CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

SUMMARY REVIEW

M E M O R A N D U M

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

DATE: 10-26-10

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

SUBJECT: Deputy Division Director's Summary Review Memo for NDA 200-327, ceftaroline fosamil 400 and 600 mg for injection (Tradename TEFLARO™)

1.0 Background

Ceftaroline fosamil (henceforth referred to as ceftaroline for the purposes of this summary, unless otherwise indicated) is an injectable, synthetic prodrug from the cephalosporin class of β-lactam antibacterial drugs. Its mechanism of action is bactericidal via inhibition of cell wall synthesis by binding to penicillin-binding proteins (PBPs) found in the bacterial cell wall of both Gram-positive and -negative bacteria. In addition, it has activity against methicillin-resistant *Staphylococcus aureus* (MRSA) because it retains high affinity binding against PBP2a that is responsible for the broad spectrum β-lactam resistance seen with MRSA. However, ceftaroline is not active against Gram-negative bacteria that produce β-lactam hydrolyzing enzymes including AmpC, or extended spectrum β-lactamases (ESBLs).

The applicant, Cerexa, a subsidiary of Forest Laboratories, Incorporated, has submitted NDA 200-327 in support of ceftaroline 600 mg injection infused IV every 12 hours for the requested indications of Community Acquired Bacterial Pneumonia (CABP) and complicated skin and skin structure infection (now referred to as Acute Bacterial Skin and Skin Structure Infection, ABSSSI) caused by susceptible isolates of designated organisms. The submission contains the data and results from two Phase 3 trials for each indication, as well as additional clinical pharmacology and Phase 2 trials. This memo will summarize elements of all reviews by discipline; for detailed discussions, please refer to the respective chemistry, manufacturing, and controls (CMC), sterility assurance/product quality microbiology, pharmacology/toxicology, microbiology, clinical, and biometrics reviews, and related consults.

2.0 Chemistry, Manufacturing and Controls

This application is recommended for approval by the CMC reviewer, Dr. Andrew Yu. (b) (4) the drug substance is available as a monohydrate monoacetate. The chemical name is listed as such in USAN. The drug substance is produced by ACS Dobfar under DMF 23167 and the information from the DMF holder concerning impurity levels, specifications and other quality information are acceptable. Ceftaroline fosamil has (b) (4) related impurities that are chemically characterized and controlled by specifications in the DMF and NDA. Three batches of sterile ceftaroline fosamil were submitted with adequate stability data to support the shelf life proposed of 24 months stored under refrigerated conditions. The drug substance (b) (4) is stable stored in the recommended vial.

The drug product consists of ceftaroline fosamil formulated with (b) (4) arginine and is supplied in single-use, clear glass vials containing either 400 mg or 600 mg of sterile ceftaroline fosamil. As the drug product (b) (4) it must be stored under refrigeration. The drug product is (b) (4) and packaged by Facta Farmaceutica in Italy. (b) (4) arginine is supplied by (b) (4), which is adequate for sterility and quality. The DMFs for the container components are also adequate. There were two manufacturing issues identified during the review regarding possible drug degradation (b) (4), and (b) (4) ; however, the applicant has adequately addressed these issues. The applicant provided data that adequate measures to protect against drug degradation due to (b) (4) were being taken. They will study another three batches of each strength to assure adequate (b) (4) and report the (b) (4) results to the FDA in annual reports. The drug product specifications for the appearance, potency, uniformity, individual and total impurities, moisture, pH, endotoxin, sterility, particulate matter are acceptable. The shelf life of 24 months for both strengths is also acceptable. Compatibility data with infusion in normal saline, D5W, and Lactated Ringers' is acceptable. (b) (4) .

The drug product should be constituted by addition of 20 mL of Water for Injection, USP. The entire volume must be further diluted in $\geq$ 250 mL before infusion. The solution should be administered over approximately 1 hour. The constituted solution should be used within six hours when stored at room temperature or within 24 hours when stored under refrigeration at 2 to 8° C.

Dr. Yu determined that from the CMC perspective, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. Acceptable site recommendations from the Office of Compliance for both ACS Dobfar and Facta Farmaceutica have been made. Therefore, Dr. Yu recommends approval of this application.

