CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

PHARMACOLOGY REVIEW(S)

The pharmacology/toxicology recommendations for the ceftaroline (Teflaro) package insert can be found in the pharm/tox review filed for this product. The recommendations made for Sections 8.1 and 13 have been accepted by the sponsor, so no further action from pharm/tox is needed.

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/s/

AMY L ELLIS
10/19/2010

Comments on NDA 200-327 Teflaro (Ceftaroline fosamil for injection)
From: A. Jacobs, AD
Oct 18, 2010

1. I concur that there are no pharm/tox related issues for this NDA.
2. I concur that B would be an appropriate pregnancy category.

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/s/

ABIGAIL ABBY C C JACOBS
10/17/2010
This N200327b.pdf supersedes review N200327.doc of A. Jacobs entered on 10/15/2010

MEMORANDUM

Date: October 15, 2010

To: NDA 200-327

From: Terrance Ocheltree, Ph.D., R. Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 200-327, ceftaroline fosamil (400 mg and 600 mg) for injection.

I have assessed the ONDQA review of NDA 200-327 by Andrew Yu, Ph.D. The first CMC review for this product was finalized on September 1, 2010 without a recommendation of approval due to uncertainty of the assurance of sterility and pending changes to the vial and carton labels. On October 1, 2010 the Microbiology Reviewer entered a review into DARRTS recommending Approval. Labeling changes were submitted by the applicant and found acceptable. Therefore, the CMC review was finalized on October 6, 2010 with a recommendation for Approval. The Office of Compliance has recommended "Acceptable" for the proposed manufacturing and testing sites, as shown in EES on August 4, 2010. Sufficient information has been provided to assure identity, strength, purity and quality.

No post marketing commitments are proposed by ONDQA.

NDA 200-327 is for a new cephalosporin antibiotic, ceftaroline fosamil, in a glass vial. Each vial contains either 400 mg or 600 mg of sterile ceftaroline fosamil powder for injection. A 24 months expiration period has been granted when the undiluted product is stored at 2 to 8°C (36 to 46°F). The reconstituted product should be used with in 6 hours when stored at room temperature and 24 hours when stored at refrigerated conditions (2 to 8°C).

I concur with the "Approval" recommendation from a CMC perspective and the absence of CMC related post marketing commitments.

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/s/

TERRANCE W OCHELTREE
10/18/2010

Comments on NDA 200-327 Teflaro (Ceftaroline fosamil for injection)
From: A. Jacobs, AD

1. I concur that there are no pharm/tox related issues for this NDA.
2. I concur that (b) (4).

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/s/

ABIGAIL ABBY C C JACOBS
10/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	200-327
Supporting document/s:	IND 71,371
Applicant's letter date:	12/30/09
CDER stamp date:	12/30/09
Product:	Teflaro (Ceftaroline Fosamil for Injection)
Indication:	Complicated skin and skin structure infections; community-acquired bacterial pneumonia
Applicant:	Cerexa
Review Division:	DAIOP
Reviewer:	Amy L. Ellis, Ph.D.
Supervisor/Team Leader:	Wendelyn Schmidt, Ph.D.
Acting Division Director:	Wiley Chambers, M.D.
Project Manager:	Carmen DeBellas, R.Ph.

Template Version: December 7, 2009

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 200-327 are owned by Cerexa or are data for which Cerexa has obtained a written right of reference.
Any information or data necessary for approval of 200-327 that Cerexa does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Cerexa does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of 200-327.

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

The pharmacologist has no objection to the approval of ceftaroline fosamil.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The label should be modified to reflect that the toxicokinetic studies were conducted separately from the developmental toxicity studies. The discussion of postnatal development and reproductive performance of the F1 animals should be moved from section 13.1 of the label to section 8.1. A dose comparison based on body surface area was inserted after the discussion of fertility data in section 13.1 because toxicokinetics were not conducted as part of the fertility study and the data from the pregnant rats may not be applicable to the nonpregnant females and the males used for the fertility study. Other changes were editorial in nature. The pharmacologist concurs with the sponsor's choice of Pregnancy Category B. Although there was an increase in spontaneous abortion and in the incidence of a common skeletal variation (angulated hyoid alae) in the developmental toxicity study conducted in rabbits, it occurred at maternally toxic doses and there was no increase in the incidence of any malformation. Other cephalosporin drugs have been labeled as Category B and there is no compelling evidence that this one is different from other members of the class. In fact, this common variation is the type of finding that may not have been discussed in study reports for older products or reports written by less thorough investigators. The manifestations of maternal toxicity observed in the rabbit developmental toxicity study were likely due to the antibacterial effect of ceftaroline on the GI flora of these animals and have been observed in similar studies of other antibacterial drugs.

The recommended wording for label sections 8.1 and 13.1 is as follows:

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.

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

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 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.

1.2 Brief Discussion of Nonclinical Findings

Ceftaroline fosamil has a nonclinical toxicity profile typical of a cephalosporin antimicrobial. Target organs of toxicity in rats and monkeys that may be of clinical relevance included the kidneys and CNS. Although ceftaroline fosamil and active ceftaroline induced chromosome aberrations in mammalian cells in the absence of metabolic activation, both were negative in all other genotoxicity studies and the results are not of concern for this drug product. Ceftaroline is not a reproductive toxicant. It did not impair fertility of male or female rats and it was not associated with developmental toxicity in rats or rabbits. It did not adversely affect pregnancy or peri/postnatal development of offspring when given to rat dams during fetal organogenesis and through lactation.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

229016-73-3

2.1.2 Generic Name

Ceftaroline fosamil for injection

2.1.3 Code Name

PPI-0903; TAK-599; (b) (4)

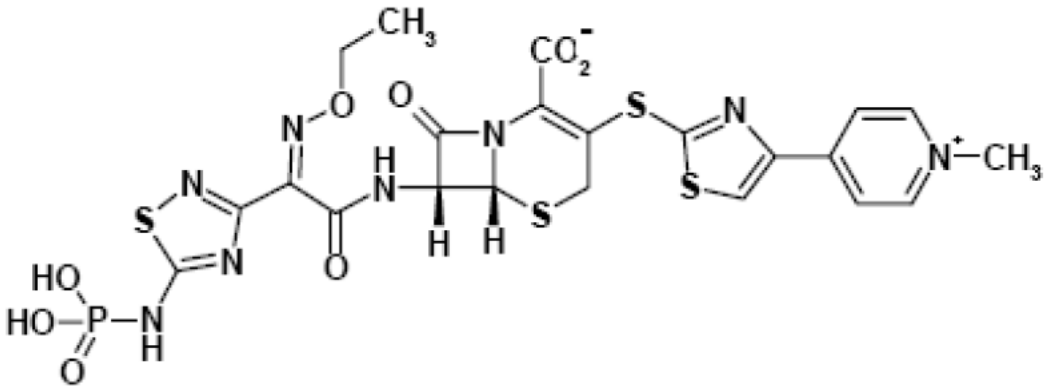
2.1.4 Chemical Name

(6R,7R)-7-{(2Z)-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

2.1.5 Molecular Formula/Molecular Weight

$C_{22}H_{21}N_8O_8PS_4$ / 684.68

2.1.6 Structure



2.1.7 Pharmacologic class

β-lactam (cephalosporin) antimicrobial- prodrug

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 71,371; DMF 23167

2.3 Clinical Formulation

2.3.1 Drug Formulation

The product will be marketed as a sterile powder for injection in vials containing either 400 mg or 600 mg. The only excipient is L-arginine (b) (4) added in sufficient quantity so that the ratio of ceftaroline to L-arginine is (b) (4) based on mass. Final pH of product after constitution is 4.8-6.5.

