

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

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

6 **Initial U.S. Approval: 2011**

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

11 -----INDICATIONS AND USAGE-----

12 Teflaro™ is a cephalosporin antibacterial indicated for the treatment  
13 of the following infections caused by designated susceptible bacteria:

- 14 • Acute bacterial skin and skin structure infections (ABSSSI) (1.1)  
15 • Community-acquired bacterial pneumonia (CABP) (1.2)

16 -----DOSAGE AND ADMINISTRATION-----

- 17 • 600 mg every 12 hours by IV infusion administered over 1 hour in  
18 adults ≥ 18 years of age (2.1)  
19 • 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

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

21 -----DOSAGE FORMS AND STRENGTHS-----

22 600 mg or 400 mg of sterile Teflaro powder in single-use 20 mL vials.  
23 (3)

24 -----CONTRAINDICATIONS-----

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

27 -----WARNINGS AND PRECAUTIONS-----

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

40 -----ADVERSE REACTIONS-----

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

43 **To report SUSPECTED ADVERSE REACTIONS, contact Forest**  
44 **Pharmaceuticals, Inc., at 1-800-678-1605 or FDA at 1-800-FDA-**  
45 **1088 or www.fda.gov/medwatch.**

46 -----USE IN SPECIFIC POPULATIONS-----

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

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51 **See 17 for PATIENT COUNSELING INFORMATION**

Revised: XX/20XX

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

122 **FULL PRESCRIBING INFORMATION**

123 **1. Indications and Usage**

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

126 **1.1 Acute Bacterial Skin and Skin Structure Infections**

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

131 **1.2 Community-Acquired Bacterial Pneumonia**

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

136 **1.3 Usage**

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

143 **2. Dosage and Administration**

144 **2.1 Recommended Dosage**

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

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

149 **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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151 **2.2 Patients with Renal Impairment**

152 **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>

- 153 <sup>a</sup> Creatinine clearance (CrCl) estimated using the Cockcroft-Gault formula.  
154 <sup>b</sup> End-stage renal disease is defined as CrCl < 15 mL/min.  
155 <sup>c</sup> Teflaro is hemodialyzable; thus Teflaro should be administered after hemodialysis on hemodialysis days.

156 **2.3 Preparation of Solutions**

157 Aseptic technique must be followed in preparing the infusion solution. The contents of Teflaro vial should be  
158 constituted with 20 mL Sterile Water for Injection, USP. The preparation of Teflaro solutions is summarized in Table  
159 3.

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

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

161  
162 The constituted solution must be further diluted in  $\geq 250$  mL before infusion. Appropriate infusion solutions include:  
163 0.9% Sodium Chloride Injection, USP (normal saline); 5% Dextrose Injection, USP; 2.5% Dextrose Injection, USP,  
164 and 0.45% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The resulting solution should be  
165 administered over approximately 1 hour.

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

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

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

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

174 **3. Dosage Forms and Strengths**

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

177 **4. Contraindications**

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

180 **5. Warnings and Precautions**

181 **5.1 Hypersensitivity Reactions**

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

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

190 **5.2 Clostridium difficile-associated Diarrhea**

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

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

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

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

### 202 **5.3 Direct Coombs Test Seroconversion**

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

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

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

### 212 **5.4 Development of Drug-Resistant Bacteria**

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

## 215 **6. Adverse Reactions**

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

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

### 220 **6.1 Adverse Reactions from Clinical Trials**

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

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

### 229 **6.2 Serious Adverse Events and Adverse Events Leading to Discontinuation**

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

### 236 **6.3 Most Common Adverse Reactions**

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

239 Table 4 lists adverse reactions occurring in  $\geq$  2% of patients receiving Teflaro in the pooled Phase 3 clinical trials.

240 **Table 4: Adverse Reactions Occurring in  $\geq$  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%

<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 IV every 24h in the Phase 3 CABP trials.

