CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2011

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

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

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

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

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

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

[#] As calculated using the Cockcroft-Gault formula

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

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

----------**CONTRAINDICATIONS**----------

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

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

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. Indications and Usage

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

1.1 Acute Bacterial Skin and Skin Structure Infections

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

1.2 Community-Acquired Bacterial Pneumonia

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

1.3 Usage

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

2. Dosage and Administration

2.1 Recommended Dosage

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

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

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

2.2 Patients with Renal Impairment

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.

2.3 Preparation of Solutions

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

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

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

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

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

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

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

3. Dosage Forms and Strengths

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

4. Contraindications

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

5. Warnings and Precautions

5.1 Hypersensitivity Reactions

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

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

5.2 *Clostridium difficile*-associated Diarrhea

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

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

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

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

5.3 Direct Coombs Test Seroconversion

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

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

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

5.4 Development of Drug-Resistant Bacteria

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 of the development of drug-resistant bacteria.

6. Adverse Reactions

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

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

6.1 Adverse Reactions from Clinical Trials

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

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

6.2 Serious Adverse Events and Adverse Events Leading to Discontinuation

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

6.3 Most Common Adverse Reactions

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

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

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

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators[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.

6.4 Other Adverse Reactions Observed During Clinical Trials of Teflaro

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%. Events are categorized by System Organ Class.

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

Cardiac disorders - Bradycardia, Palpitations

Gastrointestinal disorders - Abdominal pain

General disorders and administration site conditions - Pyrexia

Hepatobiliary disorders - Hepatitis

Immune system disorders - Hypersensitivity, Anaphylaxis

Infections and infestations - *Clostridium difficile* colitis

Metabolism and nutrition disorders - Hyperglycemia, Hyperkalemia

Nervous system disorders - Dizziness, Convulsion

Renal and urinary disorders - Renal failure

Skin and subcutaneous tissue disorders - Urticaria

7. Drug Interactions

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

8. Use in Specific Populations

8.1 Pregnancy

Category B

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

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

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

8.3 Nursing Mothers

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 is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

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

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

8.6 Patients with Renal Impairment

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

10. Overdosage

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

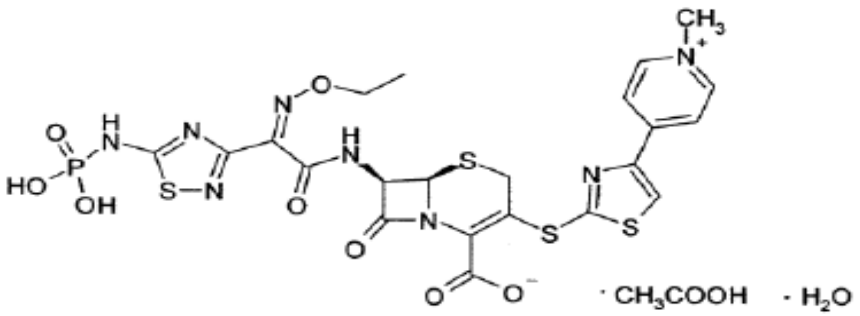
Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use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

11. Description

Teflaro is a sterile, semi-synthetic, broad-spectrum, prodrug antibacterial of cephalosporin class of beta-lactams (β-lactams). Chemically, the prodrug, ceftaroline fosamil monoacetate monohydrate is (6*R*,7*R*)-7-{(2*Z*)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-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 weight is 762.75. The empirical formula is $C_{22}H_{21}N_8O_8PS_4.C_2H_4O_2.H_2O$.

Figure 1: Chemical structure of ceftaroline fosamil



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

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

12. Clinical Pharmacology

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

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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] $AUC_{0-\infty}$ for single-dose administration, AUC_{0-tau} for multiple-dose administration, C_{max}, maximum observed concentration; T_{max}, time of C_{max}; $AUC_{0-\infty}$, 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

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 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 normal renal function.

Distribution

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

Metabolism

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

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

Excretion

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

Specific Populations

Renal Impairment

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

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 mean ceftaroline AUC0-∞ following the post-HD infusion was 167% higher compared to healthy subjects with normal renal function (CrCl > 80 mL/min, 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 adjustment is recommended in patients with ESRD (defined as CrCL < 15 mL/min), including patients on HD [see Dosage and Administration (2.2)].

Hepatic Impairment

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

Geriatric Patients

Following administration of a single 600 mg IV dose of Teflaro to healthy elderly subjects (≥ 65 years of age, n=16), the geometric mean AUC0-∞ of ceftaroline was ~33% higher compared to healthy young adult subjects (18-45 years of age, n=16). The difference in AUC0-∞ was mainly attributable to age-related changes in renal function. Dosage adjustment for Teflaro in elderly patients should be based on renal function [see Dosage and Administration (2.2)].

Pediatric Patients

The pharmacokinetics of ceftaroline were evaluated in adolescent patients (ages 12 to 17, n=7) with normal renal function following administration of a 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 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, 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 who received a single 600 mg IV dose.

Gender

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) 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%) 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 gender in Phase 2/3 patients with ABSSSI or CABP. No dose adjustment is recommended based on gender.

Race

A population pharmacokinetic analysis was performed to evaluate the impact of race on the pharmacokinetics of ceftaroline using data from Phase 2/3 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 groups for ABSSSI patients. Patients enrolled in CABP trials were predominantly categorized as White (n=115); thus there were too few patients of other races to draw any conclusions. No dosage adjustment is recommended based on race.

Drug Interactions

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

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

12.4 Microbiology

Mode of Action

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

Mechanisms of Resistance

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

Cross-Resistance

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

Interaction with Other Antimicrobials

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

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)]*.

Skin Infections

Gram-positive bacteria
Staphylococcus aureus (including methicillin-susceptible and -resistant isolates)
Streptococcus pyogenes
Streptococcus agalactiae

Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca

Community-Acquired Bacterial Pneumonia (CABP)

Gram-positive bacteria
Streptococcus pneumoniae
Staphylococcus aureus (methicillin-susceptible isolates only)

Gram-negative bacteria
Haemophilus influenzae
Klebsiella pneumoniae
Klebsiella oxytoca
Escherichia coli

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

Gram-positive bacteria
Streptococcus dysgalactiae

Gram-negative bacteria
Citrobacter koseri
Citrobacter freundii
Enterobacter cloacae
Enterobacter aerogenes
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Haemophilus parainfluenzae

Susceptibility Test Methods

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

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,3], (broth, and/or agar). Broth dilution MICs 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 Table 6.

Diffusion Techniques

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

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
Staphylococcus aureus (includes methicillin-resistant isolates - skin isolates only) - See **NOTE** below	≤1[a]	—	—	≥24	—	—
Streptococcus agalactiae [a] (*skin isolates only)*	≤0.03	—	—	≥26	—	—
Streptococcus pyogenes [a] (skin isolates only)	≤0.015	—	—	≥24	—	—
Streptococcus pneumoniae [a] (CABP isolates only)	≤ 0.25	—	—	≥27	—	—
Haemophilus influenzae (CABP isolates only)	≤0.12	—	—	≥33	—	—
Enterobacteriaceae [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)
Staphylococcus aureus ATCC 25923	Not Applicable	26 - 35
Staphylococcus aureus ATCC 22913	0.12 - 0.5	Not Applicable
Escherichia coli ATCC 25922	0.03 - 0.12	26 - 34
Haemophilus influenzae ATCC 49247	0.03 - 0.12	29 - 39
Streptococcus pneumoniae 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, noninferiority 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 any amount of study drug according to their randomized treatment group. The CE population included patients in the MITT population who demonstrated sufficient adherence to the protocol.

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

Patients with lesion size ≥ 75 cm^2 and having one of the following infection types:

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

The results of this analysis are shown in Table 8.

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)

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.

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)

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%)
Streptococcus pyogenes	56/56 (100%)	56/58 (96.6%)
Streptococcus agalactiae	21/22 (95.5%)	18/18 (100%)
Gram-negative:		
Escherichia coli	20/21 (95.2%)	19/21 (90.5%)
Klebsiella pneumoniae	17/18 (94.4%)	13/14 (92.9%)
Klebsiella oxytoca	10/12 (83.3%)	6/6 (100%)

14.2 Community-Acquired Bacterial Pneumonia (CABP)

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.

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

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)

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

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)

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

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

15. References

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - 8th ed. Approved Standard, CLSI document M07-A8, CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898. January 2009.

2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests 10th ed. Approved Standard, CLSI document M02-A10, CLSI, January 2009.

3. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing 20th Informational Supplement, CLSI document M100-S20, CLSI, January 2010.

4. Mandell, L.A., Wunderink, R.G., Anzueto, A., Bartlett, J.G., Campbell, G.D., Dean, N.C., Dowell, S.F., File, T.M., Musher, D.M., Niederman, M.S., Torres, A., Whitney, C.G. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Disease. 2007; 44:S27-72.

16. How Supplied/Storage and Handling

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

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

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

17. Patient Counseling Information

- Patients should be advised that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. They should inform their healthcare provider about any previous hypersensitivity reactions to Teflaro, other beta-lactams (including cephalosporins) or other allergens.
- Patients should be counseled that antibacterial drugs including Teflaro should be used to treat only bacterial infections. They do not treat viral 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 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 therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Teflaro or other antibacterial drugs in the future.
- Patients should be advised that diarrhea is a common problem caused by antibacterial drugs and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider.
- Keep out of reach of children

Teflaro (ceftaroline fosamil) for injection

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