2.3.2 Comments on Novel Excipients

There are no novel excipients. L-arginine was not used to formulate the ceftaroline fosamil dosing solutions in many of the nonclinical studies, but it was used in some. However, there are several approved products that contain L-arginine as an excipient including ceftazidime, cefepime, and aztreonam.

2.3.3 Comments on Impurities/Degradants of Concern

There are no concerns regarding the impurities or degradation products found in ceftaroline fosamil drug product, [redacted]. Nonclinical studies were performed with the degradation product [redacted] and a [redacted]

[redacted] was administered IV to rats daily for 28 days at a dose of 9 mg/kg without evidence of toxicity. Additionally, this degradation product was negative in 2 *in vitro* genotoxicity assays. It did not induce mutations in mouse lymphoma cells and it did not induce chromosome aberrations in cultured human peripheral blood lymphocytes.

Rats and monkeys that received intravenous ceftaroline fosamil containing an enhanced amount of the [redacted] daily for 28 days did not experience toxic effects. The dose of ceftaroline fosamil used in the rat study was 200 mg/kg/day [redacted] The ceftaroline fosamil dose for the monkey study was 100 mg/kg/day [redacted]

Clinical batches of ceftaroline fosamil containing amounts of [redacted] that would provide exposures less than or equal to those achieved in the rat and monkey studies would be considered qualified for these substances.

2.4 Proposed Clinical Population and Dosing Regimen

Adult patients (≥ 18 years of age) with complicated skin and skin structure infections (cSSSI) or community-acquired bacterial pneumonia (CABP) would receive 600 mg of ceftaroline every 12 hours via IV infusion administered over 1 hour. Treatment duration for cSSSI would be 5-14 days and for CABP would be 5-7 days.

2.5 Regulatory Background

The initial IND for this drug was submitted in December 2004 by Peninsula Pharmaceuticals, Inc., although early nonclinical studies were conducted by the drug's manufacturer, Takeda Corporation (Japan). The sponsor later changed its name to Cerexa, Inc. Cerexa is now a subsidiary of Forest Laboratories. An advisory committee meeting to discuss this product was held on September 7, 2010 because it is a new molecular entity. There have not been any particular concerns regarding the safety of ceftaroline and the AC members recommended that the Division approve the product for the clinical indications requested by the sponsor.

3 Studies Submitted

3.1 Studies Reviewed

Effects of TAK-599 on Water and Electrolyte Excretions in Rats (B040245)

Mass Balance and Metabolism of Ceftaroline Prodrug in the Sprague-Dawley Rat Following a Single Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-01; 1281-004)

Mass Balance and Metabolism of Ceftaroline Prodrug in the Cynomolgus Monkey After a Single Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-02; 1281-005)

Tissue Distribution in Rats Following Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-05; 6277-198)

(b) (4): *In Vitro* Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay) (CEF-TX-06; AC13KK.704.BTL)

(b) (4) *In Vitro* Mammalian Chromosome Aberration Test (CEF-TX-07; AC13KK.341.BTL)

3.2 Studies Not Reviewed

These were non-GLP preliminary toxicity studies performed in rats and monkeys by Takeda Chemical Industries, Ltd. (Osaka, Japan), the original developer of ceftaroline fosamil. The results of these studies were consistent with the pivotal GLP studies conducted in the same species and they were likely used as dose setting studies. Examination of these study reports by the pharmacologist did not reveal any information different from that obtained from the pivotal studies; thus, reviews were not written.

(b) (4)

3.3 Previous Reviews Referenced

The following studies were reviewed under IND 71-371:

Original IND:

Safety Pharmacology Studies of TAK-599: Effects of Irwin Test in Rats, and Amendment 1 (PPI-0903/00034 and 00034.001)

Anti- and Proconvulsant Effects of TAK-599 in Rats, and Amendment 1 (PPI-0903/00036 and 00036.001)

Safety Pharmacology Studies of TAK-599: Effects on Respiration Rate, Tidal Volume, Minute Volume, and Body Temperature in Rats (PPI-0903/00035)

Safety Pharmacology Studies of TAK-599: Effects in Conscious Telemetered, Cynomolgus Monkeys, and Amendment 1 (PPI-0903/00032 and 00032.001)

Safety Pharmacology Studies of TAK-599: Effects on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibers (PPI-0903/00033)

Safety Pharmacology Studies of TAK-599: Effects of T-91825 on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibers (PPI-0903/00013)

Characterization of TAK-599 Metabolites (TAK-599/00068)

Pharmacokinetics of TAK-599 after Intravenous Injection in Animals (TAK-599/00069)

In Vitro Metabolism of TAK-599 and M-I by Cytochrome P450 (TAK-599/00067)

Pharmacokinetic Analysis of M-I, an Active Metabolite, After Intravenous Administration of TAK-599 in Animals (TAK-599/00080)

Intravenous Single Dose Toxicity Study of TAK-599 in Rats (PPI-0903/00012)

Acute Intravenous Escalating Dose Toxicity Study of TAK-599 in Monkeys (PPI-0903/00014)

Four-week Intravenous Toxicity Study of TAK-599 in Rats with a Four-week Recovery Period (PPI-0903/00015)

Four-week Intravenous Toxicity Study of TAK-599 in Monkeys with a Four-week Recovery Period (PPI-0903/00037)

Bacterial Reversion Assay with TAK-599, Amendments 1 and 2 (PPI-0903/00018, 00018.001 and 00018.002)

Cytogenetic Assay with TAK-599 in Chinese Hamster Lung (CHL) Cells, and Amendment 1 (PPI-0903/00026 and 00026.001)

Gene Mutation Assay with TAK-599 in Mouse Lymphoma L5178Y (TK +/-) Cells (PPI-0903/00022)

Micronucleus Assay with TAK-599 in Rats (PPI-0903/00019)

Micronucleus Assay with TAK-599 in Mice (PPI-0903/00024)

In Vivo/In Vitro Unscheduled DNA Synthesis (UDS) Assay with TAK-599 in Rat Hepatocytes and Amendment 1 (PPI-0903/00025 and 00025.001)

Range-Finding Study for Effects of TAK-599 on Embryo-Fetal Development in Rats (non-GLP) (PPI-0903/00016)

Range-Finding Study for the Effects of TAK-599 on Embryo-Fetal Development in Rabbits (PPI-0903/00011)

