

**1 HIGHLIGHTS OF PRESCRIBING INFORMATION**

**2 These highlights do not include all the information needed to use Teflaro safely**  
**3 and effectively. See full prescribing information for Teflaro™.**

**4 Teflaro™ (ceftaroline fosamil) injection for intravenous (IV) use**

**5 Initial U.S. Approval: 2010**

**6 To reduce the development of drug-resistant bacteria and maintain the effectiveness**  
**7 Teflaro and other antibacterial drugs, Teflaro should be used only to treat infections that**  
**8 are proven or strongly suspected to be caused by bacteria.**

**9 -----INDICATIONS AND USAGE-----**

**10 Teflaro™ is a cephalosporin antibacterial indicated for the treatment of the**  
**11 following infections caused by designated susceptible bacteria:**

- 12 • Acute bacterial skin and skin structure infections (ABSSSI) (1.1)**
- 13 • Community-acquired bacterial pneumonia (CABP) (1.2)**

**14 -----DOSAGE AND ADMINISTRATION-----**

- 15 • 600 mg every 12 hours by IV infusion administered over 1 hour in adults ≥ 18**  
**16 years of age (2.1)**
- 17 • Dosage adjustment in patients with renal impairment (2.2)**

Estimated Creatinine Clearance <sup>#</sup> (mL/min)	Teflaro Dosage Regimen
> 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 (ESRD), including hemodialysis	200 mg IV (over 1 hour) every 12 hours

**18** <sup>#</sup>As calculated using the Cockcroft-Gault formula

**19 -----DOSAGE FORMS AND STRENGTHS -----**

**20** 600 mg or 400 mg of sterile Teflaro powder in single-use 20 mL vials. (3)

**21 -----CONTRAINDICATIONS-----**

Known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. (4)

**24 -----WARNINGS AND PRECAUTIONS-----**

- 25 • Serious hypersensitivity (anaphylactic) reactions have been reported with**  
**26 beta-lactam antibiotics, including ceftaroline. Exercise caution in patients**  
**27 with known hypersensitivity to beta-lactam antibiotics. (5.1)**
- 28 • Clostridium difficile-associated diarrhea (CDAD) has been reported with**  
**29 nearly all systemic antibacterial agents, including Teflaro. Evaluate if diarrhea**  
**30 occurs. (5.2)**
- 31 • Direct Coombs' test seroconversion has been reported with Teflaro. If anemia**  
**32 develops during or after therapy, a diagnostic workup for drug-induced**  
**33 hemolytic anemia should be performed and consideration given to**  
**34 discontinuation of Teflaro. (5.3)**

**35 -----ADVERSE REACTIONS-----**

The most common adverse reactions occurring in >2 % of patients are diarrhea, nausea, and rash. (6.3)

**To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at 1-800-678-1605 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**37 -----USE IN SPECIFIC POPULATIONS-----**

Dosage adjustment is required in patients with moderate or severe renal impairment and in ESRD patients, including patients on hemodialysis. (2.2, 12.3)

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: November 2010**

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\*Sections or subsections omitted from the full prescribing information are not listed.

101 **FULL PRESCRIBING INFORMATION**

102 **1. Indications and Usage**

103 Teflaro™ (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated  
104 microorganisms.

105 **1.1 Acute Bacterial Skin and Skin Structure Infections**

106 Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-  
107 positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*,  
108 *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

109 **1.2 Community-Acquired Bacterial Pneumonia**

110 Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive  
111 and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-  
112 susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*.

113 **1.3 Usage**

114 To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used to  
115 treat only ABSSSI or CABP that are proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological  
116 examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture  
117 and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local  
118 epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

119 **2. Dosage and Administration**

120 **2.1 Recommended Dosage**

121 The recommended dosage of Teflaro is 600 mg administered every 12 hours by intravenous (IV) infusion over 1 hour in patients ≥ 18 years of age. The  
122 duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

123 The recommended dosage and administration by infection is described in Table 1.

124 **Table 1: Dosage of Teflaro by Infection**

Infection	Dosage	Frequency	Infusion Time (hours)	Recommended Duration of Total Antimicrobial Treatment
Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	600 mg	Every 12 hours	1	5-14 days
Community-Acquired Bacterial Pneumonia (CABP)	600 mg	Every 12 hours	1	5-7 days

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126 **2.2 Patients with Renal Impairment**

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**Table 2: Dosage of Teflaro in Patients with Renal Impairment**

Estimated CrCl <sup>a</sup> (mL/min)	Recommended Dosage Regimen for Teflaro
> 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>

128 <sup>a</sup> Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.

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

130 <sup>c</sup> Teflaro is hemodialyzable; thus Teflaro should be administered after hemodialysis on hemodialysis days.

131 **2.3 Preparation of Solutions**

132 Aseptic technique must be followed in preparing the infusion solution. The contents of Teflaro vial should be constituted with 20 mL Sterile Water for  
133 Injection, USP. The preparation of Teflaro solutions is summarized in Table 3.

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**Table 3: Preparation of Teflaro for Intravenous Use**

Dosage Strength (mg)	Volume of Diluent To Be Added (mL)	Approximate Ceftriaxone fosamil Concentration (mg/mL)	Amount to Be Withdrawn
400	20	20	Total Volume
600	20	30	Total Volume

The constituted solution must be further diluted in  $\geq 250$  mL before infusion. Appropriate infusion solutions include: 0.9% Sodium Chloride Injection, USP (normal saline); 5% Dextrose Injection, USP; 2.5% Dextrose Injection, USP, and 0.45% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The resulting solution should be administered over approximately 1 hour.

