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Ceftaroline Fosamil

Cephalosporin Antibiotic

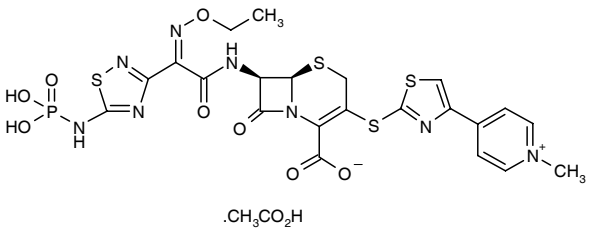
Rec INN; USAN

Abstract

Ceftaroline fosamil (PPI-0903, TAK-599) is a novel *N*-phosphono prodrug of PPI-0903M (ceftaroline, T-91825), a broad-spectrum cephalosporin antibiotic with potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains. Preclinical studies showed that PPI-0903M has high affinity for penicillin-binding protein PBP2' and the agent demonstrated promising *in vitro* and *in vivo* activity against many bacteria, including multidrug-resistant Gram-positive pathogens such as MRSA and penicillin-resistant *Streptococcus pneumoniae*. Ceftaroline fosamil proved safe, with a predictable pharmacokinetic profile in healthy male subjects, and no drug accumulation was observed. In patients with complicated skin and skin structure infections (cSSSIs), ceftaroline fosamil also exhibited a favorable safety and tolerability profile and superior efficacy to standard therapy. Two phase III clinical trials for the treatment of cSSSIs have been completed recently and phase III trials in community-acquired pneumonia (CAP) have commenced.

PPI-0903
TAK-599

(6*R*,7*R*)-7-[(*Z*)-2-(Ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-ylsulfanyl]-3-cephem-4-carboxylate acetate



$C_{24}H_{25}N_8O_{10}PS_4$
Mol wt: 744.741

CAS: 595568-96-0

CAS: 229016-73-3 (free base) (INN)

CAS: 400827-79-4 (disodium)

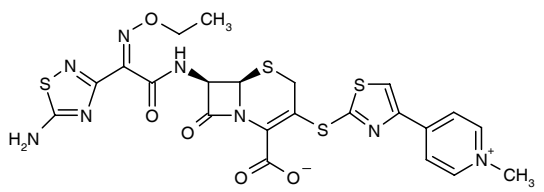
CAS: 866021-48-9 (hydrate) (USAN)

EN: 325265

PPI-0903M

Ceftaroline
T-91825

(6*R*,7*R*)-7-[(*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(ethoxyimino)acetamido]-3-[4-(1-methylpyridinium-4-yl)thiazol-2-ylsulfanyl]-3-cephem-4-carboxylate



$C_{22}H_{20}N_8O_5S_4$
Mol wt: 604.7091

CAS: 189345-04-8

EN: 325264

Synthesis

Ceftaroline fosamil can be synthesized as follows. 4-Acetylpyridine (I) is brominated with Br_2 and HBr in acetic acid, and the resulting bromo ketone (II) is cyclized with ammonium dithiocarbamate (III) in the presence of NaOMe to yield 4-(4-pyridyl)-2-thiazolethiol (IV). The sodium salt of (IV) is then condensed with the cephalosporanic mesylate (V) in THF to afford the thioether adduct (VI). Subsequent quaternization of the pyridyl ring of (VI) with iodomethane provides the pyridinium salt (VII). The ethoxycarbonyl group of (VII) is then removed by means of PCl_5 in pyridine to give the *p*-methoxybenzyl amino ester (VIII), which is hydrolyzed to the corresponding amino acid (IX) by treatment with trifluoroacetic acid and anisole (1). Reaction of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(ethoxyimino)acetic acid (X) with PCl_5 in ethyl acetate affords the (dichlorophosphorylamino)thiadiazolylacetyl chloride (XI) (1-3), which is condensed with the aminocephalosporanic acid (IX) followed by acidic hydrolysis to provide the phosphorylated cephalosporin (1-4). The acetate salt is prepared by treat-

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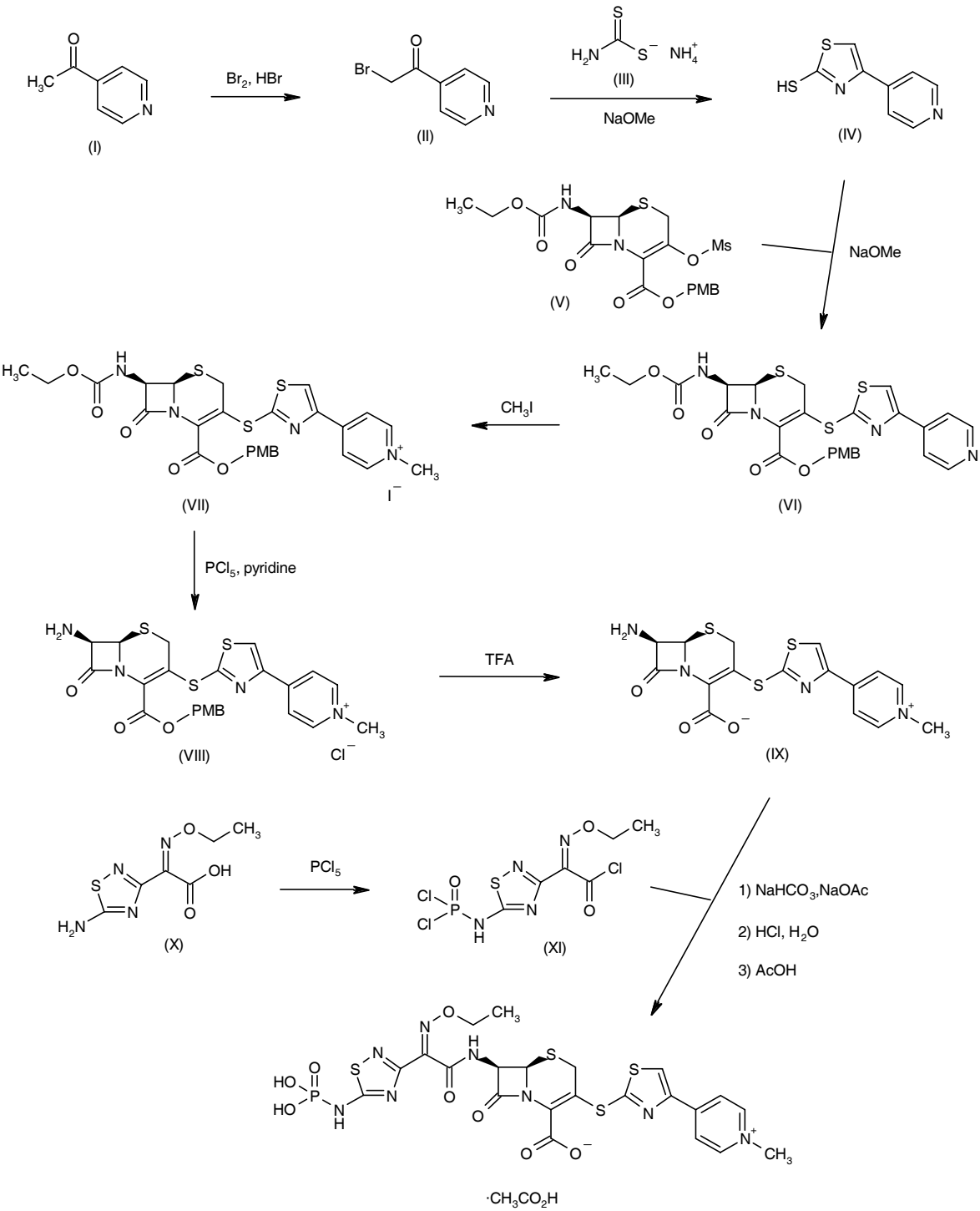
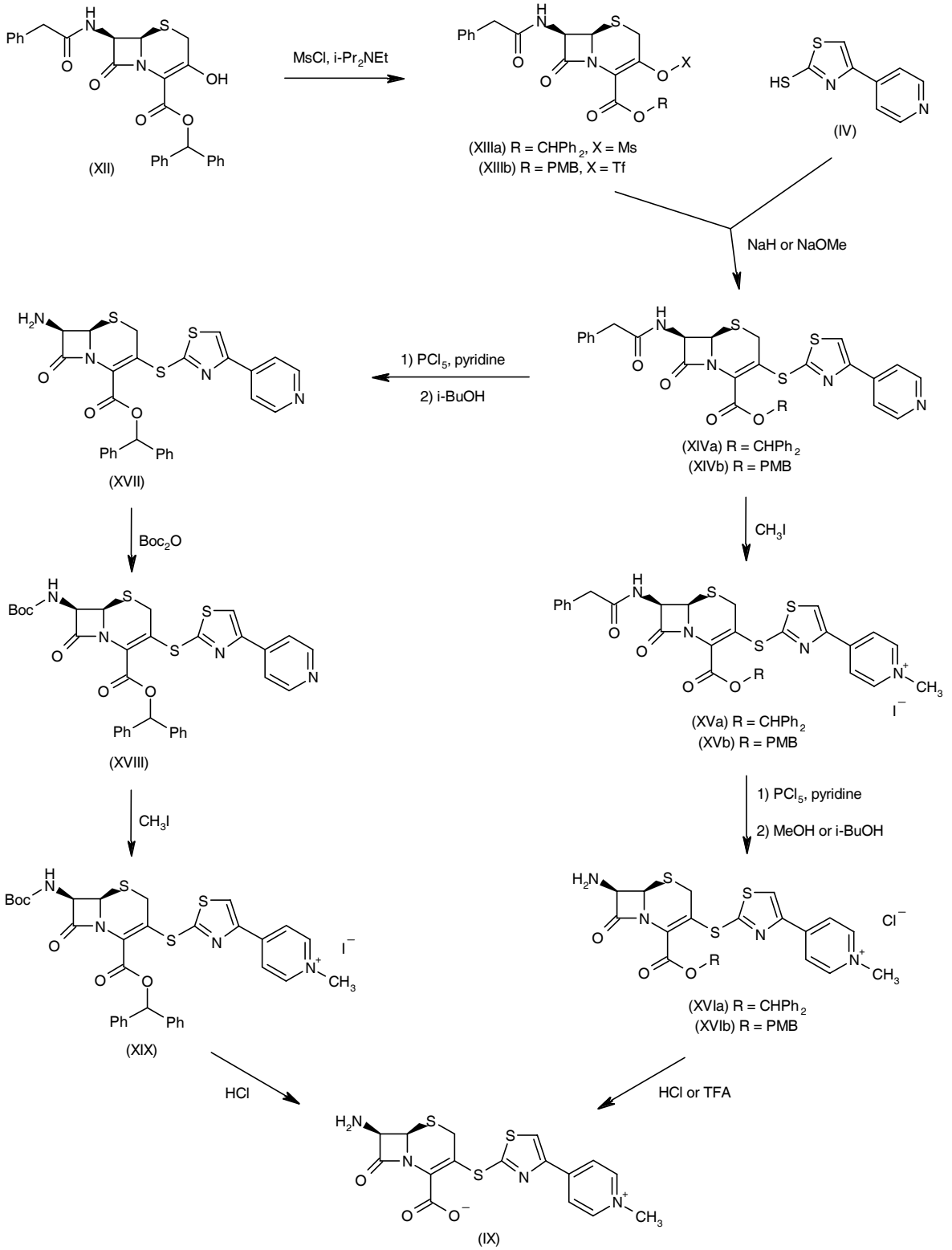
Scheme 1: Synthesis of Ceftaroline Fosamil



ment of an aqueous solution of ceftaroline fosamil with acetic acid (2, 3). Scheme 1.

The intermediate aminocephalosporanic acid (IX) can be prepared by an alternative procedure starting from *N*-phenylacetyl cephalosporanic precursors. Treatment of the 3-hydroxy cephem derivative (XII) with methanesulfonyl chloride and DIEA affords the corresponding mesylate (XIIIa) (3). Condensation of the sodium salt of 4-(4-

Scheme 2: Synthesis of Intermediate (IX)



pyridyl)-2-thiazolethiol (IV) with either the mesylate (XIIIa) or the known triflate (XIIIb) produces the thioether adducts (XIVa) and (XIVb), respectively, which are further methylated at the pyridyl ring with iodomethane in DMF to generate the pyridinium salts (XVa/b). The phenylacetyl group of (XVa/b) is then removed by reaction with PCl_5 in pyridine, followed by quenching with methanol or isobutanol to yield the benzhydryl (XVIa) and *p*-methoxybenzyl (XVIb) amino esters, respectively. Deprotection of esters (XVIa) and (XVIb) by treatment with either concentrated HCl in acetonitrile or with trifluoroacetic acid and anisole provides the target amino acid (IX) (2, 3). In a related strategy, deacylation of (XIVa) with PCl_5 and isobutanol gives the amino ester (XVII), which is further protected as the *N*-Boc derivative (XVIII) under the usual conditions. After quaternization of pyridine (XVIII) with iodomethane, simultaneous acidic cleavage of the benzhydryl ester and *N*-Boc groups in the resulting pyridinium salt (XIX) provides the target amino acid (IX) (3). Scheme 2.

Background

Bacterial resistance has become a global concern, and Gram-positive bacterial pathogens, including enterococci, staphylococci and streptococci, have demonstrated an extraordinary ability to develop resistance to currently available antimicrobial agents. Although a number of new agents have recently become available for the treatment of infections caused by resistant Gram-positive pathogens, these agents, including daptomycin, linezolid and quinupristin-dalfopristin, are not effective against common Gram-negative pathogens. Therefore, there is a high demand for a new antimicrobial agent with activity against both resistant Gram-positive and Gram-negative pathogens (5).

Developed as a water-soluble *N*-phosphono prodrug by Takeda, ceftaroline fosamil (PPI-0903, TAK-599), is a new-generation injectable cephalosporin antibiotic with broad-spectrum antimicrobial activity. Upon hydrolysis of the phosphonate group, ceftaroline fosamil is rapidly converted to PPI-0903M (ceftaroline, T-91825), the bioactive form (1, 2). In 2006, the U.S. FDA granted the antibiotic fast track designation for the treatment of complicated skin and skin structure infections (cSSSIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Licensee Cerexa (a wholly owned subsidiary of Forest) recently completed phase III clinical trials in patients with cSSSIs and is currently evaluating ceftaroline fosamil in phase III trials for community-acquired pneumonia (CAP).

Preclinical Pharmacology

The *in vitro* activity of ceftaroline has been extensively evaluated against a wide spectrum of Gram-positive and Gram-negative isolates. Early studies indicated that ceftaroline had high affinity for penicillin-binding protein PBP2' (IC_{50} = 0.90 μg/ml), and the compound demonstrated potent *in vitro* activity against MRSA and a number of other Gram-positive organisms (MIC_{90} = 2 μg/ml or less) (1, 2, 6, 7).

Sader *et al.* evaluated the *in vitro* antimicrobial activity and spectrum of ceftaroline against 1,478 clinical isolates from 80 medical centers in 22 countries, and compared the antimicrobial activity of ceftaroline with that of other currently available antimicrobial agents, including cefepime, ceftriaxone, penicillin, ampicillin, imipenem, levofloxacin, vancomycin and linezolid. Ceftaroline demonstrated broader *in vitro* activity against Gram-positive bacteria, especially multidrug-resistant staphylococci and streptococci of current clinical concern, than the other antibiotics tested. The *in vitro* activity of ceftaroline against Gram-negative pathogens was similar to that of the other antibiotics studied. Furthermore, among all the antimicrobial agents tested, ceftaroline demonstrated the greatest activity against Gram-positive organisms, including resistant isolates such as MRSA and methicillin-resistant coagulase-negative staphylococci (CoNS): the activity of ceftaroline against MRSA (MIC_{50} = 1 μg/ml, MIC_{90} = 2 μg/ml) was 8-> 16-fold more potent than that of cefepime (MIC_{50}/MIC_{90} > 16 μg/ml) and 16-> 32-fold more potent than that of ceftriaxone (MIC_{50}/MIC_{90} > 32 μg/ml), and the activity of ceftaroline against methicillin-resistant CoNS strains (MIC_{50} = 0.25 μg/ml, MIC_{90} = 0.5 μg/ml) was 16-fold more potent than that of cefepime (MIC_{50} = 4 μg/ml, MIC_{90} = 8 μg/ml) and 32-> 64-fold more potent than that of ceftriaxone (MIC_{50} = 8 μg/ml, MIC_{90} = 32 μg/ml). Ceftaroline also proved highly active against streptococci, including β-hemolytic and viridans group streptococci (MIC_{50} = 0.016 μg/ml or less for the majority of strains). Ceftaroline demonstrated high activity against key respiratory pathogens, including penicillin- and multidrug-resistant *Streptococcus pneumoniae* (MIC_{50} = 0.12 μg/ml, MIC_{90} = 0.25 μg/ml) and *Haemophilus influenzae* (MIC_{50}/MIC_{90} = 0.016 μg/ml or less), which are the main pathogens causing CAP, otitis media and bacterial meningitis. Ceftaroline was also active against anaerobes, but its activity varied depending on the strain (8).

Mushtaq *et al.* (9) studied the *in vitro* activity of ceftaroline alone or in combination with clavulanate against bacteria with known resistance mechanisms, as well as its potential for resistance selection. Ceftaroline again demonstrated high activity against *S. aureus*, including MRSA strains (MIC = 2 mg/l or less). Even in the presence of 2% NaCl, the MICs of ceftaroline against MRSA isolates and all but one methicillin-resistant CoNS strain remained at or below 2 mg/l. Ceftaroline demonstrated better activity against penicillin-resistant pneumococci (geometric mean MIC = 0.09 mg/l) than available cephalosporins. The geometric mean MICs were 0.005 and 0.05 mg/l for penicillin-susceptible and -intermediate *S. pneumoniae* strains. Ceftaroline also demonstrated activity against many Enterobacteriaceae with TEM β-lactamases. However, Enterobacteriaceae with extended-spectrum β-lactamases (ESBLs) and AmpC or K1 enzymes showed marked resistance to ceftaroline. The resistance induced by class A β-lactamases could be reversed by a combination of ceftaroline and clavulanate.

However, clavulanate was not able to overcome the resistance induced by derepressed AmpC enzymes. Resistance was not observed for *S. aureus, H. influenzae* or pneumococci.

The *in vitro* activity of ceftaroline was studied against 147 bacterial isolates from 81 patients with cSSSIs from a multinational phase II clinical trial. Ceftaroline demonstrated potent and broad-spectrum activity against both Gram-positive and Gram-negative pathogens, with MICs for MRSA and MSSA (methicillin-susceptible *S. aureus*) of 0.5 μg/ml or less and 0.25 μg/ml or less, respectively (10). Ceftaroline also demonstrated potent activity against bacterial isolates from patients with complicated urinary tract infections, complicated intra-abdominal infections and hospital-acquired pneumonia, with an MIC_{50} generally at or below 1 μg/ml (11).

Ceftaroline was tested against 1,337 isolates from patients with CAP, including susceptible and resistant strains of *H. influenzae, Moraxella catarrhalis, S. aureus, S. pneumoniae* and *Streptococcus pyogenes*. It proved active against all isolates (MIC_{90} = 2 μg/ml or less) and was more potent than ceftriaxone, amoxicillin/clavulanate and levofloxacin (12).

The bactericidal activity of ceftaroline has also been evaluated against a wide range of species, with MBC/MIC ratios of 4 or less for most strains. The antibiotic killed > 99.9% of staphylococci and Enterobacteriaceae in 8-24 h at 4 x MIC or less. The MIC was not significantly affected by medium changes or the addition of human serum (13). It also displayed potent bactericidal activity against *S. pneumoniae*, including penicillin-resistant strains (14).

Combination of ceftaroline with vancomycin, linezolid, daptomycin or tigecycline had no effect on activity against a range of staphylococci, enterococci, streptococci and Gram-negative organisms. No effect was observed for combination of ceftaroline and levofloxacin against a broad spectrum of Gram-positive and -negative organisms, for combination of ceftaroline and aztreonam, nor for combination of ceftaroline and azithromycin against pneumococci and *H. influenzae*. However, combination of ceftaroline with meropenem demonstrated a synergistic effect against *S. aureus* and *Klesiella pneumoniae*, and ceftaroline and amikacin also had synergistic activity against *Escherichia coli* (ESBL) and *Pseudomonas aeruginosa* (15).

Ceftaroline fosamil was then evaluated in murine models of septicemia, pneumonia and thigh muscle infection. Compared with vancomycin, linezolid, teicoplanin and arbekacin, ceftaroline fosamil demonstrated comparable or superior activity against systemic infection caused by MRSA (ED_{50} = 1.08-4.81 mg/kg s.c.). At a dose of 20 mg/kg s.c., ceftaroline fosamil markedly decreased the bacterial counts in lungs of mice with pneumonia caused by MRSA, whereas vancomycin and linezolid at the same dose level were ineffective. Ceftaroline fosamil and linezolid decreased the bacterial counts in muscles of mice with thigh muscle infection, whereas vancomycin was again ineffective (6, 7).

The *in vivo* efficacy of ceftaroline fosamil was also assessed and compared with that of linezolid and vancomycin in rabbit endocarditis infection models using MRSA and heterogeneous glycopeptide-intermediate *S. aureus* (hGISA). The animals were randomly assigned to receive no treatment, infusion of 10 mg/kg (human equivalent) ceftaroline fosamil every 12 h, 10 mg/kg (human equivalent) linezolid every 12 h or a constant i.v. infusion of vancomycin to reach steady-state 20 × MIC in serum. At the end of a 4-day treatment period, ceftaroline fosamil was bactericidal against MRSA strains, similar to vancomycin. The efficacy of ceftaroline fosamil against the hGISA strain was superior to that of both linezolid and vancomycin (16, 17). Similar results were obtained in rabbits with osteomyelitis infection due to MRSA and GISA (18).

Ceftaroline fosamil was further tested in rats with aortic infective endocarditis caused by biofilm-positive *S. aureus*. Animals were randomized to receive no treatment, i.v. infusion of ceftaroline fosamil (20 mg/kg b.i.d.), s.c. infusion of vancomycin (120 mg/kg b.i.d.) or s.c. infusion of daptomycin (once daily) for 3 days. The efficacy of ceftaroline fosamil, as well as vancomycin and daptomycin, was assessed in real time by using *in vivo* bioluminescent imaging. Marked correlations between cardiac bioluminescence signals (BLS) and *S. aureus* densities were observed in vegetations in all three treatment groups. Compared to placebo, both ceftaroline fosamil ($p < 0.0005$) and vancomycin ($p < 0.05$) significantly decreased *S. aureus* densities and cardiac BLS in vegetations, kidney and spleen. Ceftaroline fosamil demonstrated superior efficacy to both vancomycin and daptomycin in reducing *S. aureus* densities in all three target tissues (19).

Pharmacokinetics and Metabolism

In vitro experiments have demonstrated low protein binding for ceftaroline in mouse, rabbit, monkey and human plasma, as well as good metabolic stability in human liver microsomes (20).

Studies in rats and monkeys showed that after i.v. administration of ceftaroline fosamil (10 mg/kg), the compound was rapidly converted to ceftaroline (1, 2).

Ceftaroline fosamil was administered to rabbits at a dose of 20 mg/kg by 30-min i.v. infusion in order to evaluate its lung penetration. A mean lung penetration ratio of 42% was observed, which, together with human pharmacokinetic data, indicated that lung concentrations exceeding the MIC for most respiratory tract pathogens should be achieved (21).

The pharmacokinetics of ceftaroline fosamil were evaluated in 48 healthy male subjects assigned to receive a single i.v. infusion of ceftaroline fosamil 50, 100, 250, 500, 750 and 1000 mg over 60 min or placebo. Ceftaroline fosamil was rapidly eliminated, with the $t_{1/2}$ ranging from 2.0 to 2.9 h. C_{max} was dose-proportional over the dose range studied (1.5 μg/ml for 50 mg, 2.9 μg/ml for 100 mg, 9.9 μg/ml for 250 mg, 16.5 μg/ml for 500 mg, 23.0 μg/ml for 750 mg and 30.2 μg/ml for 1000 mg). A similar pattern was observed for AUC_{inf} (3.9, 6.6,

22.9, 44.7, 56.9 and 80.5 μg.h/ml, respectively). Ceftaroline fosamil and its metabolites were mainly eliminated by renal excretion (22).

The pharmacokinetic profile of ceftaroline fosamil was also evaluated in a double-blind, placebo-controlled, multiple-ascending-dose trial conducted in 24 healthy male subjects. Subjects were assigned to three cohorts (6 subjects receiving ceftaroline fosamil and 2 subjects receiving placebo in each cohort). Subjects in cohort 1 and 2 received doses of 300 and 600 mg, respectively, over 60 min every 12 h for 14 days, and subjects in cohort 3 received 800 mg over 60 min every 24 h for 7 days. Ceftaroline fosamil was rapidly eliminated, with a half-life of about 2.6 h. AUC and C_{max} were dose-proportional for the doses tested and no drug accumulation was observed (23).

Another study examined the pharmacokinetics of ceftaroline fosamil in 18 subjects with mild to moderate renal impairment. All subjects received a single dose (600 mg) of ceftaroline fosamil i.v. over 1 h. The antibiotic was rapidly transformed to ceftaroline in plasma. A decrease in renal function appeared to be correlated with an increase in AUC and elimination half-life: the mean AUC_{inf} in subjects with normal renal function and mild and moderate renal impairment was 68 ± 18, 95 ± 26 and 120 ± 13 μg.h/ml, respectively. The mean $t_{1/2}$ in the three cohorts was 2.8 ± 0.4, 3.7 ± 0.7 and 4.6 ± 1.1 h, respectively. Renal function had little effect on C_{max}. It was concluded that subjects with mild renal impairment will not require dose adjustment, although further assessment in subjects with moderate renal insufficiency is warranted (24).

To assess various baseline covariate factors that might affect drug exposure, safety and efficacy of ceftaroline fosamil, a population analysis was performed with pharmacokinetic data collected from 127 subjects (54 healthy subjects, 23 subjects with renal impairment, 50 subjects with cSSSI) in phase I and II studies using the NONMEM program. The data appeared to fit well into a two-compartment pharmacokinetic model with zero-order input and first-order elimination. The model-predicted pharmacokinetic profile closely resembled the observed profile of ceftaroline. Validation and performance checks demonstrated the robustness of this population pharmacokinetic model to predict ceftaroline concentration-time profiles in subjects with different levels of renal function (25).

On the basis of the above population pharmacokinetic analysis, a Monte Carlo simulation was performed to develop dose adjustment recommendations for patients with renal impairment. The S-Plus program was used to simulate plasma concentrations of ceftaroline (600 mg every 12 h by 1-h i.v. infusion) in subjects with normal renal function (CL_{cr} > 80 ml/min) or mild (CL_{cr} > 50-80 ml/min) to moderate (CL_{cr} > 30-50 ml/min) renal impairment. The model-predicted concentrations of ceftaroline were in good agreement with the observed concentrations of ceftaroline in normal subjects and those with renal impairment. The predicted C_{max} at steady state was 23.09 ± 5.44 μg/ml for subjects with normal renal function, 24.65 ± 5.85 μg/ml for subjects with mild renal impairment and 25.71 ± 6.17 μg/ml for subjects with moderate renal impairment, and the predicted $AUC_{0\text{-}24h}$ at steady state was 129 ± 29 μg.h/ml for subjects with normal renal function, 163 ± 36 μg.h/ml for those with mild renal impairment and 187 ± 40 μg.h/ml for subjects with moderate renal impairment. The findings indicated that no dose adjustment is required for subjects with mild renal insufficiency, whereas dose adjustment (400 mg instead of 600 mg i.v. over 1 h every 12 h) is required for subjects with moderate renal impairment to avoid overexposure to drug while maintaining effective plasma concentrations (26).

Safety

In the above-mentioned study in 48 healthy male subjects, subjects received single doses of ceftaroline fosamil by 60-min i.v. infusion and the agent proved safe and well tolerated at the doses tested (50, 100, 250, 500, 750 and 1000 mg). Most adverse events were mild and isolated, the most frequent being headache (22).

The safety of ceftaroline fosamil *versus* standard therapy (vancomycin) for the treatment of cSSSIs, including major abscess, deep extensive cellulitis and infected wounds, was evaluated in a multinational, randomized, observer-blinded phase II clinical trial in 100 hospitalized patients. Adult patients with cSSSI were randomized (2:1) to receive i.v. ceftaroline fosamil (600 mg over 60 min) every 12 h or i.v. vancomycin (1 g) every 12 h, with or without adjunctive i.v. aztreonam (1 g) every 8 h, for 7-14 days. Most adverse events on ceftaroline were mild (87.9% *vs.* 70.8% on standard therapy) and the most common were urinary crystals (9.0% *vs.* 15.6% for standard therapy), increased blood creatine phosphokinase (7.5% *vs.* 6.3%), elevated alanine aminotransferase (6.0% *vs.* 12.5%) and aspartate aminotransferase (6.0% *vs.* 9.4%), headache (6.0% *vs.* 6.3%), insomnia (6.0% *vs.* 6.3%), nausea (6.0% *vs.* 0%) and rash (1.5% *vs.* 6.3%). Five serious adverse events were reported: one case each of recurrent skin infection, pulmonary edema and gangrene in a toe on ceftaroline fosamil and one case each of interstitial nephritis and reinfection on standard therapy. Infusion-related reactions occurred in 4 and 8 subjects on ceftaroline fosamil and standard therapy, respectively, and no significant laboratory abnormalities were seen (27, 28).

Clinical Studies

Among the 88 clinically evaluable subjects in the above study, the clinical cure rate for ceftaroline fosamil and vancomycin was 96.7% and 88.9%, respectively. In the microbiologically evaluable population, the microbiological response rate for ceftaroline fosamil and vancomycin was 95.2% and 85.7%, respectively (27, 28).

Phase III clinical studies of ceftaroline fosamil *vs.* vancomycin + aztreonam in patients with cSSSIs have been completed (29, 30), and two phase III clinical trials in patients with CAP are currently under way (31, 32).

Sources

Cerexa, Inc. (US), a wholly owned subsidiary of Forest Laboratories; licensed worldwide, except Japan, from Takeda.

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