120x300mm

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Ceflaro
(Ceftaroline Fosamil)

Highnoon

COMPOSITION:
Ceflaro 400mg IV Injection:
Each vial contains Ceftaroline Fosamil Monoacetate Monohydrate Equivalent to Ceftaroline Fosamil 400mg (with L-Arginine).

Ceflaro 600mg IV Injection:
Each vial contains Ceftaroline Fosamil Monoacetate Monohydrate Equivalent to Ceftaroline Fosamil 600mg (with L-Arginine).

DESCRIPTION:
Ceflaro (Ceftaroline Fosamil) for injection, is a sterile, semi-synthetic, prodrug of the cephalosporin antibacterial class of beta-lactams (β-lactams) for intravenous use.

PHARMACOLOGY:
Ceflaro (Ceftaroline Fosamil) is a cephalosporin antibacterial drug.

Mechanism of action
Ceftaroline is a cephalosporin antibacterial drug 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.

PHARMACOKINETICS:
After infusion, Ceftaroline fosamil is rapidly converted in the plasma to Ceftaroline, the bio-active form of the drug. Mean peak plasma concentration of 19 mcg/ml have been reported after a single 600mg dose of Ceftaroline fosamil given intravenously over 1 hour. Ceftaroline is about 20 % bound to plasma proteins, and in healthy patients has a mean steady state volume of distribution of about 20.3 liters. Ceftaroline is metabolized in small amounts to the microbiologically inactive metabolite Ceftaroline M-1 via hydrolysis of the β-lactam ring. Ceftaroline and its metabolites are excreted mainly by the kidneys, with about 88% of a dose recovered in the urine within 48 hours (mainly as unchanged drug); a small amount of drug is excreted in feces. The elimination half-life of Ceftaroline is about 2.66 hours. Ceftaroline exposure and half-life are significantly increased in renal impairment.

MICROBIOLOGY:
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*.

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 metallobeta lactamases, or class C (AmpC cephalosporinases). 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).

Antimicrobial Activity
Ceftaroline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections

Skin Infection
Gram-positive Bacteria: Staphylococcus aureus (including methicillin-susceptible and-resistant isolates), *Streptococcus pyogenes and Streptococcus agalactiae.*
Gram-negative Bacteria: Escherichia coli, Klebsiella pneumoniae and Klebsiella oxytoca.

Community-Acquired Bacterial Pneumonia (CABP)
Gram-positive Bacteria: Streptococcus pneumoniae and Staphylococcus aureus (methicillin-susceptible isolates only).
Gram-negative Bacteria: Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella oxytoca and Escherichia coli.
The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ceftaroline against isolates of similar genus or organism group. However, the efficacy of ceftaroline in treating clinical infections due to these bacteria has 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 and *Haemophilus parainfluenzae.*

INDICATIONS AND USAGE:
- It is indicated in adult and pediatric patients (at least 34 weeks gestational age and 12 days postnatal age) 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.*
- It is indicated in adult and pediatric patients 2 months of age and older 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.*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ceftaroline and other antibacterial drugs, Ceftaroline should be used to treat or prevent infections 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 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.

DOSAGE AND ADMINISTRATION:
Recommended Dosage in Adult Patients
The recommended dosage of Ceflaro is 600mg administered every 12 hours by intravenous (IV) infusion over 5 to 60 minutes 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 as given below;

Indication	Dosage	Frequency	Infusion Time	Recommended Duration of Treatment
Acute Bacterial Skin and Skin Structure Infections (ABSSSI)	600 mg	Every 12 hours	5 to 60 minutes	5-14 days
Community Acquired Bacterial Pneumonia (CABP)	600 mg	Every 12 hours	5 to 60 minutes	5-7 days

Recommended Dosage in Pediatric Patients
The recommended dosage of Ceflaro in pediatric patients is based on the age and weight of the child. The duration of therapy should be guided by the severity, site of infection and the patients clinical and bacteriological progress.

- For pediatric patients 2 months of age and older, it is administered every 8 hours by intravenous infusion over 5 to 60 minutes.
- The dosing regimen is dependent on the type of infection (ABSSSI, CABP).

Indication	Age Range	Dosage & Frequency	Infusion Time	Recommended Duration of Treatment
Acute Bacterial Skin and Skin Structure Infections (ABSSSI) OR Community Acquired Bacterial Pneumonia (CABP)	2 months to <2 years	8mg/kg every 8 hours	5 to 60 minutes	5-14 days
	≥ 2 years to <18 years (≤ 33 kg)	12mg/kg every 8 hours		
	≥ 2 years to <18 years (> 33 kg)	400 mg every 8 hours Or 600 mg every 12 hours		

Pediatric Patients Less Than 2 Months of Age
- o It is administered every 8 hours by intravenous infusion over 30 to 60 minutes for patients less than 2 months of age.
- o The dosing regimen is only recommended for patients with ABSSSI.
- o Its concentrations in the cerebrospinal fluid have not been evaluated.

There is no information for dosing Ceftaroline in infants less than 34 weeks gestational age and less than 12 days postnatal age.

Indication	Age Range	Dosage & Frequency	Infusion Time	Recommended Duration of Treatment
Acute Bacterial Skin and Skin Structure infections (ABSSSI)	0* to <2 months	6mg/kg every 8 hours	30 to 60 minutes	5-14 days

*Gestational age 34 weeks and older and postnatal age 12 days and older.