Constitution time is less than 2 minutes. Mix gently to constitute and check to see that the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration.

The color of Teflaro infusion solutions ranges from clear, light to dark yellow depending on the concentration and storage conditions. When stored as recommended, the product potency is not affected.

Studies have shown that the constituted solution in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration at 2 to 8° C (36 to 46° F).

The compatibility of Teflaro with other drugs has not been established. Teflaro should not be mixed with or physically added to solutions containing other drugs.

### 3. Dosage Forms and Strengths

Teflaro is supplied in single-use, clear glass vials containing either 600 mg or 400 mg of sterile ceftaroline fosamil powder.

### 4. Contraindications

Teflaro is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

### 5. Warnings and Precautions

#### 5.1 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterials. Before therapy with Teflaro is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established.

If an allergic reaction to Teflaro occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated.

#### 5.2 *Clostridium difficile*-associated Diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Teflaro, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated [see Adverse Reactions (6.3)].

#### 5.3 Direct Coombs Test Seroconversion

Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving Teflaro and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials.

In the pooled Phase 3 CABP trials, 51/520 (9.8%) of Teflaro-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group.

If anemia develops during or after treatment with Teflaro, drug-induced hemolytic anemia should be considered. Diagnostic studies including a direct Coombs' test, should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of Teflaro should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated.

183 **5.4 Development of Drug-Resistant Bacteria**

184 Prescribing Teflaro in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk  
185 of the development of drug-resistant bacteria.

186 **6. Adverse Reactions**

187 The following serious events are described in greater detail in the Warnings and Precautions section

- 188 • Hypersensitivity reactions [see Warnings and Precautions (5.1)]
- 189 • *Clostridium difficile*-associated diarrhea [see Warnings and Precautions (5.2)]
- 190 • Direct Coombs' test seroconversion [see Warnings and Precautions (5.3)]

191 **6.1 Adverse Reactions from Clinical Trials**

192 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared  
193 directly to rates from clinical trials of another drug and may not reflect rates observed in practice.

194 Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CABP) which included 1300 adult patients treated  
195 with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone)  
196 for a treatment period up to 21 days. The median age of patients treated with Teflaro was 54 years, ranging between 18 and 99 years old. Patients treated  
197 with Teflaro were predominantly male (63%) and Caucasian (82%).

198 **6.2 Serious Adverse Events and Adverse Events Leading to Discontinuation**

199 In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving Teflaro and 100/1297 (7.7%) of patients  
200 receiving comparator drugs. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system  
201 organ classes (SOC). Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving Teflaro and 48/1297 (3.7%) of  
202 patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a  
203 rate of 0.3% in the Teflaro group and 0.5% in comparator group.

204 **6.3 Most Common Adverse Reactions**

205 No adverse reactions occurred in greater than 5% of patients receiving Teflaro. The most common adverse reactions occurring in > 2% of patients  
206 receiving Teflaro in the pooled phase 3 clinical trials were diarrhea, nausea, and rash.

207 Table 4 lists adverse reactions occurring in ≥ 2% of patients receiving Teflaro in the pooled Phase 3 clinical trials.

208 **Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Phase 3 Clinical Trials**

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators <sup>a</sup> (N=1297)
<b>Gastrointestinal disorders</b>		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
<b>Investigations</b>		
Increased transaminases	2%	3 %
<b>Metabolism and nutrition disorders</b>		
Hypokalemia	2 %	3 %
<b>Skin and subcutaneous tissue disorders</b>		
Rash	3%	2%
<b>Vascular disorders</b>		
Phlebitis	2%	1%

209 <sup>a</sup> Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram  
210 IV every 24h in the Phase 3 CABP trials.

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213 **6.4 Other Adverse Reactions Observed During Clinical Trials of Teflaro**

214 Following is a list of additional adverse reactions reported by the 1740 patients who received Teflaro in any clinical trial with incidences less than 2%.  
215 Events are categorized by System Organ Class.

216 **Blood and lymphatic system disorders** - Anemia, Eosinophilia, Neutropenia, Thrombocytopenia

217 **Cardiac disorders** - Bradycardia, Palpitations

218 **Gastrointestinal disorders** - Abdominal pain

219 **General disorders and administration site conditions** - Pyrexia

220 **Hepatobiliary disorders** - Hepatitis

221 **Immune system disorders** - Hypersensitivity, Anaphylaxis

222 **Infections and infestations** - *Clostridium difficile* colitis

223 **Metabolism and nutrition disorders** - Hyperglycemia, Hyperkalemia

224 **Nervous system disorders** - Dizziness, Convulsion

225 **Renal and urinary disorders** - Renal failure

226 **Skin and subcutaneous tissue disorders** - Urticaria

227 **7. Drug Interactions**

228 No clinical drug-drug interaction studies have been conducted with Teflaro. There is minimal potential for drug-drug interactions between Teflaro and  
229 CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow [see *Clinical*  
230 *Pharmacology (12.3)*].