Local Tolerance Study of Intravenously Injected TAK-599 in Rabbits (TAK-599/000890)

Antigenicity Study of TAK-599 in Guinea Pigs and Amendment 1 (PPI-0903/00020 and 00020.001)

In Vitro Compatibility Study of TAK-599 Using Human Blood (TAK-599/00090)

N-008:

PPI-0903: An Intravenous Injection Teratology Study in the Rat (Study No. P0903-T-040)

Intravenous Developmental Toxicity Study of PPI-0903 API in Rabbits (Study No. P0903-T-041)

N-038:

Plasma Protein Binding by Ultrafiltration in 4 Species (Study No. P0903-P001)

In Vitro Metabolic Stability (Study No. P0903-P-002)

Plasma Protein Binding by Ultrafiltration in Human Plasma for PPI-0903M (Study No. P0903-P-003)

N-041:

In Vitro Mammalian Chromosome Aberration Test (Study No. P0903-T-03)

In Vitro Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay) (Study No. P0903-T-42)

N-047:

Pharmacokinetics of Ceftaroline after Intramuscular (IM) Administration in the Rabbit. Comparison with a Very Short IV Bolus (Study No. P0903-P-005)

N-049:

Penetration of Ceftaroline into Lung Tissues after IV Administration in the Rabbit. Measurement of Plasma and Lung Tissue Concentrations (P-0903-P-004)

N-067:

A 13 Week Intravenous Toxicity Study in Rats Followed by a 4-Week Recovery Period (P0903-T-010)

A 13 Week Intravenous Toxicity Study in Monkeys Followed by a 4-Week Recovery Period (P0903-T-011)

PPI-0903: Study of Fertility and Early Embryonic Development to Implantation in Rats (P0903-T-012)

PPI-0903: Study for Toxic Effects on Pre- and Postnatal Development, including Maternal Function in Rats (P0903-T-013)

N-083:

Evaluation of the Effects of PPI-0903 (ceftaroline fosamil [prodrug]) on hERG Using HEK293 Transfected Cells AND Evaluation of the Effects of PPI-0903M (ceftaroline [active metabolite]) on hERG Using HEK293 Transfected Cells (Study No. P903-T-014)

Ceftaroline Acetate: A Comparison Pharmacokinetic Study in Male Sprague Dawley Rats Following a Single Intramuscular or Intravenous Injection (Study No. P0903-P006)

Ceftaroline Acetate: A Comparison Pharmacokinetic Study in Female New Zealand White Rabbits Following a Single Intramuscular or Intravenous Injection (Study No. P0903-P007)

Ceftaroline Acetate: A Comparison Pharmacokinetic Study in Cynomolgus Monkeys Following a Single Intramuscular or Intravenous Injection (Study No. P0903-P008)

N-090:

PPI-0903: A Single-Dose Intravenous Irritation Study in New Zealand White Rabbits (Study No. P0903-T-015)

SDN-324:

In Vitro Evaluation of Ceftaroline Fosamil, Ceftaroline, and Ceftaroline M-1 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes (Study No. CEF-PK-01; XT083061)

SND-325 and SND-341 (same final report submitted twice):

L-Arginine with (b) (4) 4-Week Intravenous Toxicity Study in Femoral-Cannulated Rats (CEF-TX-11)

SDN-328:

Ceftaroline for Injection: A Local Intramuscular Tolerance Study in New Zealand White Rabbits (Study No. P0903-T-016)

SDN-348:

Ceftaroline: An Intravenous Dose Range Finding Juvenile Toxicity Study in Rats (CPT-TX-03)

SDN-365:

Ceftaroline Fosamil (PPI-0903): An Intravenous Toxicokinetic Bridging Study in Pregnant Rats (Study No. CEF-TX-10)

Ceftaroline Fosamil (PPI-0903): An Intravenous Toxicokinetic Bridging Study in Pregnant Rabbits (Study No. CEF-TX-14)

4 Pharmacology

4.1 Primary Pharmacology

Antimicrobial activity due to inhibition of peptidoglycan biosynthesis via PBP binding and inactivation- interferes with bacterial cell wall synthesis.

4.2 Secondary Pharmacology

N/A

4.3 Safety Pharmacology

Neurological effects: During the Irwin test, a 2000 mg/kg dose of ceftaroline fosamil caused seizures in rats, but doses ≤497 mg/kg did not. Doses ≥200 mg/kg potentiated pentylenetetrazole-induced seizures, but a 100 mg/kg dose did not. However, in a

pulmonary safety pharmacology study, convulsions were observed in rats that received ≥200 mg/kg of ceftaroline fosamil. It is possible that the stress of being placed in plethysmography chambers caused the rats to be more sensitive to the proconvulsant effects of ceftaroline.

Cardiovascular effects: Ceftaroline fosamil and its primary active metabolite ceftaroline (dephosphorylated parent) did not demonstrate any potential for inhibiting cardiac potassium or sodium channels in isolated canine cardiac Purkinje fibers at concentrations up to 100 or 300 µmol/L, respectively. Ceftaroline fosamil did not have any effect on the hERG current in HEK293 cells at concentrations up to 1070 µg/ml. Active ceftaroline (dephosphorylated parent) concentrations ≥ 800 µg/ml caused statistically significant inhibition of the hERG current. The investigators estimated that the IC_{50} for I_{Kr} current inhibition is approximately 656 µg/ml for active ceftaroline. This IC_{50} value is relatively high, thus, the potential of ceftaroline to cause hERG current inhibition is unlikely to be clinically relevant. The monkey study discussed below supports this likelihood. In addition, a thorough QT study conducted in human volunteers using supratherapeutic doses of ceftaroline fosamil revealed no evidence of compound-induced QT prolongation (see the Clinical Safety review by Dr. Ariel Porcalla and the Clinical Pharmacology review by Dr. Eileen Kim).

Mean arterial blood pressure and mean heart rate of male cynomolgus monkeys were not affected by ceftaroline fosamil. The QT interval (absolute or corrected) was not affected by drug treatment, nor were the PR interval and QRS duration. Brief runs of ventricular tachycardia were seen in 2 monkeys following the 400 mg/kg dose of ceftaroline fosamil, but premature ventricular contractions had been observed in both of these monkeys following vehicle administration. Additionally, PK studies in rats with radiolabeled ceftaroline fosamil suggest that the levels of drug/active metabolite in cardiac tissue are unlikely to have been at their maximal concentration at the time when the runs of ventricular tachycardia occurred (monkey tissue PK studies were not performed). Thus, it is difficult to determine whether the observations following the 400 mg/kg dose are related to drug. No other changes in ECG waveforms appeared to be associated with drug. Additionally, in the repeat dose 4 week monkey study, no drug-related changes in ECG were noted at doses ≤400 mg/kg.

Pulmonary effects: No effects at ceftaroline fosamil doses ≤60 mg/kg. A dose of 200 mg/kg transiently increased respiratory rate and decreased tidal volume, but had no effect on minute volume.