Dosage Adjustments in Patients with Renal Impairment
Adults: No dosage adjustment is required in adult patients with CrCl > 50 mL/min. The dose in adult patients should be adjusted when creatinine clearance (CrCl) is < 50 mL/min as mentioned below;

Estimated CrCl (mL/min)Recommended Dosage Regimen

Estimated CrCl[a] (mL/min)	Recommended Dosage Regimen
> 50 > 30 to ≤ 50 ≥ 15 to ≤ 30 End-stage renal disease, including hemodialysis[b]	No dosage adjustment necessary 400 mg IV (over 5 to 60 minutes) every 12 hours 300 mg IV (over 5 to 60 minutes) every 12 hours 200 mg IV (over 5 to 60 minutes) 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] Ceftaroline is hemodialyzable; thus it should be administered after hemodialysis on hemodialysis days.

Pediatrics: No dosage adjustment is required in pediatric patients with CrCl > 50 mL / min/1.73 m^2, estimated using the Schwartz equation. There is insufficient information to recommend a dosage regimen for pediatric patients with CrCl < 50 mL/min/1.73 m^2.

Preparation of Ceflaro for Administration
Reconstitution of Ceflaro Powder for Injection

Ceflaro is administered by intravenous infusion. Standard aseptic techniques should be used for solution preparation and administration. Ceflaro should be reconstituted with 20 mL of sterile water for injections and the resulting reconstituted solution must then be immediately diluted prior to use.

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

The resulting reconstituted solution at the range of diluted concentrations of Ceftaroline fosamil 20 mg/mL to 30 mg/mL should be shaken prior to being transferred to an infusion bag or bottle containing one of the following diluents.
- 0.9% sodium chloride injection
- 5% dextrose injection
- lactated ringer's injection.

Storage of Reconstituted Solutions
The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 to 8°C and up to 6 hours at room temperature.

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

CONTRAINDICATIONS:
It is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis has been reported with ceftaroline.

WARNINGS AND PRECAUTIONS:
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before therapy with ceftaroline is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. Maintain clinical supervision if this product is to be given to a penicillin- or other beta-lactam allergic patient, because cross sensitivity among beta-lactam antibacterial agents has been clearly established. If an allergic reaction to ceftaroline occurs, discontinue it and institute appropriate treatment and supportive measures.
- *Clostridioides difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ceftaroline, 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.
- Neurological adverse reactions have been reported with cephalosporins, including ceftaroline. These reactions include encephalopathy and seizures. Most cases occurred in patients with renal impairment who did not receive appropriate dosage adjustment. The neurological adverse reactions were reversible and resolved after discontinuation of ceftaroline or after hemodialysis. If neurological adverse reactions associated with ceftaroline therapy occur, consider discontinuing it or making appropriate dosage adjustments in patients with renal impairment.
- If anemia develops during or after treatment with ceftaroline, 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 ceftaroline should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated.
- Prescribing ceftaroline in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

ADVERSE REACTIONS:
The reported adverse events are; hypersensitivity reaction, neurotoxicity, clostridium difficile associated diarrhea, direct coombs test seroconversion, rash, diarrhea, constipation, vomiting, increased transaminase, hypokalemia, phlebitis, anemia, eosinophilia, neutropenia, thrombocytopenia, bradycardia, palpitations, abdominal pain, pyrexia, hepatitis, anaphylaxis, dizziness, convulsion, clostridioides difficile colitis, hyperglycemia, hyperkalemia, renal failure, urticaria, headache, alanine aminotransferase increased, aspartate aminotransferase increased, pruritus, agranulocytosis, leukopenia, eosinophilic pneumonia, encephalopathy and seizures.

USE IN SPECIFIC POPULATIONS:
Pregnancy
Risk Summary:
There are no adequate studies with ceftaroline in pregnant women that informed any drug associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. The background risk of major birth defects is 2-4% and of miscarriage is 15 - 20 % of clinically recognized pregnancies within the general population.

Nursing Mothers:
No data is available regarding the presence of ceftaroline in human milk, the effects of ceftaroline on breastfed infants, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ceftaroline and any potential adverse effects on the breastfed child from ceftaroline or from the underlying maternal condition.

Pediatric Use:
The safety and effectiveness of ceftaroline in the treatment of ABSSSI have been established in pediatric patients (at least 34 weeks gestational age and 12 days postnatal age). The safety and effectiveness of ceftaroline in the treatment of CABP have been established in the age groups 2 months to less than 18 years old. Safety and effectiveness of ceftaroline in pediatric patients less than 34 weeks gestational age and less than 12 days postnatal age for the treatment of ABSSSI have not been established. Safety and effectiveness of ceftaroline in pediatric patients below the age of 2 months for the treatment of CABP have not been established as no data are available.

Geriatric Use:
The clinical cure rates in the ceftaroline were similar in patients ≥ 65 years of age compared with patients < 65 years of age in both the ABSSSI and CABP studies. The adverse reaction profiles in patients ≥ 65 years of age and in patients < 65 years of age were similar. 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 ceftaroline. 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.

Renal Impairment:
Dosage adjustment is required in adult patients with moderate (CrCl > 30 to ≤ 50 mL/min) or severe (CrCl ≥ 15 to ≤ 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). There is insufficient information to recommend a dosage regimen for pediatric patients with CrCl < 50 ml/min.

OVERDOSAGE:
Ceftaroline overdosage has occurred in patients with renal impairment. Reactions have included neurological sequelae, including encephalopathy. In the event of overdose, ceftaroline should be discontinued and general supportive treatment given. Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of ceftaroline, the mean total recovery of ceftaroline in the dialysate following a 4 hours 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.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light. Detailed prescribing information is available at **www.curexa.com.pk**

PRESENTATION:
Ceflaro 400mg IV Injection: 1 vial of 400mg Ceftaroline Fosamil and 1 ampoule of 20mL sterile water for injection.
Ceflaro 600mg IV Injection: 1 vial of 600mg Ceftaroline Fosamil and 1 ampoule of 20mL sterile water for injection.

سیفلیرو
(سیفٹیرولین فوسامل)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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