231 **8. Use in Specific Populations**

232 **8.1 Pregnancy**

233 **Category B**

234 Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects  
235 on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats (based on AUC) at this dose level was approximately 8 times the  
236 exposure in humans given 600 mg every 12 hours. There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and  
237 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-  
238 spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at  $\geq$  50  
239 mg/kg; these were associated with an increase in spontaneous abortion at 50 and 100 mg/kg. The highest dose was also associated with maternal  
240 moribundity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic  
241 doses of 50 and 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was approximately 0.8 times the  
242 exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg.

243 Ceftaroline fosamil did not affect the postnatal development or reproductive performance of the offspring of rats given IV doses up to 450 mg/kg/day.  
244 Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was  $\geq$  8 times the exposure in humans  
245 given 600 mg every 12 hours.

246 There are no adequate and well-controlled trials in pregnant women. Teflaro should be used during pregnancy only if the potential benefit justifies the  
247 potential risk to the fetus.

248 **8.3 Nursing Mothers**

249 It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Teflaro  
250 is administered to a nursing woman.

251 **8.4 Pediatric Use**

252 Safety and effectiveness in pediatric patients have not been established.

253 **8.5 Geriatric Use**

254 Of the 1300 patients treated with Teflaro in the Phase 3 ABSSSI and CABP trials, 397 (30.5%) were  $\geq$  65 years of age. The clinical cure rates in the  
255 Teflaro group (Clinically Evaluable [CE] Population) were similar in patients  $\geq$  65 years of age compared with patients < 65 years of age in both the  
256 ABSSSI and CABP trials.

257 The adverse event profiles in patients  $\geq$  65 years of age and in patients < 65 years of age were similar. The percentage of patients in the Teflaro group who  
258 had at least one adverse event was 52.4% in patients  $\geq$  65 years of age and 42.8% in patients < 65 years of age for the two indications combined.

259 Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly  
260 patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal  
261 function. Elderly subjects had greater ceftaroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However,  
262 higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based  
263 on renal function [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

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266 **8.6 Patients with Renal Impairment**

267 Dosage adjustment is required in patients with moderate (CrCl > 30 to ≤ 50 mL/min) or severe (CrCl ≥ 15 to ≤ 30 mL/min) renal impairment and in  
268 patients with end-stage renal disease (ESRD – defined as CrCl < 15 mL/min), including patients on hemodialysis (HD) [see *Dosage and Administration*  
269 (2.2) and *Clinical Pharmacology* (12.3)].

270 **10. Overdosage**

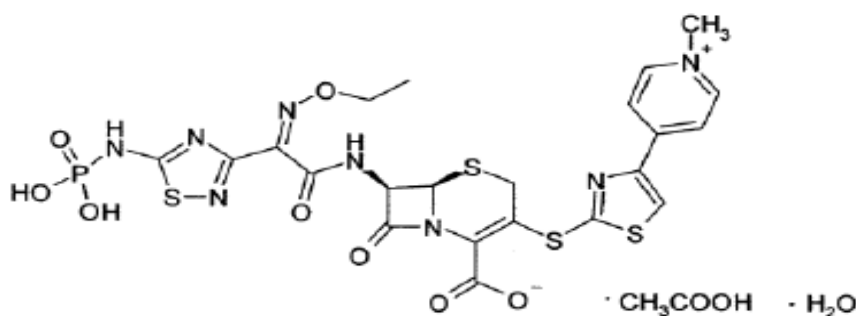
271 In the event of overdose, Teflaro should be discontinued and general supportive treatment given.

272 Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the  
273 dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on  
274 the use of hemodialysis to treat overdose [see *Clinical Pharmacology* (12.3)].

275 **11. Description**

276 Teflaro is a sterile, semi-synthetic, broad-spectrum, prodrug antibacterial of cephalosporin class of beta-lactams (β-lactams). Chemically, the prodrug,  
277 ceftaroline fosamil monoacetate monohydrate is (6*R*,7*R*)-7-[(2*Z*)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiazol-3-yl]acetamido]-3-[[4-(1-  
278 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. Its molecular  
279 weight is 762.75. The empirical formula is C<sub>22</sub>H<sub>21</sub>N<sub>8</sub>O<sub>8</sub>PS<sub>4</sub>·C<sub>2</sub>H<sub>4</sub>O<sub>2</sub>·H<sub>2</sub>O.

280 **Figure 1: Chemical structure of ceftaroline fosamil**



291 Teflaro vials contain either 600 mg or 400 mg of anhydrous ceftaroline fosamil. The powder for injection is formulated from ceftaroline fosamil  
292 monoacetate monohydrate, a pale yellowish-white to light yellow sterile powder. All references to ceftaroline activity are expressed in terms of the  
293 prodrug, ceftaroline fosamil. The powder is constituted for IV injection [see *Dosage and Administration* (2.3)].

294 Each vial of Teflaro contains ceftaroline fosamil and L-arginine, which results in a constituted solution at pH 4.8 to 6.5.

295 **12. Clinical Pharmacology**

296 Ceftaroline fosamil is the water-soluble prodrug of the bioactive ceftaroline [see *Clinical Pharmacology* (12.3)].

297 **12.1 Mechanism of Action**

298 Ceftaroline is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

299 **12.2 Pharmacodynamics**

300 As with other beta-lactam antimicrobial agents, the time that unbound plasma concentration of ceftaroline exceeds the minimum inhibitory concentration  
301 (MIC) of the infecting organism has been shown to best correlate with efficacy in a neutropenic murine thigh infection model with *S. aureus* and *S.*  
302 *pneumoniae*.