Renal effects: Increased urine production (cloudy, yellow) was seen following a 2000 mg/kg dose of ceftaroline fosamil in rats during the Irwin test and following a 120 mg/kg dose in cynomolgus monkeys during a cardiovascular safety study. Urinary precipitate was observed in the monkeys following a 400 mg/kg dose.

A safety pharmacology study conducted in rats that was submitted for this first time in this NDA (Effects of TAK-599 on Water and Electrolyte Excretions in Rats; Study No. B040245) showed that IV administration of single ceftaroline fosamil doses up to 600 mg/kg did not have any effect on the urinary excretion of Na^+, K^+, or Cl^- in saline-loaded

rats compared to its vehicle(normal saline plus 21.7 mg/ml sodium bicarbonate, which increased excretion of Na^+ by itself, compared to a saline control). The positive control, hydrochlorothiazide, increased urine volume and urinary excretion of all 3 ions.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The prodrug ceftaroline fosamil (also known as ceftaroline acetate, TAK-599, and PPI-0903) is rapidly dephosphorylated in plasma to its active metabolite ceftaroline (also called T-91825) in both rats and monkeys. There is significant distribution of ceftaroline to the kidneys, skin, and lungs of rats. In vitro studies suggested that ceftaroline is not extensively bound to plasma proteins (< 40%) in mice, rabbits, monkeys, or humans. The primary route of elimination for ceftaroline in rats and monkeys is the kidney, although fecal elimination is also observed. Some ceftaroline undergoes metabolism to an open β-lactam ring form (also called ceftaroline M-1), but the majority appears to be excreted unchanged in the urine. Data with radiolabeled ceftaroline fosamil suggests that there are some other minor metabolites, but these were not identified. Of a radiolabeled dose of ceftaroline fosamil, about 90% of the administered radiolabel was recovered in the urine of rats and 10% in the feces; these percentages in monkeys were 54% in urine plus cage rinse and 23% in feces.

Data submitted from animal studies and *in vitro* experiments with CYPs from various species (including humans), suggest that neither ceftaroline fosamil nor its active metabolite ceftaroline undergoes significant hepatic microsomal metabolism, so they are unlikely to interfere with the hepatic metabolism of other drugs.

An intramuscular administration study in rabbits showed that a significant portion of a ceftaroline fosamil dose was bioavailable via this route, but the sponsor has not pursued this route of administration in the clinic, thus far. Additional studies conducted in rats and monkeys also suggest significant bioavailability following IM administration.

The table below, from the Nonclinical Pharmacokinetics Written Summary in the NDA submission, summarizes the pharmacokinetic parameters of ceftaroline fosamil, active ceftaroline, and the open-ring metabolite M-1 following IV and IM injection to rats, rabbits, and monkeys:

Table 2–2. Mean or Mean ±SD Pharmacokinetic Parameters for Ceftaroline Following Intramuscular or Intravenous Administration of a Single Dose of 20 mg/kg Ceftaroline Fosamil in Sprague Dawley Rats, Rabbits, and Monkeys

Species	*Route*	*Analyte*	*C_{max}, ng/mL*	*T_{max}, h*	*$T_{½}$, h*	*$AUC_{0-\infty}$, ng • h/mL*	*CL mL/ min/kg*	*V_{ss}, mL/kg*	*Study No.*
SD rat	IM	Ceftaroline fosamil	4330	0.083	0.436	2300	NC	NC	P0903-P-006
		Ceftaroline	25500	0.5	0.621	37400	NC	NC	
		Ceftaroline M-1	10400	0.5	0.880	21600	NC	NC	
	IV	Ceftaroline fosamil	1172	0.083	0.349	355	940	6970	
		Ceftaroline	27133	0.083	0.426	16300	NC	NC	
		Ceftaroline M-1	21867	0.083	0.911	20800	NC	NC	
Rabbit	IM	Ceftaroline fosamil	10500 ± 5180	0.271 ± 0.172	0.698 ± 0.19	9350 ± 418	NC	NC	P0903-P-007
		Ceftaroline	25800 ± 11600	0.438 ± 0.125	0.833 ± 0.18	39700 ± 11400	NC	NC	
		Ceftaroline M-1	14900 ± 2210	1.88 ± 0.25	1.01 ± 0.23	48100 ± 2900	NC	NC	
	IV	Ceftaroline fosamil	NC	NC	0.42 ± 0.24	7960 ± 3080	47.2 ± 17.4	290 ± 170	
		Ceftaroline	67800 ± 3770	0.083 ± 0.0	0.410 ± 0.007	37000 ± 7840	NC	NC	
		Ceftaroline M-1	35800 ± 45300	1.0 ± 0.41	0.772 ± 0.04	14000 ±15500	NC	NC	
Monkey	IM	Ceftaroline fosamil	2340 ± 665	0.083 ± 0.0	1.22 ± 0.568	2340 ± 815	NC	NC	P0903-P-008
		Ceftaroline	25600 ± 7820	0.5 ± 0.0	1.17 ± 0.152	72100 ± 21400	NC	NC	
		Ceftaroline M-1	2380 ± 941	1.75 ± 0.289	2.34 ± 0.449	12500 ± 4140	NC	NC	
	IV	Ceftaroline fosamil	NC	NC	0.157 ± 0.096	1790 ± 1120	297 ± 255	988 ± 814	
		Ceftaroline	69100 ± 12800	0.083 ± 0.0	1.16 ± 0.068	64000 ± 12100	NC	NC	
		Ceftaroline M-1	4550 ± 944	0.187 ± 0.209	1.87 ± 0.212	12000 ± 2040	NC	NC	

$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time zero to infinity; Cl = clearance; C_{max} = maximum plasma drug concentration; IM = intramuscular; IV = intravenous; NC = not calculated; $T_{½}$ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration; V_{SS} = apparent volume of distribution at steady state.

The following PK studies were submitted for the first time with the NDA:

Mass Balance and Metabolism of Ceftaroline Prodrug in the Sprague-Dawley Rat Following a Single Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-01; 1281-004), conducted by (b) (4)

Summary: Male Sprague-Dawley rats received a single IV injection of [^{14}C]-ceftaroline fosamil (average dose 26.7 mg/kg, 77.8 µCi/kg). Three rats were placed in metabolism cages for collection of urine and feces (collection intervals were 0-8, 8-24, 24-48, and 48-72 hours after dosing) and blood samples were drawn prior to sacrifice 72 hours after dosing. Samples of the carcasses of these animals were collected for measurement of radiolabel. The remaining animals were sacrificed 1, 8, 24, 48, and 72 hours after administration of drug. Blood was collected at these times and, in addition, blood samples were also collected 5 minutes after dosing from the animals scheduled for the 1 hour sacrifice. Liquid scintillation counting was used to measure the amount of radiolabel in samples of blood, plasma, carcass, excreta, and cage rinse/wash. HPLC and mass spectrometry were used to determine the identities of radiolabeled compounds in significant peaks of radioactivity detected in the excreta. In the rats that were assigned to the mass/balance part of the study, approximately 100% of the administered dose was recovered, 99% within the first 24 hours. Most of the radiolabel (~90%) was excreted in the urine, the majority as ceftaroline (60% of administered dose) and a lesser amount (~7 % of administered dose) as the open-ring metabolite M-1. Of the ~10% of the dose excreted in the feces, some was ceftaroline and open-ring metabolite, but the remainder consisted of 2 other minor metabolites of ceftaroline that were not specifically identified as neither exceeded 7% of the administered dose. Blood samples from the rats that were assigned to the kinetic portion of the study showed that levels of radioactivity were approximately twice as high in plasma as in whole blood. The mean levels of radioactivity in the plasma declined quickly between 5 minutes and 8 hours after dosing, then fell more slowly after that. PK parameters were estimated as $AUC_{0\text{-}72}$ = 280 hr•µg-eq/g, $AUC_{0\text{-}\infty}$ = 340 hr•µg-eq/g, and C_0 = 155 µg-eq/g, with an apparent terminal half-life of 51.3 hr.

