

1 HIGHLIGHTS OF PRESCRIBING INFORMATION

2 These highlights do not include all the information needed to use TEFLARO
3 safely 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
7 effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used only
8 to treat infections that are proven or strongly suspected to be caused by bacteria.

9 -----RECENT MAJOR CHANGES-----

10 Dosage and Administration, Preparation of Solutions (2.3) 12/2011

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

12 Teflaro® is a cephalosporin antibacterial indicated for the treatment of the
13 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 adults ≥ 18**
18 years of age (2.1)
- 19 • Dosage adjustment in patients with renal impairment (2.2)**

Estimated Creatinine Clearance# (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

21 #As calculated using the Cockcroft-Gault formula

22 -----DOSAGE FORMS AND STRENGTHS-----

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

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

- 25 • Known serious hypersensitivity to ceftaroline or other members of**
26 the 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 beta-
31 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 performed
38 and consideration given to discontinuation of Teflaro. (5.3)

39 -----ADVERSE REACTIONS-----

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

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

45 -----USE IN SPECIFIC POPULATIONS-----

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

51 See 17 for PATIENT COUNSELING INFORMATION

Revised: December 2011

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

110 **FULL PRESCRIBING INFORMATION**

111 **1. INDICATIONS AND USAGE**

112 Teflaro® (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated
113 microorganisms.

114 **1.1 Acute Bacterial Skin and Skin Structure Infections**

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

118 **1.2 Community-Acquired Bacterial Pneumonia**

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

122 **1.3 Usage**

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

128 **2. DOSAGE AND ADMINISTRATION**

129 **2.1 Recommended Dosage**

130 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
131 duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

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

133 **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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135 **2.2 Patients with Renal Impairment**

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

Estimated CrCl ^a (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 ^b	200 mg IV (over 1 hour) every 12 hours ^c

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

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

^c Teflaro is hemodialyzable; thus Teflaro should be administered after hemodialysis on hemodialysis days.

140 **2.3 Preparation of Solutions**

141 Aseptic technique must be followed in preparing the infusion solution. The contents of Teflaro vial should be constituted with 20 mL Sterile Water for
142 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 Ceftaroline fosamil Concentration (mg/mL)	Amount to Be Withdrawn
400	20	20	Total Volume
600	20	30	Total Volume

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The constituted solution must be further diluted in range between 50 mL to 250 mL before infusion into ~~the~~ patients. 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.

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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.

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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.

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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).

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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.

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Only for the 50 mL infusion bags dilution, see the instructions listed in 2.3.1 and 2.3.2.

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2.3.1 Preparation of 600 mg of Teflaro dose in 50 mL

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Withdraw 20 mL of diluent from the infusion bag. Proceed to inject entire content of the Teflaro vial into the bag to provide a total volume of 50 mL. The resultant concentration is approximately 12 mg/mL.

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2.3.2 Preparation of 400 mg of Teflaro dose in 50 mL

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Withdraw 20 mL of diluent from the infusion bag. Proceed to inject entire content of the Teflaro vial into the bag to provide a total volume of 50 mL. The resultant concentration is approximately 8 mg/mL.

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3. DOSAGE FORMS AND STRENGTHS

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

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4. CONTRAINDICATIONS

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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.

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5. WARNINGS AND PRECAUTIONS

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5.1 Hypersensitivity Reactions

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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.

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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.

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5.2 *Clostridium difficile*-associated Diarrhea

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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.

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

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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.

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

195 **5.3 Direct Coombs' Test Seroconversion**

196 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
197 patients receiving comparator drugs in the four pooled Phase 3 trials.

198 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
199 from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group.

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

203 **5.4 Development of Drug-Resistant Bacteria**

204 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
205 of the development of drug-resistant bacteria.

206 **6. ADVERSE REACTIONS**

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

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

211 **6.1 Adverse Reactions from Clinical Trials**

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

214 Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CABP) which included 1300 adult patients treated
215 with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone)
216 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
217 with Teflaro were predominantly male (63%) and Caucasian (82%).

218 **6.2 Serious Adverse Events and Adverse Events Leading to Discontinuation**

219 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
220 receiving comparator drugs. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system
221 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
222 patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a
223 rate of 0.3% in the Teflaro group and 0.5% in comparator group.

224 **6.3 Most Common Adverse Reactions**

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

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

228 **Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Pooled 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 ^a (N=1297)
Gastrointestinal disorders		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
Investigations		
Increased transaminases	2%	3 %
Metabolism and nutrition disorders		

Hypokalemia	2 %	3 %
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

^a 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.

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231 **6.4 Other Adverse Reactions Observed During Clinical Trials of Teflaro**

232 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%.
233 Events are categorized by System Organ Class.

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

235 **Cardiac disorders** - Bradycardia, Palpitations

236 **Gastrointestinal disorders** - Abdominal pain

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

238 **Hepatobiliary disorders** - Hepatitis

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

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

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

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

243 **Renal and urinary disorders** - Renal failure

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

245 **7. DRUG INTERACTIONS**

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

249 **8. USE IN SPECIFIC POPULATIONS**

250 **8.1 Pregnancy**

251 **Teratogenic Effects: Category B.**

252 Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects
253 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
254 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
255 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-
256 spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at ≥ 50
257 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
258 morbidity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic
259 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
260 exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg.

261 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.
262 Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was ≥ 8 times the exposure in humans
263 given 600 mg every 12 hours.

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

266 **8.3 Nursing Mothers**

267 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
268 is administered to a nursing woman.

269 **8.4 Pediatric Use**

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

271 **8.5 Geriatric Use**

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

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

277 Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly
278 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
279 function. Elderly subjects had greater cefataroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However,
280 higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based
281 on renal function [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

282 8.6 Patients with Renal Impairment

283 Dosage adjustment is required in patients with moderate ($\text{CrCl} > 30$ to ≤ 50 mL/min) or severe ($\text{CrCl} \geq 15$ to ≤ 30 mL/min) renal impairment and in
284 patients with end-stage renal disease (ESRD – defined as $\text{CrCl} < 15$ mL/min), including patients on hemodialysis (HD) [see *Dosage and Administration*
285 (2.2) and *Clinical Pharmacology* (12.3)].

286 10. OVERDOSAGE

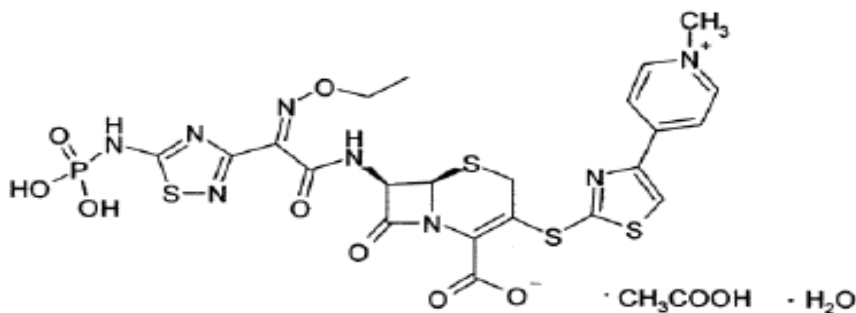
287 In the event of overdose, Teflaro should be discontinued and general supportive treatment given.

288 Cefataroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of cefataroline in the
289 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
290 the use of hemodialysis to treat overdosage [see *Clinical Pharmacology* (12.3)].

291 11. DESCRIPTION

292 Teflaro is a sterile, semi-synthetic, broad-spectrum, prodrug antibacterial of cephalosporin class of beta-lactams (β -lactams). Chemically, the prodrug,
293 cefataroline fosamil monoacetate monohydrate is (6R,7R)-7-[(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[[4-(1-
294 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
295 weight is 762.75. The empirical formula is $\text{C}_{22}\text{H}_{21}\text{N}_8\text{O}_8\text{PS}_4 \cdot \text{C}_2\text{H}_4\text{O}_2 \cdot \text{H}_2\text{O}$.

296 **Figure 1: Chemical structure of cefataroline fosamil**



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

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

311 12. CLINICAL PHARMACOLOGY

312 Cefataroline fosamil is the water-soluble prodrug of the bioactive cefataroline [see *Clinical Pharmacology* (12.3)].

313 12.1 Mechanism of Action

314 Cefataroline is an antibacterial drug [see *Clinical Pharmacology* (12.4)].

315 12.2 Pharmacodynamics

316 As with other beta-lactam antimicrobial agents, the time that unbound plasma concentration of cefataroline exceeds the minimum inhibitory concentration
317 (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.*
318 *pneumoniae*.

319 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
320 1 hour. For Phase 3 CABP trials, an exposure-response relationship could not be identified due to the limited range of cefataroline exposures in the
321 majority of patients.

322 Cardiac Electrophysiology

323 In a randomized, positive- and placebo-controlled crossover thorough QTc study, 54 healthy subjects were each administered a single dose of Teflaro
324 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
325 peak plasma concentration or at any other time.

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327 **12.3 Pharmacokinetics**

328 The mean pharmacokinetic parameters of ceftaroline in healthy adults (n=6) with normal renal function after single and multiple 1-hour IV infusions of
329 600 mg ceftaroline fosamil administered every 12 hours are summarized in Table 5. Pharmacokinetic parameters were similar for single and multiple dose
330 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)
C_{max} (mcg/mL)	19.0 (0.71)	21.3 (4.10)
T_{max} (h)^a	1.00 (0.92-1.25)	0.92 (0.92-1.08)
AUC (mcg•h/mL)^b	56.8 (9.31)	56.3 (8.90)
T_{1/2} (h)	1.60 (0.38)	2.66 (0.40)
CL (L/h)	9.58 (1.85)	9.60 (1.40)
^a Reported as median (range) ^b AUC _{0-∞} , for single-dose administration; AUC _{0-tau} , for multiple-dose administration; C _{max} , maximum observed concentration; T _{max} , time of C _{max} ; AUC _{0-∞} , area under concentration-time curve from time 0 to infinity; AUC _{0-tau} , area under concentration-time curve over dosing interval (0-12 hours); T _{1/2} , terminal elimination half-life; CL, plasma clearance		

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335 The C_{max} and AUC of ceftaroline increase approximately in proportion to dose within the single dose range of 50 to 1000 mg. No appreciable
336 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
337 normal renal function.

338 **Distribution**

339 The average binding of ceftaroline to human plasma proteins is approximately 20% and decreases slightly with increasing concentrations over 1-50
340 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
341 dose of radiolabeled ceftaroline fosamil was 20.3 L (18.3-21.6 L), similar to extracellular fluid volume.

342 **Metabolism**

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

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

349 **Excretion**

350 Ceftaroline and its metabolites are primarily eliminated by the kidneys. Following administration of a single 600 mg IV dose of radiolabeled ceftaroline
351 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
352 recovered in urine approximately 64% was excreted as ceftaroline and approximately 2% as ceftaroline M-1. The mean (SD) renal clearance of ceftaroline
353 was 5.56 (0.20) L/h, suggesting that ceftaroline is predominantly eliminated by glomerular filtration.

354 **Specific Populations**

355 **Renal Impairment**

356 Following administration of a single 600 mg IV dose of Teflaro, the geometric mean AUC_{0-∞} of ceftaroline in subjects with mild (CrCl > 50 to ≤ 80
357 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
358 normal renal function (CrCl > 80 mL/min, n=6). Following administration of a single 400 mg IV dose of Teflaro, the geometric mean AUC_{0-∞} of
359 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
360 function (CrCl > 80 mL/min, n=6). Dosage adjustment is recommended in patients with moderate and severe renal impairment [see *Dosage and*
361 *Administration (2.2)*].

362 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
363 mean ceftaroline AUC_{0-∞} following the post-HD infusion was 167% higher compared to healthy subjects with normal renal function (CrCl > 80 mL/min,
364 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
365 adjustment is recommended in patients with ESRD (defined as CrCl < 15 mL/min), including patients on HD [see *Dosage and Administration (2.2)*].

366

367

368 **Hepatic Impairment**

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

371 **Geriatric Patients**

372 Following administration of a single 600 mg IV dose of Teflaro to healthy elderly subjects (≥ 65 years of age, n=16), the geometric mean $AUC_{0-\infty}$ of
373 ceftaroline was ~33% higher compared to healthy young adult subjects (18-45 years of age, n=16). The difference in $AUC_{0-\infty}$ was mainly attributable to
374 age-related changes in renal function. Dosage adjustment for Teflaro in elderly patients should be based on renal function [see *Dosage and Administration*
375 (2.2)].

376 **Pediatric Patients**

377 The pharmacokinetics of ceftaroline were evaluated in adolescent patients (ages 12 to 17, n=7) with normal renal function following administration of a
378 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
379 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,
380 the mean C_{max} and $AUC_{0-\infty}$ for ceftaroline in adolescent subjects who received a single 8 mg/kg dose were 10% and 23% less than in healthy adult subjects
381 who received a single 600 mg IV dose.

382 **Gender**

383 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)
384 and females (n=10), the mean C_{max} and $AUC_{0-\infty}$ for ceftaroline were similar between males and females, although there was a trend for higher C_{max} (17%)
385 and $AUC_{0-\infty}$ (6-15%) in female subjects. Population pharmacokinetic analysis did not identify any significant differences in ceftaroline AUC_{0-tau} based on
386 gender in Phase 2/3 patients with ABSSSI or CABP. No dose adjustment is recommended based on gender.

387 **Race**

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

392 **Drug Interactions**

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

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

400 **12.4 Microbiology**

401 **Mode of Action**

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

405 **Mechanisms of Resistance**

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

408 **Cross-Resistance**

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

410 **Interaction with Other Antimicrobials**

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

413 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)*].

414 **Skin Infections**

415 Gram-positive bacteria
416 *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates)
417 *Streptococcus pyogenes*
418 *Streptococcus agalactiae*

419 Gram-negative bacteria
420 *Escherichia coli*
421 *Klebsiella pneumoniae*
422 *Klebsiella oxytoca*

425
426 **Community-Acquired Bacterial Pneumonia (CABP)**
427

428 Gram-positive bacteria
429 *Streptococcus pneumoniae*
430 *Staphylococcus aureus* (methicillin-susceptible isolates only)
431

432 Gram-negative bacteria
433 *Haemophilus influenzae*
434 *Klebsiella pneumoniae*
435 *Klebsiella oxytoca*
436 *Escherichia coli*

437 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
438 ($\geq 90\%$) isolates of the following bacteria; however, the safety and effectiveness of Teflaro in treating clinical infections due to these bacteria have not
439 been established in adequate and well-controlled clinical trials.

440 Gram-positive bacteria
441 *Streptococcus dysgalactiae*
442

443 Gram-negative bacteria
444 *Citrobacter koseri*
445 *Citrobacter freundii*
446 *Enterobacter cloacae*
447 *Enterobacter aerogenes*
448 *Moraxella catarrhalis*
449 *Morganella morganii*
450 *Proteus mirabilis*
451 *Haemophilus parainfluenzae*
452

453 **Susceptibility Test Methods**

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

457 **Dilution Techniques**

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

462 **Diffusion Techniques**

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

467 **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	$\leq 1^a$	—	—	≥ 24	—	—
<i>Streptococcus agalactiae</i> ^a (skin isolates only)	≤ 0.03	—	—	≥ 26	—	—
<i>Streptococcus pyogenes</i> ^a (skin isolates only)	≤ 0.015	—	—	≥ 24	—	—
<i>Streptococcus pneumoniae</i> ^a (CABP isolates only)	≤ 0.25	—	—	≥ 27	—	—

<i>Haemophilus influenzae</i> (CABP isolates only)	≤ 0.12	—	—	≥ 33	—	—
<i>Enterobacteriaceae</i> ^b (CABP and skin isolates)	≤ 0.5	1	≥ 2	≥ 23	20-22	≤ 19

S = susceptible, I = intermediate, R = resistant

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

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

^b Clinical efficacy was shown for the following *Enterobacteriaceae*: *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

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

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.^{1,2,3} Standard ceftaroline powder should provide the following range 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.

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

ATCC = American Type Culture Collection

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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 than the maximum recommended human dose based on body surface area.

14. CLINICAL TRIALS

14.1 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

A total of 1396 adults with clinically documented complicated skin and skin structure infection were enrolled in two identical 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) to vancomycin plus aztreonam (1 g vancomycin administered IV over 1 hour followed by 1 g aztreonam administered IV over 1 hour every 12 hours). Treatment 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

502 any amount of study drug according to their randomized treatment group. The CE population included patients in the MITT population who demonstrated
503 sufficient adherence to the protocol.

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

507 Patients with lesion size ≥ 75 cm² and having one of the following infection types:

- 508 • Major abscess with ≥ 5 cm of surrounding erythema
- 509 • Wound infection
- 510 • Deep/extensive cellulitis

511 The results of this analysis are shown in Table 8.
512
513

514
515 **Table 8: Clinical Responders at Study Day 3 from Two Phase 3 ABSSSI Trials**

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

516 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 co-primary CE
517 and MITT populations (Table 9) and clinical cure rates at TOC by pathogen in the Microbiologically Evaluable (ME) population (Table 10). However,
518 there are insufficient historical data to establish the magnitude of drug effect for antibacterial drugs compared with placebo at a TOC time point.
519 Therefore, comparisons of Teflaro to vancomycin plus aztreonam based on clinical response rates at TOC can not be utilized to establish non-inferiority.
520

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

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

522
523
524 **Table 10: Clinical Cure Rates at TOC by Pathogen from Two Integrated Phase 3 ABSSSI Trials**

	Teflaro n/N (%)	Vancomycin/Aztreonam n/N (%)
Gram-positive:		
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%)
Gram-negative:		
<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%)

525
526 **14.2 Community-Acquired Bacterial Pneumonia (CABP)**

527 A total of 1231 adults with a diagnosis of CABP were enrolled in two randomized, multi-center, multinational, double-blind, non-inferiority trials (Trials
528 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
529 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
530 therapy starting on Study Day 1. No adjunctive macrolide therapy was used in CABP Trial 2. Patients with known or suspected MRSA were excluded
531 from both trials. Patients with new or progressive pulmonary infiltrate(s) on chest radiography and signs and symptoms consistent with CABP with the
532 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
533 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
534 vs. 12/610 (2.0%) for the ceftriaxone group, and the difference in mortality rates was not statistically significant.

535 To evaluate the treatment effect of ceftaroline, an analysis was conducted in CABP patients for whom the treatment effect of antibacterials may be
536 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
537 (a) be in stable condition according to consensus treatment guidelines of the Infectious Diseases Society of America and American Thoracic Society,
538 based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status;⁴ (b) show improvement from baseline on at least
539 one symptom of cough, dyspnea, pleuritic chest pain, or sputum production, while not worsening on any of these four symptoms. The analysis used a
540 microbiological intent-to-treat population (mITT population) containing only subjects with a confirmed bacterial pathogen at baseline. Results for this
541 analysis are presented in Table 11.

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

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

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

550 **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)
CABP Trial 1			
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)
CABP Trial 2			
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)

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

	Teflaro n/N (%)	Ceftriaxone n/N (%)
Gram-positive:		
<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%)
Gram-negative:		
<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%)

552 **15. REFERENCES**

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564 **16. HOW SUPPLIED/STORAGE AND HANDLING**

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

- 566 • 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10)
- 567 • 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10)

568 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
569 25°C (77°F) for no more than 7 days.
570

571 **17. PATIENT COUNSELING INFORMATION**

572 • Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate
573 treatment. They should inform their healthcare provider about any previous hypersensitivity reactions to Teflaro, other beta-lactams (including
574 cephalosporins) or other allergens.

575 • Patients should be counseled that antibacterial drugs including Teflaro should be used to treat only bacterial infections. They do not treat viral
576 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
577 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
578 therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will
579 not be treatable by Teflaro or other antibacterial drugs in the future.

580 • Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued.
581 Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody
582 diarrhea develops, patients should contact their healthcare provider.

- 583 • Keep out of reach of children

584 Teflaro® (ceftaroline fosamil) for injection

585 **Distributed by:**

586 Forest Pharmaceuticals, Inc.
587 Subsidiary of Forest Laboratories, Inc.
588 St. Louis, MO 63045, USA
589

590 **Manufactured by:**

591 Facta Farmaceutici S.p.A.
592 Nucleo Industriale S. Atto-S. Nicolò a Tordino
593 64020 Teramo, Italy
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