303 Exposure-response analysis of Phase 2/3 ABSSSI trials supports the recommended dosage regimen of Teflaro 600 mg every 12 hours by IV infusion over  
304 1 hour. For Phase 3 CABP trials, an exposure-response relationship could not be identified due to the limited range of ceftaroline exposures in the  
305 majority of patients.

306 **Cardiac Electrophysiology**

307 In a randomized, positive- and placebo-controlled crossover thorough QTc study, 54 healthy subjects were each administered a single dose of Teflaro  
308 1500 mg, placebo, and a positive control by IV infusion over 1 hour. At the 1500 mg dose of Teflaro, no significant effect on QTc interval was detected at  
309 peak plasma concentration or at any other time.

310 **12.3 Pharmacokinetics**

311 The mean pharmacokinetic parameters of ceftaroline in healthy adults (n=6) with normal renal function after single and multiple 1-hour IV infusions of  
312 600 mg ceftaroline fosamil administered every 12 hours are summarized in Table 5. Pharmacokinetic parameters were similar for single and multiple dose  
313 administration.

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**Table 5: Mean (Standard Deviation) Pharmacokinetic Parameters of Ceftaroline IV in Healthy Adults**

Parameter	Single 600 mg Dose Administered as a 1-Hour Infusion (n=6)	Multiple 600 mg Doses Administered Every 12 Hours as 1-Hour Infusions for 14 Days (n=6)
<b>C<sub>max</sub> (mcg/mL)</b>	<b>19.0 (0.71)</b>	<b>21.3 (4.10)</b>
<b>T<sub>max</sub> (h)<sup>a</sup></b>	<b>1.00 (0.92-1.25)</b>	<b>0.92 (0.92-1.08)</b>
<b>AUC (mcg•h/mL)<sup>b</sup></b>	<b>56.8 (9.31)</b>	<b>56.3 (8.90)</b>
<b>T<sub>1/2</sub> (h)</b>	<b>1.60 (0.38)</b>	<b>2.66 (0.40)</b>
<b>CL (L/h)</b>	<b>9.58 (1.85)</b>	<b>9.60 (1.40)</b>
<sup>a</sup> Reported as median (range) <sup>b</sup> AUC <sub>0-∞</sub> for single-dose administration, AUC <sub>0-tau</sub> for multiple-dose administration, C <sub>max</sub> , maximum observed concentration; T <sub>max</sub> , time of C <sub>max</sub> ; AUC <sub>0-∞</sub> , area under concentration-time curve from time 0 to infinity; AUC <sub>0-tau</sub> , area under concentration-time curve over dosing interval (0-12 hours); T <sub>1/2</sub> , terminal elimination half-life; CL, plasma clearance		

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319 The C<sub>max</sub> and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to 1000 mg. No appreciable  
320 accumulation of ceftaroline is observed following multiple IV infusions of 600 mg administered every 12 hours for up to 14 days in healthy adults with  
321 normal renal function.

322 **Distribution**

323 The average binding of ceftaroline to human plasma proteins is approximately 20% and decreases slightly with increasing concentrations over 1-50  
324 mcg/mL (14.5-28.0%). The median (range) steady-state volume of distribution of ceftaroline in healthy adult males (n=6) following a single 600 mg IV  
325 dose of radiolabeled ceftaroline fosamil was 20.3 L (18.3-21.6 L), similar to extracellular fluid volume.

326 **Metabolism**

327 Ceftaroline fosamil is converted into bioactive ceftaroline in plasma by a phosphatase enzyme and concentrations of the prodrug are measurable in plasma  
328 primarily during IV infusion. Hydrolysis of the beta-lactam ring of ceftaroline occurs to form the microbiologically inactive, open-ring metabolite  
329 ceftaroline M-1. The mean (SD) plasma ceftaroline M-1 to ceftaroline AUC<sub>0-∞</sub> ratio following a single 600 mg IV infusion of ceftaroline fosamil in  
330 healthy adults (n=6) with normal renal function is 28% (3.1%).

331 When incubated with pooled human liver microsomes, ceftaroline was metabolically stable (< 12% metabolic turnover), indicating that ceftaroline is not a  
332 substrate for hepatic CYP450 enzymes.

333 **Excretion**

334 Ceftaroline and its metabolites are primarily eliminated by the kidneys. Following administration of a single 600 mg IV dose of radiolabeled ceftaroline  
335 fosamil to healthy male adults (n=6), approximately 88% of radioactivity was recovered in urine and 6% in feces within 48 hours. Of the radioactivity  
336 recovered in urine approximately 64% was excreted as ceftaroline and approximately 2% as ceftaroline M-1. The mean (SD) renal clearance of ceftaroline  
337 was 5.56 (0.20) L/h, suggesting that ceftaroline is predominantly eliminated by glomerular filtration.

338 **Specific Populations**

339 **Renal Impairment**

340 Following administration of a single 600 mg IV dose of Teflaro, the geometric mean AUC<sub>0-∞</sub> of ceftaroline in subjects with mild (CrCl > 50 to ≤ 80  
341 mL/min, n=6) or moderate (CrCl > 30 to ≤ 50 mL/min, n=6) renal impairment was 19% and 52% higher, respectively, compared to healthy subjects with  
342 normal renal function (CrCl > 80 mL/min, n=6). Following administration of a single 400 mg IV dose of Teflaro, the geometric mean AUC<sub>0-∞</sub> of  
343 ceftaroline in subjects with severe (CrCl ≥ 15 to ≤ 30 mL/min, n=6) renal impairment was 115% higher compared to healthy subjects with normal renal  
344 function (CrCl > 80 mL/min, n=6). Dosage adjustment is recommended in patients with moderate and severe renal impairment [see *Dosage and*  
345 *Administration (2.2)*].

346 A single 400 mg dose of Teflaro was administered to subjects with ESRD (n=6) either 4 hours prior to or 1 hour after hemodialysis (HD). The geometric  
347 mean ceftaroline AUC<sub>0-∞</sub> following the post-HD infusion was 167% higher compared to healthy subjects with normal renal function (CrCl > 80 mL/min,  
348 n=6). The mean recovery of ceftaroline in the dialysate following a 4-hour HD session was 76.5 mg, or 21.6% of the administered dose. Dosage  
349 adjustment is recommended in patients with ESRD (defined as CrCl < 15 mL/min), including patients on HD [see *Dosage and Administration (2.2)*].

350 **Hepatic Impairment**

351 The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established. As ceftaroline does not appear to undergo significant  
352 hepatic metabolism, the systemic clearance of ceftaroline is not expected to be significantly affected by hepatic impairment.

353 **Geriatric Patients**

354 Following administration of a single 600 mg IV dose of Teflaro to healthy elderly subjects (≥ 65 years of age, n=16), the geometric mean AUC<sub>0-∞</sub> of  
355 ceftaroline was ~33% higher compared to healthy young adult subjects (18-45 years of age, n=16). The difference in AUC<sub>0-∞</sub> was mainly attributable to  
356 age-related changes in renal function. Dosage adjustment for Teflaro in elderly patients should be based on renal function [see *Dosage and Administration*  
357 (2.2)].

358

359 **Pediatric Patients**

360 The pharmacokinetics of ceftaroline were evaluated in adolescent patients (ages 12 to 17, n=7) with normal renal function following administration of a  
361 single 8 mg/kg IV dose of Teflaro (or 600 mg for subjects weighing > 75 kg). The mean plasma clearance and terminal phase volume of distribution for  
362 ceftaroline in adolescent subjects were similar to healthy adults (n=6) in a separate study following administration of a single 600 mg IV dose. However,  
363 the mean C<sub>max</sub> and AUC<sub>0-∞</sub> for ceftaroline in adolescent subjects who received a single 8 mg/kg dose were 10% and 23% less than in healthy adult subjects  
364 who received a single 600 mg IV dose.

365 **Gender**

366 Following administration of a single 600 mg IV dose of Teflaro to healthy elderly males (n=10) and females (n=6) and healthy young adult males (n=6)  
367 and females (n=10), the mean C<sub>max</sub> and AUC<sub>0-∞</sub> for ceftaroline were similar between males and females, although there was a trend for higher C<sub>max</sub> (17%)  
368 and AUC<sub>0-∞</sub> (6-15%) in female subjects. Population pharmacokinetic analysis did not identify any significant differences in ceftaroline AUC<sub>0-tau</sub> based on  
369 gender in Phase 2/3 patients with ABSSSI or CABP. No dose adjustment is recommended based on gender.

370 **Race**

371 A population pharmacokinetic analysis was performed to evaluate the impact of race on the pharmacokinetics of ceftaroline using data from Phase 2/3  
372 ABSSSI and CABP trials. No significant differences in ceftaroline AUC<sub>0-tau</sub> was observed across White (n=35), Hispanic (n=34), and Black (n=17) race  
373 groups for ABSSSI patients. Patients enrolled in CABP trials were predominantly categorized as White (n=115); thus there were too few patients of other  
374 races to draw any conclusions. No dosage adjustment is recommended based on race.

375 **Drug Interactions**

376 *In vitro* studies in human liver microsomes indicate that ceftaroline does not inhibit the major cytochrome P450 isoenzymes CYP1A1, CYP1A2,  
377 CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. *In vitro* studies in human hepatocytes also demonstrate that  
378 ceftaroline and its inactive open-ring metabolite are not inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Therefore Teflaro  
379 is not expected to inhibit or induce the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

380 Population pharmacokinetic analysis did not identify any clinically relevant differences in ceftaroline exposure (C<sub>max</sub> and AUC<sub>0-tau</sub>) in Phase 2/3 patients  
381 with ABSSSI or CABP who were taking concomitant medications that are known inhibitors, inducers, or substrates of the cytochrome P450 system;  
382 anionic or cationic drugs known to undergo active renal secretion; and vasodilator or vasoconstrictor drugs that may alter renal blood flow.

383 **12.4 Microbiology**

384 **Mode of Action**

385 Ceftaroline is a cephalosporin with *in vitro* activity against Gram-positive and -negative bacteria. The bactericidal action of ceftaroline is mediated  
386 through binding to essential penicillin-binding proteins (PBPs). Ceftaroline is bactericidal against *S. aureus* due to its affinity for PBP2a and against  
387 *Streptococcus pneumoniae* due to its affinity for PBP2x.

388 **Mechanisms of Resistance**

389 Ceftaroline is not active against Gram-negative bacteria producing extended spectrum beta-lactamases (ESBLs) from the TEM, SHV or CTX-M families,  
390 serine carbapenemases (such as KPC), class B metallo-beta-lactamases, or class C (AmpC cephalosporinases).

391 **Cross-Resistance**

392 Although cross-resistance may occur, some isolates resistant to other cephalosporins may be susceptible to ceftaroline.

393 **Interaction with Other Antimicrobials**

394 *In vitro* studies have not demonstrated any antagonism between ceftaroline or other commonly used antibacterial agents (e.g., vancomycin, linezolid,  
395 daptomycin, levofloxacin, azithromycin, amikacin, aztreonam, tigecycline, and meropenem).

396 Ceftaroline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

397 **Skin Infections**

398 Gram-positive bacteria  
399 *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)  
400 *Streptococcus pyogenes*  
401 *Streptococcus agalactiae*

402 Gram-negative bacteria  
403 *Escherichia coli*  
404 *Klebsiella pneumoniae*  
405 *Klebsiella oxytoca*

406 **Community-Acquired Bacterial Pneumonia (CABP)**

407 Gram-positive bacteria  
408 *Streptococcus pneumoniae*  
409 *Staphylococcus aureus* (methicillin-susceptible isolates only)

410 Gram-negative bacteria  
411 *Haemophilus influenzae*  
412 *Klebsiella pneumoniae*  
413 *Klebsiella oxytoca*



419 *Escherichia coli*

420 The following *in vitro* data are available, but their clinical significance is unknown. Ceftaroline exhibits *in vitro* MICs of 1 mcg/mL or less against most  
421 ( $\geq 90\%$ ) isolates of the following bacteria; however, the safety and effectiveness of Teflaro in treating clinical infections due to these bacteria have not  
422 been established in adequate and well-controlled clinical trials.

423 Gram-positive bacteria  
424 *Streptococcus dysgalactiae*

425  
426 Gram-negative bacteria  
427 *Citrobacter koseri*  
428 *Citrobacter freundii*  
429 *Enterobacter cloacae*  
430 *Enterobacter aerogenes*  
431 *Moraxella catarrhalis*  
432 *Morganella morganii*  
433 *Proteus mirabilis*  
434 *Haemophilus parainfluenzae*  
435

436 **Susceptibility Test Methods**

437 When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in local  
438 hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens.  
439 These reports should aid the physician in selecting an antibacterial drug product for treatment.

440 **Dilution Techniques**

441 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility  
442 of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,3</sup>, (broth, and/or agar). Broth dilution MICs  
443 need to be read within 18 hours due to degradation of cefataroline activity by 24 hours. The MIC values should be interpreted according to the criteria in  
444 Table 6.

445 **Diffusion Techniques**

446 Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial  
447 compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a  
448 standardized method. This procedure uses paper disks impregnated with 30 mcg of cefataroline to test the susceptibility of bacteria to cefataroline. The disk  
449 diffusion interpretive criteria are provided in Table 6.

450 **Table 6: Susceptibility Interpretive Criteria for Cefataroline**

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (includes methicillin-resistant isolates - skin isolates only) -See NOTE below	$\leq 1^a$	—	—	$\geq 24$	—	—
<i>Streptococcus agalactiae</i> <sup>a</sup> (skin isolates only)	$\leq 0.03$	—	—	$\geq 26$	—	—
<i>Streptococcus pyogenes</i> <sup>a</sup> (skin isolates only)	$\leq 0.015$	—	—	$\geq 24$	—	—
<i>Streptococcus pneumoniae</i> <sup>a</sup> (CABP isolates only)	$\leq 0.25$	—	—	$\geq 27$	—	—
<i>Haemophilus influenzae</i> (CABP isolates only)	$\leq 0.12$	—	—	$\geq 33$	—	—
<i>Enterobacteriaceae</i> <sup>b</sup> (CABP and skin isolates)	$\leq 0.5$	1	$\geq 2$	$\geq 23$	20-22	$\leq 19$

451 S = susceptible, I = intermediate, R = resistant

452 **NOTE:** Clinical efficacy of Teflaro to treat lower respiratory infections such as community-acquired bacterial pneumonia due to MRSA has  
453 not been studied in adequate and well controlled trials (See “Clinical Trials” section 14)

454 <sup>a</sup> The current absence of resistant isolates precludes defining any results other than “Susceptible.” Isolates yielding MIC results other than  
455 “Susceptible” should be submitted to a reference laboratory for further testing.

456 <sup>b</sup> Clinical efficacy was shown for the following *Enterobacteriaceae*: *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

457 A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the  
458 concentration at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered  
459 equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies  
460 possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small  
461 uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the antimicrobial is not likely to  
462 inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be  
463 selected.

464 **Quality Control**

465 Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and  
466 reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3</sup> Standard ceftaroline powder should provide the following range  
467 of MIC values provided in Table 7. For the diffusion technique using the 30-mcg ceftaroline disk the criteria provided in Table 7 should be achieved.

468 **Table 7: Acceptable Quality Control Ranges for Susceptibility Testing**

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	26 - 35
<i>Staphylococcus aureus</i> ATCC 29213	0.12 - 0.5	Not Applicable
<i>Escherichia coli</i> ATCC 25922	0.03 - 0.12	26 - 34
<i>Haemophilus influenzae</i> ATCC 49247	0.03 - 0.12	29 - 39
<i>Streptococcus pneumoniae</i> ATCC 49619	0.008 - 0.03	31 - 41

469 ATCC = American Type Culture Collection

470 **13. Nonclinical Toxicology**

471 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

472 Long-term carcinogenicity studies have not been conducted with ceftaroline.

473 Ceftaroline fosamil did not show evidence of mutagenic activity in *in vitro* tests that included a bacterial reverse mutation assay and the mouse lymphoma  
474 assay. Ceftaroline was not mutagenic in an *in vitro* mammalian cell assay. *In vivo*, ceftaroline fosamil did not induce unscheduled DNA synthesis in rat  
475 hepatocytes and did not induce the formation of micronucleated erythrocytes in mouse or rat bone marrow. Both ceftaroline fosamil and ceftaroline were  
476 clastogenic in the absence of metabolic activation in an *in vitro* chromosomal aberration assays, but not in the presence of metabolic activation.

477 IV injection of ceftaroline fosamil had no adverse effects on fertility of male and female rats given up to 450 mg/kg. This is approximately 4-fold higher  
478 than the maximum recommended human dose based on body surface area.

479 **14. Clinical Trials**

480 **14.1 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)**

481 A total of 1396 adults with clinically documented complicated skin and skin structure infection were enrolled in two identical randomized, multi-center,  
482 multinational, double-blind, non-inferiority trials (Trials 1 and 2) comparing Teflaro (600 mg administered IV over 1 hour every 12 hours) to vancomycin  
483 plus aztreonam (1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours). Treatment  
484 duration was 5 to 14 days. A switch to oral therapy was not allowed. The Modified Intent-to-Treat (MITT) population included all patients who received  
485 any amount of study drug according to their randomized treatment group. The CE population included patients in the MITT population who demonstrated  
486 sufficient adherence to the protocol.

487 To evaluate the treatment effect of ceftaroline, an analysis was conducted in 797 patients with ABSSSI (such as deep / extensive cellulitis or a wound  
488 infection [surgical or traumatic]) for whom the treatment effect of antibacterials may be supported by historical evidence. This analysis evaluated  
489 responder rates based on achieving both cessation of lesion spread and absence of fever on Trial Day 3 in the following subgroup of patients:

490 Patients with lesion size  $\geq 75$  cm<sup>2</sup> and having one of the following infection types:

- 491 • Major abscess with  $\geq 5$  cm of surrounding erythema
- 492 • Wound infection
- 493 • Deep/extensive cellulitis

494 The results of this analysis are shown in Table 8.

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**Table 8: Clinical Responders at Study Day 3 from Two Phase 3 ABSSSI Trials**

	<b>Teflaro</b> n/N (%)	<b>Vancomycin/ Aztreonam</b> n/N (%)	<b>Treatment Difference</b> (2-sided 95% CI)
<b>ABSSSI Trial 1</b>	148/200 (74.0)	135/209 (64.6)	9.4 (0.4, 18.2)
<b>ABSSSI Trial 2</b>	148/200 (74.0)	128/188 (68.1)	5.9 (-3.1, 14.9)

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The protocol-specified analyses included clinical cure rates at the Test of Cure (TOC) (visit 8 to 15 days after the end of therapy) in the coprimary CE and MITT populations (Table 9) and clinical cure rates at TOC by pathogen in the Microbiologically Evaluable (ME) population (Table 10). However, there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point. Therefore, comparisons of Teflaro to vancomycin plus aztreonam based on clinical response rates at TOC can not be utilized to establish non-inferiority.

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**Table 9: Clinical Cure Rates at TOC from Two Phase 3 ABSSSI Trials**

	<b>Teflaro</b> n/N (%)	<b>Vancomycin/ Aztreonam</b> n/N (%)	<b>Treatment Difference</b> (2-sided 95% CI)
<b>Trial 1</b>			
<b>CE</b>	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
<b>MITT</b>	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)
<b>Trial 2</b>			
<b>CE</b>	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)
<b>MITT</b>	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)

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**Table 10: Clinical Cure Rates at TOC by Pathogen from Two Integrated Phase 3 ABSSSI Trials**

	<b>Teflaro</b> n/N (%)	<b>Vancomycin/Aztreonam</b> n/N (%)
<b>Gram-positive:</b>		
MSSA (methicillin-susceptible)	212/228 (93.0%)	225/238 (94.5%)
MRSA (methicillin-resistant)	142/152 (93.4%)	115/122 (94.3%)
<i>Streptococcus pyogenes</i>	56/56 (100%)	56/58 (96.6%)
<i>Streptococcus agalactiae</i>	21/22 (95.5%)	18/18 (100%)
<b>Gram-negative:</b>		
<i>Escherichia coli</i>	20/21 (95.2%)	19/21 (90.5%)
<i>Klebsiella pneumoniae</i>	17/18 (94.4%)	13/14 (92.9%)
<i>Klebsiella oxytoca</i>	10/12 (83.3%)	6/6 (100%)

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**14.2 Community-Acquired Bacterial Pneumonia (CABP)**

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A total of 1231 adults with a diagnosis of CABP were enrolled in two randomized, multi-center, multinational, double-blind, non-inferiority trials (Trials 1 and 2) comparing Teflaro (600 mg administered IV over 1 hour every 12 hours) with ceftriaxone (1 g ceftriaxone administered IV over 30 minutes every 24 hours). In both treatment groups of CABP Trial 1, two doses of oral clarithromycin (500 mg every 12 hours), were administered as adjunctive therapy starting on Study Day 1. No adjunctive macrolide therapy was used in CABP Trial 2. Patients with known or suspected MRSA were excluded from both trials. Patients with new or progressive pulmonary infiltrate(s) on chest radiography and signs and symptoms consistent with CABP with the need for hospitalization and IV therapy were enrolled in the trials. Treatment duration was 5 to 7 days. A switch to oral therapy was not allowed. Among all subjects who received any amount of study drug in the two CABP trials, the 30-day all-cause mortality rates were 11/609 (1.8%) for the Teflaro group vs. 12/610 (2.0%) for the ceftriaxone group, and the difference in mortality rates was not statistically significant.

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To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be supported by historical evidence. The analysis endpoint required subjects to meet sign and symptom criteria at Day 4 of therapy: a responder had to both (a) be in stable condition according to consensus treatment guidelines of the Infectious Diseases Society of America and American Thoracic Society, based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status;<sup>4</sup> (b) show improvement from baseline on at least one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms. The analysis used a microbiological intent-to-treat population (MITT population) containing only subjects with a confirmed bacterial pathogen at baseline. Results for this analysis are presented in Table 11.

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**Table 11: Response Rates at Study Day 4 (72-96 hours) from Two Phase 3 CABP Trials**

	<b>Teflaro</b> n/N (%)	<b>Ceftriaxone</b> n/N (%)	<b>Treatment Difference</b> (2-sided 95% CI)
<b>CABP Trial 1</b>	48/69 (69.6%)	42/72 (58.3%)	11.2(-4.6,26.5)
<b>CABP Trial 2</b>	58/84(69.0%)	51/83 (61.4%)	7.6 (-6.8,21.8)

526 The protocol-specified analyses included clinical cure rates at the TOC (8 to 15 days after the end of therapy) in the coprimary Modified Intent-to-Treat  
527 Efficacy (MITTE) and CE populations (Table 12) and clinical cure rates at TOC by pathogen in the Microbiologically Evaluable (ME) population (Table  
528 13). However, there are insufficient historical data to establish the magnitude of drug effect for antibacterials drugs compared with placebo at a TOC time  
529 point. Therefore, comparisons of Teflaro to ceftriaxone based on clinical response rates at TOC cannot be utilized to establish non-inferiority. Neither trial  
530 established that Teflaro was statistically superior to ceftriaxone in terms of clinical response rates. The MITTE population included all patients who  
531 received any amount of study drug according to their randomized treatment group and were in PORT (Pneumonia Outcomes Research Team) Risk Class  
532 III or IV. The CE population included patients in the MITTE population who demonstrated sufficient adherence to the protocol.

533 **Table 12: Clinical Cure Rates at TOC from Two Phase 3 CABP Trials**

	Teflaro n/N (%)	Ceftriaxone n/N (%)	Treatment Difference (2-sided 95% CI)
<b>CABP Trial 1</b>			
CE	194/224 (86.6%)	183/234 (78.2%)	8.4 (1.4, 15.4)
MITTE	244/291 (83.8%)	233/300 (77.7%)	6.2 (-0.2, 12.6)
<b>CABP Trial 2</b>			
CE	191/232 (82.3%)	165/214 (77.1%)	5.2 (-2.2, 12.8)
MITTE	231/284 (81.3%)	203/269 (75.5%)	5.9 (-1.0, 12.8)

534 **Table 13: Clinical Cure Rates at TOC by Pathogen from Two Integrated Phase 3 CABP Trials**

	Teflaro n/N (%)	Ceftriaxone n/N (%)
<b>Gram-positive:</b>		
<i>Streptococcus pneumoniae</i>	54/63 (85.7%)	41/59 (69.5%)
<i>Staphylococcus aureus</i> (methicillin-susceptible isolates only)	18/25 (72.0%)	14/25 (56.0%)
<b>Gram-negative:</b>		
<i>Haemophilus influenzae</i>	15/18 (83.3%)	17/20 (85.0%)
<i>Klebsiella pneumoniae</i>	12/12 (100%)	10/12 (83.3%)
<i>Klebsiella oxytoca</i>	5/6 (83.3%)	7/8 (87.5%)
<i>Escherichia coli</i>	10/12 (83.3%)	9/12 (75.0%)

535 **15. References**

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546 **16. How Supplied/Storage and Handling**

547 Teflaro (ceftaroline fosamil) for injection is supplied in single-use, clear glass vials containing:

- 548 • 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10)
- 549 • 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10)

550 Teflaro vials should be stored refrigerated at 2 to 8° C (36 to 46° F). Unrefrigerated, unconstituted Teflaro can be stored at temperatures not exceeding  
551 25°C (77°F) for no more than 7 days.

552 **17. Patient Counseling Information**

- 553 • Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate  
554 treatment. They should inform their healthcare provider about any previous hypersensitivity reactions to Teflaro, other beta-lactams (including  
555 cephalosporins) or other allergens.
- 556 • Patients should be counseled that antibacterial drugs including Teflaro should be used to treat only bacterial infections. They do not treat viral  
557 infections (e.g., the common cold). When Teflaro is prescribed to treat a bacterial infection, patients should be told that although it is common to  
558 feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of  
559

560 therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will  
561 not be treatable by Teflaro or other antibacterial drugs in the future.

- 562 • Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued.  
563 Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody  
564 diarrhea develops, patients should contact their healthcare provider.
- 565 • Keep out of reach of children

566 Teflaro (ceftaroline fosamil) for injection  
567

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576 64020 Teramo, Italy  
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