Mass Balance and Metabolism of Ceftaroline Prodrug in the Cynomolgus Monkey After a Single Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-02; 1281-005), conducted by (b) (4)

Summary: Three male cynomolgus monkeys received a single IV injection of [^{14}C]-ceftaroline fosamil (average dose 9.24 mg/kg, 10.2 µCi/kg). Urine and feces were collected 0-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours after dosing. Blood samples were collected 5 and 30 minutes and 1, 3, 6, 24, 48, and 96 hours after dosing. HPLC and mass spectrometry were used to determine the identities of radiolabeled compounds in significant peaks of radioactivity detected in the plasma and excreta. Mean recovery of administered radioactivity was 81.5 $\pm$ 4.9%. Most of the radiolabel was excreted in the urine. About 28.5% of administered radioactivity was recovered in urine and 25.3% was recovered in the cage rinse. Feces accounted for 22.5% of the radioactive dose and cage wash/wipe for another 3.5%. The urine and

cage rinse together contained ceftaroline accounting for 13.3% of the dose of radiolabel. The open ring metabolite M-1 was also found in the urine and accounted for another 5.7% of the administered dose. Ceftaroline fosamil at a level equivalent to about 1% of the administered radioactive dose was found in the urine as well. Three additional peaks not exceeding 6.2% of the dose were observed in the urine, but their structures were not elucidated as they were considered to be minor metabolites. The feces contained ceftaroline fosamil, ceftaroline, and M-1 each at levels 0.2-0.3% of the administered radioactive dose. Two additional peaks accounting for the remainder of the radiolabel detected in the feces did not exceed 8.4% of the radioactive dose and they were not identified specifically, but considered minor metabolites of ceftaroline. In the plasma, ceftaroline fosamil was rapidly converted to ceftaroline and the open ring metabolite M-1 was also detected, as were 3 minor metabolites that were not elucidated. PK parameters of radiolabel were estimated as AUC_{0-96} = 197 hr•µg-eq/g, $AUC_{0-\infty}$ = 508 hr•µg-eq/g, and C_0 = 48.4 µg-eq/g, with an apparent terminal half-life of 167 hr.

Tissue Distribution in Rats Following Intravenous Administration of [14C] Ceftaroline Fosamil (CEF-TX-05; 6277-198), conducted by **(b) (4)**

Summary: Male Long-Evans rats (a pigmented species) received a single IV 10 mg/kg dose of [^{14}C]-ceftaroline fosamil (specific activity 5.06 µCi/mg). Three animals per time point were sacrificed 5 minutes, 8, 72, 168, and 336 hours after dosing. Blood (whole and plasma), eyes, and pigmented skin were collected from each rat and analyzed for radioactivity by liquid scintillation counting. Radioactivity in blood, plasma, and skin were measurable at all time points, but levels in the eyes could be quantified only through the 8 hour time point. Nonpigmented skin was not collected, so it is not known whether there would have be a difference in the level of radioactivity between the two. The data from the eyes suggest that ceftaroline does not bind irreversibly to melanin because if it did, it would have been associated with the uveal tract of the eye.

From the Study Report:

Estimated pharmacokinetics parameters used to calculate radiation absorbed from selected tissues after a single intravenous administration of [^{14}C] ceftaroline fosamil (10 mg/kg)

Matrix	AUC_{0-t} (ng-eq·hr/g)	$AUC_{0-\infty}$ (ng-eq·hr/g)	C_{max} (ng-eq/g)	T_{max} (hr)	Half-Life (hr)	xy corr coefficient (Terminal Phase)	Dose Exposure (µCi·Hr)	Radiation Absorbed Dose (mRad or mrem)[b]
Blood	143142	144502	24700	0.083	71.4	0.998	98.2	1.85
Eyes (both)[a]	14155	14323	3460	0.083	1.46	1.000	0.130	0.911
Plasma	230520	230716	41200	0.083	41.0	0.995	69.9	2.29
Skin (pigmented dorsal, shaved)	109657	134186	13600	0.083	213	0.998	308	9.79

eq Equivalents.
a $t_{½}$ was calculated using only two time points.
b Calculated for a 100-µCi dose for [^{14}C] ceftaroline fosamil.

5.2 Toxicokinetics

Toxicokinetic reports were included with the majority of the repeat dose toxicity studies conducted with ceftaroline fosamil. They showed that the animals in those studies were exposed to active ceftaroline and demonstrated that accumulation of this active moiety did not occur. At most, there may have been slight accumulation of the inactive open ring metabolite M-1. There were no significant gender differences in TK parameters.

6 General Toxicology

6.1 Single-Dose Toxicity

The acute lethal dose of TAK-599 in rats is higher than 2000 mg/kg, the largest dose tested. The NOAEL was 500 mg/kg; cloudy urine was observed in a few animals at this dose. Crystalluria was observed at 1000 and 2000 mg/kg and some animals in these groups were prone for a time after dosing. Tonic/clonic convulsions occurred in one high dose female. Rats recovered from these clinical signs of toxicity within 24 hours of dosing (within 2 hours for all non-urinary signs).

Ascending doses of TAK-599 up to 2000 mg/kg did not cause mortality in monkeys. The NOAEL was 20 mg/kg; no clinical signs were observed at this dose. Cloudy urine was observed in all animals following 200 and 2000 mg/kg doses. Vomiting was observed in 3/4 monkeys at 200 mg/kg and mydriasis was seen in 2/4; both resolved within 5 hours of dosing. These signs were seen in all high dose animals and generally took longer to resolve. Additional clinical signs seen in some monkeys after the 2000 mg/kg dose included reduced motor activity and paleness. There was a dose-related transient drop in body temperature at the mid and high doses of TAK-599 and the high dose was also associated with a transient 40% drop in heart rate.

6.2 Repeat-Dose Toxicity

Studies conducted in rats and monkeys showed that the primary target organs of toxicity for intravenous ceftaroline fosamil were the kidney and CNS, consistent with other cephalosporins. High doses of ceftaroline fosamil (1000 mg/kg, rat; 400 mg/kg, cynomolgus monkey) were associated with tonic/clonic convulsions during 4 week studies. Clinical chemistry changes and microscopic evaluation of the kidneys demonstrated renal toxicity in rats at $\geq$ 300 mg/kg and in monkeys at $\geq$ 80 mg/kg when these doses were administered daily for one month. At the same doses of ceftaroline fosamil, hypertrophy of the germinal centers of the spleen was observed in rats and hyperplasia of the lymphoid follicles of the spleen was seen in monkeys. In the high dose monkey group, hyperplasia of mandibular or mesenteric lymph nodes or GALT was also observed in some animals. Reductions in several RBC parameters (RBC number, hematocrit, hemoglobin) were observed in several high dose monkeys and as this observation might have be related to immune complex formation, Coombs tests were conducted in some Phase 2 clinical trials.

Splenic and lymphoid changes were not observed in 13-week studies in rats and monkeys where the highest doses administered were 270 and 64 mg/kg/day, respectively, and no signs of anemia were observed in the monkeys. There were no drug-related histopathologic findings in the monkeys at 64 mg/kg in the longer study; a single death (moribund sacrifice) at this dose was difficult to attribute to ceftaroline, although an association could not be ruled out completely. The animal's moribund condition appeared to be associated with respiratory distress and no other animals in the study demonstrated clinical signs of toxicity. The 13-week rat study confirmed the kidney and CNS to be targets of toxicity for ceftaroline. Treatment-related mortality, clonic convulsions, and kidney changes including granulomas associated with the presence of foreign material and hyperplasia of transitional renal epithelium were observed in rats that received IV doses of 270 mg/kg/day. At 90 mg/kg/day, minimal vacuolation of renal collecting ducts was the predominant microscopic observation, but a granuloma associated with foreign material was seen in the kidney of one animal at this dose level.

Postweanling rats do not appear to be more sensitive to ceftaroline-induced toxicity than adult rats. In a 15-day repeat dose toxicity study, the NOAEL was 270 mg/kg/day in 21 day old pups given IV ceftaroline fosamil. This was the highest dose tested. It is important to note that a full battery of tissues was not collected for histopathology in this juvenile rat study, as the sponsor conducted it as a dose-ranging study.

7 Genetic Toxicology

Genetic toxicity studies were performed *in vitro* with ceftaroline fosamil and active ceftaroline (dephosphorylated), as well as a degradation product, (b) (4).

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Ceftaroline fosamil levels up to 1000 µg/plate (*S. typhimurium* TA 98 and TA 100) or 31.3 µg/plate (*S. typhimurium* TA 1535, TA 1537, and *E. coli* WP2 *uvr*A) were not mutagenic in the Ames assay.

7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Ceftaroline fosamil induced chromosome aberrations in Chinese Hamster lung cells in the absence of S-9 at concentrations $\geq$ 988 µg/ml with a 6 hour incubation and $\geq$ 293 µg/ml with a 24 hour incubation. In the presence of S-9, the assay was negative at concentrations $\leq$ 5000 µg/ml.

In the absence of metabolic activation, ceftaroline (active) induced structural chromosome aberrations in CHO cells at 5000 µg/ml with a 4 hour incubation and 200

µg/ml with a 20 hour incubation. In the presence of S-9, the assay was negative at concentrations ≤ 5000 µg/ml.

(b) (4) did not induce chromosome aberrations in cultured lymphocytes from human peripheral blood at concentrations up to 1250 µg/ml regardless of metabolic activation.

(b) (4): *In Vitro* Mammalian Chromosome Aberration Test (CEF-TX-07)

Study no.:	AC13KK.341.BTL
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/21/08
GLP compliance:	U.S. and OECD
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) Lot No. FMD-CEF-018, 94.8% pure

Key Study Findings

(b) (4) did not induce chromosome aberrations in cultured lymphocytes from human peripheral blood.

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	No S-9, 4 hr: 500, 1000, 1250, 1500, 1750, 2000 µg/ml; 20 hr: 250, 500, 750, 1000, 1250, 1350, 1500 µg/ml + S-9: 500, 1000, 1250, 1350, 1500, 1750 µg/ml The 3 concentrations chosen for evaluation from each treatment group were 500, 1000, and 1250 µg/ml
Basis of concentration selection:	Preliminary cytotoxicity assay with up to 5000 µg/ml; concentrations chosen for definitive assay were based on mitotic index reduction compare to control.
Negative control:	DMSO
Positive controls:	No S-9: Mitomycin C, MMC; 0.3 and 0.6 µg/ml + S-9: Cyclophosphamide; 20 and 40 µg/ml
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were cultured for 4 hours with and without S-9 and for 20 hours without S-9. Each treatment was performed in duplicate. The 4 hour cultures were washed after treatment and incubated for an additional 16 hours in drug-free medium before harvest. Colcemid was added to all cultures 2 hours before harvest. Cells were washed and fixed after harvesting before slides were prepared. Mitotic inhibition was determined for each treatment and 100 metaphase spreads were scored from each of the duplicate treatments whenever possible.

Study Validity

The vehicle control must be within its historical control range for the lab. The percentage of cells with chromosome aberrations in the positive controls should be statistically significantly higher ($p \leq 0.05$ by Fisher's Exact test) than the solvent control.

To be considered a positive response, a test article should show an increase in the percentage of cells with chromosome aberrations statistically higher than the solvent control for at least 1 concentration, following a dose/response. If a value is statistically higher than a positive control, but it is within the historical range for the solvent control, it may not be judged as biologically significant.

The current assay appeared valid.

Results

(b) (4) did not induce chromosome aberrations in the absence or presence of metabolic activation. In the 4 hour incubation without S-9, mitotic inhibition was 51% at the highest concentration evaluated, 1250 µg/ml, compared to the negative control. The percentage of cells with chromosome aberrations did not exceed those observed in controls. The positive control, MMC, contained about 15% of cells with chromosome aberrations. In the 20 hour incubation without S-9, mitotic inhibition was 54% at the highest concentration evaluated, 1250 µg/ml, compared to the negative control. The percentage of cells with chromosome aberrations did not exceed those observed in controls. The positive control, MMC, contained about 16% of cells with chromosome aberrations.

In the presence of S-9, mitotic inhibition was 63% at the highest concentration evaluated, 1250 µg/ml, compared to the negative control. The percentage of cells with chromosome aberrations did not exceed those observed in controls. The positive control, cyclophosphamide, contained about 15% of cells with chromosome aberrations.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Doses of ceftaroline fosamil up to 2000 mg/kg did not induce the formation of micronucleated erythrocytes in male rats or mice after intravenous administration.

7.4 Other Genetic Toxicity Studies

Ceftaroline fosamil and (b) (4) were not genotoxic to L5178Y (TK +/-) mouse lymphoma cells at concentrations up to 5000 µg/ml ± S-9.

Ceftaroline (active) did not induce mutations at the HGPRT locus in CHO cells regardless of metabolic activation at concentrations up to 1505 µg/ml.

Ceftaroline fosamil did not induce unscheduled DNA synthesis in hepatocytes from male rats 2 or 16 hours after intravenous administration of 2000 or 1000 mg/kg, respectively.

(b) (4) *In Vitro* Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay) (CEF-TX-06)

Study no.:	AC13KK.704.BTL
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/16/08
GLP compliance:	U.S. GLP
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) Lot No. FMD-CEF-018, 94.8% pure

Key Study Findings

(b) (4) did not induce mutations in L5178Y mouse lymphoma cells.

Methods

Cell line:	L5178Y/TK+/- Mouse Lymphoma cells
Concentrations in definitive study:	4 hr exposure: 237-1420 µg/mL 24 hr exposure: 4.7 to 237 µg/mL Concentrations chosen for cloning should generally have ≥ 20% total relative growth compared to controls, with a high concentration having ≥10%, but ≤ 20%
Basis of concentration selection:	Preliminary cytotoxicity assay with concentrations 0.474-3320 µg/mL; concentrations chosen for definitive assay were based on growth of treated cells compared to controls
Negative control:	DMSO
Positive controls:	No S-9: Methyl methanesulfonate (MMS), 4-hour exposure: 15 and 20 µg/mL; 24-hour exposure: 5 and 7.5 µg/mL +S-9: 7,12-Dimethyl-benz(a)anthracene (DMBA), 1.0 and 1.25 µg/mL
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Without S-9, duplicate cultures were treated for 4 and 24 hours. With S-9, duplicate cultures were treated for 4 hours. After incubation with test articles, cells were washed and cultured for 24-48 or 48-72 hours (depending on treatment time) to allow expression of the mutant phenotype. To determine which cells had mutated, cultures were then plated in agar medium in the presence and absence of the selection agent, trifluorothymidine and allowed to incubate for 14 days before colonies were counted and sized.

Study Validity

Negative controls should have spontaneous mutant frequency range of 35-140 per 10^6 surviving cells (lower frequencies 20-34 are acceptable if small colonies are recovered). Average cloning efficiency of negative controls should be 65-120% and total suspension growth should be 8-32% for the 4 hour exposure and 20-180% for the 24 hour exposure.

For the positive controls, at least one dose should demonstrate a positive response with mutation frequencies of ≥ 300 X 10^{-6} when 40% of colonies are small and ≥ 150 X 10^{-6} if only small colonies are recovered.

For the test article, the highest concentration should generally exhibit 80-90% toxicity (10-20% relative growth), though if the toxicity curve is steep, this may be modified.

The current study met these criteria and was considered valid. The mutation frequencies of MMS were 315 and 641 X 10^{-6} at 4 hours and 422 and 635 X 10^{-6} at 24 hours. The mutation frequencies of DMBA were 332 and 350 X 10^{-6}. Adequate colony sizing was demonstrated.

Results

For the 4 hour treatments with (b) (4) (both ± S-9), the cultures chosen for cloning were 664, 758, 853, 948, and 1190 µg/mL. Relative suspension growth was 79-94% in the absence of S-9 and 47-79% in its presence. Mutation frequency of cultures treated with (b) (4) (32-54 X 10^{-6} no S-9; 50-81 with S-9) were not higher than negative controls (25-27 no S-9; 50-55 with S-9) regardless of S-9 activation. Total growth in selection medium was 63-95% without S-9 and 46-71% with S-9.

For the 24 hour treatment with (b) (4) in the absence of metabolic activation, the cultures chosen for cloning were 9.5, 14, 24, 33, and 47 µg/mL (relative suspension growth 11-109%). Mutation frequency of the cultures treated with (b) (4) (21-58 X 10^{-6}) were not higher than controls (27-35 X 10^{-6}). Total growth in the selection medium was 5-122%. The culture (one of the duplicates at the highest concentration) that had less than 10% total growth was not assessed for mutation frequency.

8 Carcinogenicity

Not necessary for this product.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Ceftaroline fosamil doses of 50, 150, or 450 mg/kg did not affect the fertility or mating performance of male or female rats, although the high dose was associated with signs of clinical toxicity including clonic convulsions and mortality in this study. The high dose has been better tolerated in other rat studies; it was not clear as to why the dams in this study were much more sensitive. Toxicokinetics were not performed as part of this study; they may have provided some relevant information regarding increased sensitivity. Sperm evaluation did not reveal drug-related changes in their concentration, motility, or morphology.

9.2 Embryonic Fetal Development

Daily IV doses of ceftaroline fosamil up to 300 mg/kg given to pregnant rats on GD 6-17 did not cause developmental toxicity. Although maternal toxicity was not observed in this study, the high dose has been associated with renal toxicity in previous rat studies, so it was considered adequate by the pharmacology reviewer.

Daily IV 25, 50 and 100 mg/kg doses of ceftaroline fosamil given to pregnant rabbits on GD 7-19 caused dose-related changes in fecal output (soft, liquid, or nonexistent) likely associated with the antimicrobial activity of the drug. Feed consumption was reduced during the treatment period at 50 and 100 mg/kg/day, accompanied by reduced body weight gain at the high dose. Maternal mortality occurred at 100 mg/kg/day and spontaneous abortions were seen at 50 and 100 mg/kg/day. Such events are not uncommon in pregnant rabbits treated with antibacterial drug products. At 50 and 100 mg/kg/day, the litter incidence of the common skeletal variation angulated hyoid alae was increased, but there was no increased incidence of external or visceral variations or malformations.

9.3 Prenatal and Postnatal Development

Doses of ceftaroline fosamil of 50, 150, or 450 mg/kg administered IV to rat dams from GD 6 to LD 20 had no effect on pre- or postnatal development of their offspring. The dosed dams did not experience signs of clinical toxicity or difficult parturition and maternal behavior was not affected. The F_1 rats did not show signs of toxicity. Their survival and body weight gain were comparable to controls, they attained developmental landmarks at approximately the same rate as controls, and they did not appear to have altered behavior or learning/memory difficulties. The F_1 rats were fertile and the uterine contents of the females appeared normal at the time of their sacrifice on GD 13.

10 Special Toxicology Studies

Local tolerance studies showed that ceftaroline fosamil in a vehicle containing L-arginine in normal saline did not cause excessive irritation or inflammation when injected into the rabbit ear vein or when injected intramuscularly to these animals.

In vitro studies demonstrated hemocompatibility of ceftaroline fosamil in its clinical vehicle.

Ceftaroline fosamil does not appear to be highly antigenic when administered intravenously, but it was not devoid of antigenic potential in guinea pigs when combined with Freund's complete adjuvant and sensitizing doses were given subcutaneously. Antibodies were detected in the serum of 2/6 animals using a passive cutaneous anaphylaxis test when recipients were intradermally injected with serum from

subcutaneously sensitized donors. However, no signs of active systemic anaphylaxis were observed when the SC-sensitized animals were challenged with an IV dose of ceftaroline fosamil. Additionally, ceftaroline fosamil was not antigenic in guinea pigs when administered IV daily for one month at 200 mg/kg. The antigenic potential of cephalosporins in the human population is well known.

11 Integrated Summary and Safety Evaluation

Following IV administration, the prodrug ceftaroline fosamil is quickly dephosphorylated in plasma to its active form, which is rapidly distributed to tissues. Significant levels of a metabolite (open β-lactam ring) of the active form, M-1, are also detected in plasma from animals in repeat dose toxicity tests. The primary route of excretion for ceftaroline is renal, with some fecal excretion also observed. In rats, about 90% of IV-administered radiolabel was recovered in the urine and 10% in the feces. In monkeys, 54% IV-administered of radiolabel was recovered in urine plus cage rinse and 23% in feces. Most urinary radioactivity appeared to be associated with the active (dephosphorylated) form of ceftaroline, but M-1 was also detected in the excreta along with 2-3 minor metabolites.

In repeat dose toxicity studies conducted in rats and monkeys, the primary target organs of toxicity for intravenous ceftaroline fosamil were the kidneys and CNS, consistent with other cephalosporins. High doses of ceftaroline (1000 mg/kg, rat; 400 mg/kg, cynomolgus monkey) were associated with tonic/clonic convulsions during 4 week studies. This high dose in rats provided a Cmax over 40 times greater than the average observed in humans receiving the recommended clinical dose and the high dose in monkeys provides a Cmax about 6-fold higher than the human average.

Renal toxicity was seen in rats and monkeys in a 4-week toxicity studies, as were splenic and lymphoid changes. The 13-week study in rats confirmed the kidneys and CNS as target organs of toxicity in this species. Splenic and/or lymphoid changes were not observed during the 13 week studies in either rats or monkeys where the highest doses administered were 270 and 64 mg/kg/day, respectively. There were no drug-related histopathologic findings (including renal) in the monkeys at 64 mg/kg in the longer study; a single death (moribund sacrifice) at this dose was difficult to attribute to ceftaroline. The animal's moribund condition appeared to be associated with respiratory distress and no other animals in the study demonstrated clinical signs of toxicity. An association to drug could not be ruled out completely, so the mid dose of 32 mg/kg was considered the NOAEL. Exposure comparisons between rats and monkeys at the NOAELs in these repeat dose toxicity studies and humans receiving the recommended clinical dose of 600 mg every 12 hours can be found in the table at the end of this section.

Reproductive or developmental toxicity does not appear to be of great concern following ceftaroline exposure. IV ceftaroline fosamil doses up to 450 mg/kg/day did not cause impairment of fertility in adult male or female rats. The same dose did not appear toxic to rat pups exposed *in utero* from GD 6 through lactation. Survival and body weight gain of F_1 pups from dams that received ceftaroline fosamil were comparable to controls and the ceftaroline-exposed groups attained developmental landmarks at approximately the same rate as controls. Their behavior, motor activity, learning, and

reproductive capacity did not appear different from controls. Daily IV doses of ceftaroline fosamil up to 300 mg/kg given to pregnant rats on GD 6-17 did not cause developmental toxicity to their offspring. Ceftaroline exposure (based on AUC) in pregnant rats at 300 mg/kg was about 8-fold higher than seen in humans at the recommended clinical dose. Daily 25, 50 and 100 mg/kg doses of ceftaroline fosamil given to pregnant rabbits on GD 7-19 were associated with dose-related GI disturbances common in pregnant rabbits treated with antibacterial drug products. These effects appeared related to maternal mortality at 100 mg/kg/day and spontaneous abortions at 50 and 100 mg/kg/day. At 50 and 100 mg/kg/day, the litter incidence of the common skeletal variation angulated hyoid alae was increased, but there was no increased incidence of external or visceral variations or malformations at these doses. Ceftaroline exposure (based on AUC) in pregnant does was approximately 0.8 times the human exposure at the recommended clinical dose at 25 mg/kg and about 1.5 times human exposure at 50 mg/kg.

A 15-day dose ranging toxicity study in juvenile rats suggests that ceftaroline fosamil is not more toxic to a young animal than to adults of the same species.

The genotoxic potential of ceftaroline fosamil and ceftaroline (active, dephosphorylated form) appears low and is not a clinical concern, especially for a product that will be used short-term. Ceftaroline fosamil was negative in the Ames bacterial reverse mutation assay and mouse lymphoma assay. Ceftaroline fosamil and its dephosphorylated active form induced chromosome aberrations in Chinese hamster lung cells and Chinese hamster ovary cells, respectively, in the absence of metabolic activation, but not in the presence of hepatic microsomal enzymes derived from rats. Ceftaroline (active) did not induce mutations at the HGPRT locus of Chinese hamster ovary cells. Ceftaroline fosamil doses of up to 2000 mg/kg (given IV) did not induce the formation of micronucleated erythrocytes in male rats or mice and it did not induce unscheduled DNA synthesis in rat hepatocytes.

The table below, from the NDA submission, summarizes the TK data from several repeat dose animal toxicology studies and provides exposure comparisons between the NOAEL dose in animals and a standard clinical dose in humans. It should be noted that although no malformations were observed at the 100 mg/kg dose in the rabbit developmental toxicity, there was significant maternal toxicity at this dose and an increased incidence of a common skeletal variation (angulated hyoid alae) was observed at both 50 and 100 mg/kg. The exposure margins for ceftaroline between humans given the standard clinical dose of the drug and the NOAEL in animals are in line with those commonly observed for antimicrobial products. Ceftaroline fosamil appears to be reasonably safe for its intended clinical use as described in the package insert and the pharmacologist has no objection to the approval of this NDA.

Table 5–1. Summary of Ceftaroline Animal to Human Margins of Exposure

IV Toxicity Study	*Animal NOAEL (mg/kg)*	*Animal C_{max} (ng/mL)[b]*	*Animal AUC (ng•h/mL)[b]*	*Human Exposure Margins At 600 mg BID[a]*	
				C_{max} Margin	*AUC Margin*
28-day repeat dose study in rats	100	247300	124500	12	2
28-day repeat dose study in monkeys	16	21150	41550	1	~1
13-week-day repeat dose study in rats	30	75500	44550	4	~1
13-week repeat dose study in monkeys	32	32900	42600	~2	~1
Developmental toxicity in rats	300	561000	470000	27	8
Developmental toxicity in rabbits	100	68800	43400	3	~1
Juvenile repeat dose study in rats	270	45000	220000	2	4

a MRHD (600 BID): C_{max} = 21024 ng/mL; AUC = 55694 (ng•h/mL) at steady state MHRD (Study P903-01).

b Toxicokinetic data for the bioactive form of ceftaroline fosamil, ceftaroline, are cited.

AUC = area under the plasma concentration versus time curve; C_{max} = maximum plasma drug concentration; NOAEL = no observed adverse effect level.

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/s/

AMY L ELLIS
10/15/2010

WENDELYN J SCHMIDT
10/15/2010

I agree with Dr. Ellis's conclusions as to the adequacy of the data as well as her evaluations of the non-clinical toxicities.