241  
242

243 **6.4 Other Adverse Reactions Observed During Clinical Trials of Teflaro**

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

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

247 **Cardiac disorders** - Bradycardia, Palpitations

248 **Gastrointestinal disorders** - Abdominal pain

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

250 **Hepatobiliary disorders** - Hepatitis

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

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

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

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

255 **Renal and urinary disorders** - Renal failure

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

257

258 **7. Drug Interactions**

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

262 **8. Use in Specific Populations**

263 **8.1 Pregnancy**

264 **Category B**

265 Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated  
266 no maternal toxicity and no effects on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats  
267 (based on AUC) at this dose level was approximately 8 times the exposure in humans given 600 mg every 12 hours.  
268 There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and 100 mg/kg, despite  
269 maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system  
270 to broad-spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body  
271 weight gain and food consumption at  $\geq 50$  mg/kg; these were associated with an increase in spontaneous abortion at 50  
272 and 100 mg/kg. The highest dose was also associated with maternal moribundity and mortality. An increased incidence  
273 of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic doses of 50 and  
274 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was  
275 approximately 0.8 times the exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human  
276 exposure at 50 mg/kg.

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

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

282 **8.3 Nursing Mothers**

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

285 **8.4 Pediatric Use**

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

287 **8.5 Geriatric Use**

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

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

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

301 **8.6 Patients with Renal Impairment**

302 Dosage adjustment is required in patients with moderate ( $\text{CrCl} > 30$  to  $\leq 50$  mL/min) or severe ( $\text{CrCl} \geq 15$  to  $\leq 30$   
303 mL/min) renal impairment and in patients with end-stage renal disease (ESRD – defined as  $\text{CrCl} < 15$  mL/min),  
304 including patients on hemodialysis (HD) [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

305 **10. Overdosage**

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

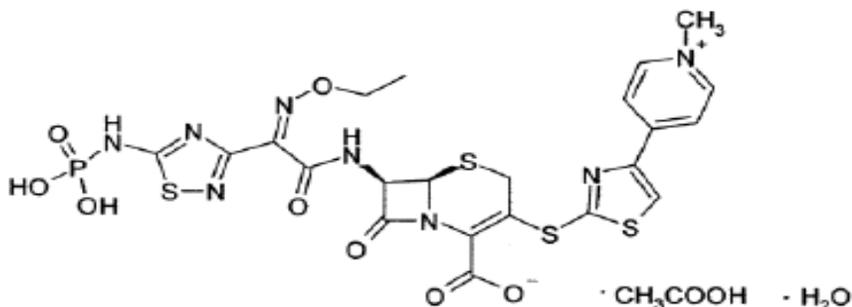
307 Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total  
308 recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5  
309 mg (21.6% of the dose). However, no information is available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

311 **11. Description**

312 Teflaro is a sterile, semi-synthetic, broad-spectrum, prodrug antibacterial of cephalosporin class of beta-lactams ( $\beta$ -  
313 lactams). Chemically, the prodrug, ceftaroline fosamil monoacetate monohydrate is (6R,7R)-7-[(2Z)-2-(ethoxyimino)-  
314 2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-

315 yl)sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monoacetate monohydrate. Its molecular weight  
316 is 762.75. The empirical formula is  $C_{22}H_{21}N_8O_8PS_4 \cdot C_2H_4O_2 \cdot H_2O$ .

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



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

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

## 333 12. Clinical Pharmacology

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

### 335 12.1 Mechanism of Action

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

### 337 12.2 Pharmacodynamics

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

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

### 344 Cardiac Electrophysiology

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

### 349 12.3 Pharmacokinetics

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

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354

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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	Multiple 600 mg Doses Administered Every 12 Hours as 1- Hour Infusions for 14 Days
	(n=6)	

(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

356

357 The C<sub>max</sub> and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to  
358 1000 mg. No appreciable accumulation of ceftaroline is observed following multiple IV infusions of 600 mg  
359 administered every 12 hours for up to 14 days in healthy adults with normal renal function.

### 360 **Distribution**

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

### 365 **Metabolism**

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

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

### 373 **Excretion**

374 Ceftaroline and its metabolites are primarily eliminated by the kidneys. Following administration of a single 600 mg IV  
375 dose of radiolabeled ceftaroline fosamil to healthy male adults (n=6), approximately 88% of radioactivity was  
376 recovered in urine and 6% in feces within 48 hours. Of the radioactivity recovered in urine approximately 64% was  
377 excreted as ceftaroline and approximately 2% as ceftaroline M-1. The mean (SD) renal clearance of ceftaroline was  
378 5.56 (0.20) L/h, suggesting that ceftaroline is predominantly eliminated by glomerular filtration.

### 379 **Specific Populations**

#### 380 **Renal Impairment**

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

388 A single 400 mg dose of Teflaro was administered to subjects with ESRD (n=6) either 4 hours prior to or 1 hour after  
389 hemodialysis (HD). The geometric mean ceftaroline AUC<sub>0-∞</sub> following the post-HD infusion was 167% higher  
390 compared to healthy subjects with normal renal function (CrCl > 80 mL/min, n=6). The mean recovery of ceftaroline in

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391 the dialysate following a 4-hour HD session was 76.5 mg, or 21.6% of the administered dose. Dosage adjustment is  
392 recommended in patients with ESRD (defined as CrCL < 15 mL/min), including patients on HD [see Dosage and  
393 Administration (2.2)].

#### 394 **Hepatic Impairment**

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

#### 398 **Geriatric Patients**

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

#### 403 **Pediatric Patients**

404 The pharmacokinetics of ceftaroline were evaluated in adolescent patients (ages 12 to 17, n=7) with normal renal  
405 function following administration of a single 8 mg/kg IV dose of Teflaro (or 600 mg for subjects weighing > 75 kg).  
406 The mean plasma clearance and terminal phase volume of distribution for ceftaroline in adolescent subjects were  
407 similar to healthy adults (n=6) in a separate study following administration of a single 600 mg IV dose. However, the  
408 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%  
409 less than in healthy adult subjects who received a single 600 mg IV dose.

#### 410 **Gender**

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

#### 416 **Race**

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

#### 422 **Drug Interactions**

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

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

### 433 **12.4 Microbiology**

#### 434 **Mode of Action**

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

439

#### 440 **Mechanisms of Resistance**

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

444 **Cross-Resistance**

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

446 **Interaction with Other Antimicrobials**

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

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

452 **Skin Infections**

453 Gram-positive bacteria  
454 *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)  
455 *Streptococcus pyogenes*  
456 *Streptococcus agalactiae*  
457

458 Gram-negative bacteria  
459 *Escherichia coli*  
460 *Klebsiella pneumoniae*  
461 *Klebsiella oxytoca*  
462

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

464 Gram-positive bacteria  
465 *Streptococcus pneumoniae*  
466 *Staphylococcus aureus* (methicillin-susceptible isolates only)  
467  
468 Gram-negative bacteria  
469 *Haemophilus influenzae*  
470 *Klebsiella pneumoniae*  
471 *Klebsiella oxytoca*  
472 *Escherichia coli*  
473

474 The following in vitro data are available, but their clinical significance is unknown. Ceftaroline exhibits in vitro MICs  
475 of 1 mcg/mL or less against most ( $\geq 90\%$ ) isolates of the following bacteria; however, the safety and effectiveness of  
476 Teflaro in treating clinical infections due to these bacteria have not been established in adequate and well-controlled  
477 clinical trials.  
478

479 Gram-positive bacteria  
480 *Streptococcus dysgalactiae*  
481

482 Gram-negative bacteria  
483 *Citrobacter koseri*  
484 *Citrobacter freundii*  
485 *Enterobacter cloacae*  
486 *Enterobacter aerogenes*  
487 *Moraxella catarrhalis*  
488 *Morganella morganii*  
489 *Proteus mirabilis*  
490 *Haemophilus parainfluenzae*  
491

492 **Susceptibility Test Methods**

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

497 **Dilution Techniques**

498 Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs  
499 provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a  
500 standardized test method<sup>1,3</sup>, (broth, and/or agar). Broth dilution MICs need to be read within 18 hours due to  
501 degradation of ceftaroline activity by 24 hours. The MIC values should be interpreted according to the criteria in Table  
502 6.

503 **Diffusion Techniques**

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

509

**Table 6: Susceptibility Interpretive Criteria for Ceftaroline**

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	≤1 <sup>a</sup>	—	—	≥24	—	—
<i>Streptococcus agalactiae</i> <sup>a</sup> (skin isolates only)	≤0.03	—	—	≥26	—	—
<i>Streptococcus pyogenes</i> <sup>a</sup> (skin isolates only)	≤0.015	—	—	≥24	—	—
<i>Streptococcus pneumoniae</i> <sup>a</sup> (CABP isolates only)	≤ 0.25	—	—	≥27	—	—
<i>Haemophilus influenzae</i> (CABP isolates only)	≤0.12	—	—	≥33	—	—
<i>Enterobacteriaceae</i> <sup>b</sup> (CABP and skin isolates)	≤ 0.5	1	≥2	≥23	20-22	≤19

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

511 **NOTE:** Clinical efficacy of Teflaro to treat lower respiratory infections such as community-acquired bacterial  
512 pneumonia due to MRSA has not been studied in adequate and well controlled trials (See “Clinical Trials” section  
513 14)

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

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

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

526

527 **Quality Control**

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

532 **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 22913	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

533 ATCC = American Type Culture Collection

534 **13. Nonclinical Toxicology**

535 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

545 **14. Clinical Trials**

546 **14.1 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)**

547 A total of 1396 adults with clinically documented complicated skin and skin structure infection were enrolled in two  
548 identical randomized, multi-center, multinational, double-blind, noninferiority trials (Trials 1 and 2) comparing Teflaro  
549 (600 mg administered IV over 1 hour every 12 hours) to vancomycin plus aztreonam (1 g vancomycin administered IV  
550 over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours). Treatment duration was 5 to 14  
551 days. A switch to oral therapy was not allowed. The Modified Intent-to-Treat (MITT) population included all patients  
552 who received any amount of study drug according to their randomized treatment group. The CE population included  
553 patients in the MITT population who demonstrated sufficient adherence to the protocol.

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

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

- 559 • Major abscess with  $\geq 5$  cm of surrounding erythema
- 560 • Wound infection
- 561 • Deep/extensive cellulitis

562  
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The results of this analysis are shown in Table 8.

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

	<b>Teflaro</b>	<b>Vancomycin/ Aztreonam</b>	<b>Treatment Difference</b>
	<b>n/N (%)</b>	<b>n/N (%)</b>	<b>(2-sided 95% CI)</b>
<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>	<b>Vancomycin/ Aztreonam</b>	<b>Treatment Difference</b>
	<b>n/N (%)</b>	<b>n/N (%)</b>	<b>(2-sided 95% CI)</b>
<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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576

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

	<b>Teflaro</b>	<b>Vancomycin/Aztreonam</b>
	<b>n/N (%)</b>	<b>n/N (%)</b>
<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, noninferiority 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.

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

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

	<b>Teflaro n/N (%)</b>	<b>Ceftriaxone n/N (%)</b>	<b>Treatment Difference (2-sided 95% CI)</b>
<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)

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

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

	<b>Teflaro n/N (%)</b>	<b>Ceftriaxone n/N (%)</b>	<b>Treatment Difference (2-sided 95% CI)</b>
<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)

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

	<b>Teflaro n/N (%)</b>	<b>Ceftriaxone n/N (%)</b>
<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%)

610 **15. References**

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

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

- 624 • 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10)
- 625 • 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10)

626 Teflaro vials should be stored refrigerated at 2 to 8° C (36 to 46° F).

627 **17. Patient Counseling Information**

- 628 • Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious  
629 reactions require immediate treatment. They should inform their healthcare provider about any previous  
630 hypersensitivity reactions to Teflaro, other beta-lactams (including cephalosporins) or other allergens.
- 631 • Patients should be counseled that antibacterial drugs including Teflaro should be used to treat only bacterial  
632 infections. They do not treat viral infections (e.g., the common cold). When Teflaro is prescribed to treat a  
633 bacterial infection, patients should be told that although it is common to feel better early in the course of therapy,  
634 the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy  
635 may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will  
636 develop resistance and will not be treatable by Teflaro or other antibacterial drugs in the future.
- 637 • Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves  
638 when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a  
639 more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their  
640 healthcare provider.
- 641 • Keep out of reach of children

642 Teflaro (ceftaroline fosamil) for injection

643 **Distributed by:**

644 Forest Pharmaceuticals, Inc.

645 Subsidiary of Forest Laboratories, Inc.

646 St. Louis, MO 63045, USA

647 **Manufactured by:**

648 Facta Farmaceutici S.p.A.

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