3.0 Summary of Product Quality Microbiology

The product quality/sterility assurance review was conducted by Dr. Vinayak Pawar and the application has been recommended for approval. The critical steps in the manufacturing process of the drug substance are identified as (b) (4) The applicant reports that the microbial contamination level, where (b) (4) is performed, meets Grade A, ISO5, or Class 100 requirements. The DMF for the (b) (4) processes at ACS Dobfar was reviewed and found adequate. The ACS Dobfar facility has been approved for manufacturing sterile drug substance (b) (4) Intermediate drug bulk product is manufactured at (b) (4) and the process consists of (b) (4) (b) (4). Final drug product is manufactured at Facta and consists of filling the vials with the intermediate bulk (b) (4) to produce the finished product for injection. The finished drug product is filled in vials (b) (4) The (b) (4) stoppers are purchased from (b) (4) and sterilized by means of a (b) (4) process. All components used for finished product manufacturing are appropriately sterilized. Results of container closure integrity complied with acceptance criteria. The applicant conducted a study of the ceftaroline fosamil for injection 600 mg/vial drug product for microbial ingress for up to thirty-six months and the results were determined to be acceptable.

4.0 Summary of Pharmacology/Toxicology

Based on the review of the nonclinical pharmacology and toxicology information by Dr. Amy Ellis, this application is recommended for approval. Key findings from her review include: 1) ceftaroline did not show evidence of mutagenicity in *in vitro* tests, was clastogenic in the absence of metabolic activation in *in vitro* chromosomal aberration assays but not in the presence of metabolic activation; 2) intravenous ceftaroline had no adverse effects on the fertility of male and female rats given up to 450 mg/kg which is approximately fourfold higher than the maximum recommended human dose based on body surface area; 3) ceftaroline has a nonclinical toxicity profile typical of a cephalosporin antibacterial drug and target organs of toxicity in rats and monkeys that may be clinically relevant include the kidneys and CNS; 4) ceftaroline did not adversely affect pregnancy or peri/postnatal development of offspring when given to rat dams during fetal organogenesis and through lactation and 5) 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 any malformation. Dr. Ellis concurs with the applicant that the pregnancy category

should be B. She received concurrence on her review and conclusions from Dr. Wendelyn Schmidt and Dr. Abigail Jacobs.

5.0 Summary of Clinical Pharmacology

The applicant conducted seven *in vitro* studies to assess protein binding, biotransformation of prodrug in plasma, metabolism in hepatic microsomes, and inhibition/induction of cytochrome P450 isoenzymes, eleven Phase 1 studies evaluating the pharmacokinetics (PK) of ceftaroline and relevant metabolites including single and multidose PK, metabolism and elimination, effect of renal impairment and hemodialysis, age, gender, impact on intestinal microflora and QT prolongation, two supportive Phase 2 trials in skin infections, and four Phase 3 trials (two in pneumonia and two in skin infections). The clinical pharmacology data from these studies were reviewed by Dr. Aryun Kim, and the pharmacometrics data by Dr. Yongheng Zhang. The QT study was reviewed by the Interdisciplinary Review Team for QT Studies.

The recommended dose is 600 mg IV q 12 h for adults $\geq$ 18 years of age for 5-14 days for the treatment of ABSSSI and for 5-7 days for CABP. Some of the key points from the clinical pharmacology and pharmacometrics review include:

- Ceftaroline fosamil prodrug is rapidly converted during IV infusion by *in vivo* phosphatase enzymes to the active ceftaroline. It exhibits linear PK with approximately dose-proportional increase in exposure over the studied single dose range of 50-1000 mg. The β-lactam ring undergoes hydrolysis to form the inactive, open-ring metabolite, ceftaroline M-1.
- The percentage of the dosing interval that free drug concentrations are greater than the MIC for ceftaroline was best associated with the *in vivo* efficacy in a neutropenic murine thigh model against *S. aureus* and *Streptococcus pneumoniae*.
- Exposure-response analysis with population PK models indicated a significant relationship between the %T>MIC and per-patient microbiological response in microbiologically evaluable patients with mono- or polymicrobial *S. aureus* or *Streptococcus pyogenes* skin infections. Unlike for ABSSSI, an exposure-response relationship was not identified for CABP, as a majority of the Phase 3 subjects had a high and limited range of ceftaroline exposure.
- Based on PK/PD target attainment analyses by Monte Carlo simulation, ceftaroline exposures associated with bacteriostasis were predicted to be achieved at MIC $\leq$ 2 mcg/mL against *S. aureus* and at MIC $\leq$ 1 mcg/mL against *S. pneumoniae* for the proposed clinical dose and regimen of ceftaroline 600 mg q 12h.
- