CEFTAROLINE

Ceftaroline fosamil (Teflaro®), the prodrug of ceftaroline (formerly PPI-0903, T-91825, TAK-599) is a novel, bactericidal, broad-spectrum, oxyimino cephalosporin that was approved by the United States Food and Drug Administration (US FDA) in October, 2010 for the treatment of acute bacterial skin and skin structure infections caused by susceptible Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and for community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae*, methicillin-susceptible *S. aureus* as well as commonly encountered facultative Gram-negative bacilli such as *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*.

Ceftaroline has the ability to bind to penicillin-binding protein (PBP) 2a, an MRSA-specific PBP that has low affinity for most other β-lactam antibiotics. Ceftaroline is active *in vitro* against Gram-positive cocci, including MRSA, methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and some vancomycin-resistant Enterococcus faecalis (not Enterococcus faecium). The broad-spectrum activity of ceftaroline includes many Gram-negative pathogens but does not extend to extended-spectrum β-lactamase (ESBL)-producing or AmpC-derepressed Enterobacteriaceae or most nonfermentative gram-negative bacilli. Ceftaroline demonstrates limited activity against anaerobes such as *Bacteroides fragilis* and non-fragilis *Bacteroides spp*. Limited data show that ceftaroline has low propensity to select for resistant subpopulations.

Ceftaroline fosamil is rapidly converted in vivo by plasma phosphatases to its microbiologically active form, ceftaroline, by hydrolysis of its phosphonate group. Ceftaroline demonstrates low protein binding (<20%), a serum half-life of 2.6 hours, and a volume of distribution of 0.37L/kg (28.3 L).

In gaining US FDA approval for its first two indications, Forest Laboratories conducted four Phase 3 clinical trials. FOCUS I and FOCUS II studied adult patients who were hospitalized with moderate to severe community-associated bacterial pneumonia requiring treatment with intravenous antimicrobials and CANVAS I and CANVAS II evaluated ceftaroline monotherapy versus vancomycin plus aztreonam in adult patients with complicated skin and skin structure infections caused by Gram-positive and Gram-negative bacteria.

Each of the four Phase 3 clinical trials demonstrated ceftaroline to be well-tolerated by patients. The overall rate of adverse events was comparable between the two treatment groups in each trial. The overall discontinuation rate for ceftaroline-treated patients was 2.7% compared to a rate of 3.7% for the comparator group-treated patients. The most common adverse reactions occurring in > 2% of patients receiving ceftaroline in the pooled Phase 3 clinical trials were diarrhea, nausea, and rash. No clinical drug-drug interaction studies have been conducted with ceftaroline. *In vitro* studies in human liver microsomes indicated that ceftaroline did not inhibit the major cytochrome P450 isoenzymes. Therefore ceftaroline is not expected to inhibit or induce the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

For pregnant or nursing mothers, ceftaroline should only be used if the potential benefit outweighs the potential risk to the fetus or child. Safety and effectiveness in pediatric patients has not been studied. Because elderly patients greater-than or equal to 65 years of age are more likely to have decreased renal function and ceftaroline is excreted primarily by the kidney, care should be taken in dose selection in this age group as in younger patients with

impaired renal function. Dosage adjustment is required in patients with moderately (30 to less-than or equal to 50 mL/min) or severely (< 30 mL/min) impaired renal function. The pharmacokinetics of ceftaroline in patients with hepatic impairment have not been established.

Forest Laboratories, Inc. holds the worldwide rights (excluding Japan, where Takeda Pharmaceuticals holds rights) to ceftaroline-Teflaro® which it obtained in 2007 when it acquired Cerexa, Inc., a privately held biopharmaceutical company. In August 2009, Forest Laboratories and AstraZeneca entered into a definitive collaboration agreement to co-develop and commercialize ceftaroline fosamil in all markets outside the United States, Canada, and Japan. Forest Laboratories has indicated that it intends to seek Health Canada approval for ceftaroline.