td>
<td>20 L</td>
<td>20</td>
</tr>
</tbody>
</table>

## Subcutaneous tissue penetration

- Ceftaroline fosamil subcutaneous tissue concentrations **in patients with diabetic foot infection** assessed by insertion of microdialysis probe near wound (IV ceftaroline fosamil 600mg q12h + avibactam 600mg q8h x 3 days)
- The \( C_{\text{max}} \) of ceftaroline fosamil in the infected tissue was 69% of the \( C_{\text{max}} \) in plasma within 2 hours of a steady-state dose

## Ceftaroline has good tissue penetration in SSTI compared with other therapies

**In healthy volunteers or patients**

**NOTE:** There is limited experience with ceftaroline fosamil in treating patients with diabetic foot infections. Caution is advised when treating such patients.

\( C_{\text{max}} \), maximum serum concentration; cSSTI, complicated skin and soft tissue infection; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; q8h, every 8 hours; q12h, every 12 hours; SSTI, skin and soft tissue infection

Dosage in Adults and Renal Impairment

Ceftaroline dosage in adults and adolescents (aged from 12 to <18 years with bodyweight ≥33kg) with CrCL >50mL/min

<table>
<thead>
<tr>
<th>Infection</th>
<th>Dosage regimen</th>
<th>Frequency</th>
<th>Duration of treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cSSTI⁹</td>
<td>600mg intravenously (over 60 minutes)</td>
<td>Every 12 hours</td>
<td>5-14</td>
</tr>
<tr>
<td>CAP</td>
<td>600mg intravenously (over 60 minutes)</td>
<td>Every 12 hours</td>
<td>5-7</td>
</tr>
</tbody>
</table>

⁹Based on pharmacokinetic and pharmacodynamic analyses, the recommended dosage for the treatment of cSSTI due to S. aureus for which the ceftaroline fosamil MIC is 2 or 4mg/L is 600mg every 8 hours using 2-hour infusions

Ceftaroline dosage in renal impairment in adults and adolescents (12 to <18 years of age with bodyweight ≥33kg) with a CrCL ≤50mL/min

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Dosage regimen</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 to ≤50</td>
<td>400mg intravenously (over 60 minutes)</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>≥15 to ≤30</td>
<td>300mg intravenously (over 60 minutes)</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>ESRD, including hemodialysis</td>
<td>200mg intravenously (over 60 minutes)</td>
<td>Every 12 hours</td>
</tr>
</tbody>
</table>

Ceftaroline is hemodialyzable; thus, Ceftaroline should be administered after hemodialysis on hemodialysis days

Simple dosing with no routine monitoring, low risk of drug–drug interaction, no dose adjustment based on bodyweight

NOTE: There are limited clinical data on the use of ZINFORO® to treat cSSTI caused by S. aureus with a MIC of >1mg/L. Ceftaroline should not be used to treat cSSTI due to S. aureus for which ceftaroline fosamil MIC is >4mg/L

cSSTI, complicated skin and soft tissue infection; CrCL, creatinine clearance; ESRD, end-stage renal disease
ZINFORO® SmPC, 2017
Safety/Tolerability

Ceftaroline
Tolerability Profile and TEAEs

- In Phase III trials in cSSTI and CAP, 1,305 patients received **Ceftaroline**, 600 mg BID IV (879 for 5–7d, 236 for 8–10d)
- Most patients (~75%) had either no TEAEs or mild TEAEs\(^1,2\)
- The proportion of patients experiencing mild, moderate, or severe TEAEs was similar between **Ceftaroline** and comparator antibiotics\(^1,2\)
  - These TEAEs were generally mild or moderate in severity\(^3\)
- Overall, the safety profile of **Ceftaroline** in pediatric patients aged from 2 months to 17 years with cSSTI or CAP (227 patients in two trials) was similar to that observed in the adult population

\(^4\)Two patients in the ZINFORO\(^\circledR\) arm had *Clostridium difficile* reported in the CANVAS trials; no patient had *C. difficile* reported in either treatment group during the FOCUS trials, although *C. difficile* testing was not required as part of the study procedures\(^4,5,6\)

\(^5\)Pruritis occurred in 1.9% of patients receiving ZINFORO\(^\circledR\) and 4.5% of patients receiving comparators (pooled analysis)

**Ceftaroline** has a similar tolerability profile to other cephalosporins and a low incidence of discontinuation due to AEs\(^4-7\)
<table>
<thead>
<tr>
<th></th>
<th>Cumulative data (CANVAS 1&amp;2, FOCUS 1&amp;2), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftaroline (N=1,305)</td>
</tr>
<tr>
<td>Patients ≥1 TAE</td>
<td>597 (45.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (4.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (4.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>57 (4.4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (1.9)</td>
</tr>
<tr>
<td>Rash</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Ceftaroline (N=1,305)  Comparators (N=1,301)

Patients ≥1 TAE  597 (45.7)  607 (46.7)

Diarrhea  60 (4.6)  42 (3.2)

Nausea  55 (4.2)  49 (3.8)

Headache  57 (4.4)  40 (3.1)

Pruritus  25 (1.9)  59 (4.5)

Rash  1.8%  1.5%

Zinforo SmPC, Jul 2017,
Corrado ML. J Antimicrob Chemother 2010;65(Suppl. 4):iv67–71
CAP, community-acquired pneumonia; cSSTI, complicated skin and soft tissue infection
Hypersensitivity reactions

❖ 3-5%

❖ Contraindications
  ❖ Hypersensitivity to the class of cephalosporins
  ❖ Direct and severe allergic reactions to any lactamic antibiotic
Direct antiglobulin test – DAGT Coombs

- The incidence of DAGT seroconversion in patients receiving Ceftaroline was
  - 11.2% patients receiving Ceftaroline q12 hr and
  - 32.3% in patients receiving Ceftaroline q8hr³

- No hemolysis in patients who developed DAGT during treatment with ceftaroline

- Hemolytic anemia should be considered in patients who develop anemia during treatment with ceftaroline
Drug–Drug Interactions

Ceftaroline
Drug–Drug Interactions and Compatibility with Other Antibiotics

**Ceftaroline** has low potential for drug–drug interactions involving:

1. Hepatic CYP P430 enzymes
2. Renal uptake transporters (OCT2, OAT1, OAT3)
   - Including drugs that are inhibitors (e.g., probenecid) or substrates of these transporters
3. Vasodilator or vasoconstrictor drugs that may alter renal blood flow

**Compatibility with other antibiotics** (checkerboard analysis):

- Amikacin
- Azithromycin
- Aztreonam
- Daptomycin
- Levofloxacin
- Linezolid
- Meropenem
- Tigecycline
- Vancomycin

*In vitro* studies have not demonstrated any antagonism between **Ceftaroline** in combination with other commonly used antibacterial agents (shown above)

**NOTE:** No clinical drug–drug interaction studies have been conducted with **Ceftaroline**

OAT, organic anion transporter; OCT, organic cation transporter
1. Frampton JE. Drugs 2013;73:1067-94; 2. ZINFORO® SmPC, 2017
Summary

• Bactericidal antibiotic
• Broad range: Gram pos + Gram neg
• MRSA activity
• No induction of resistance
• Excellent tissue penetration in both soft tissues and lungs
• Favorable safety profile
• No significant drug-drug interactions
• Synergy with a wide range of antibiotics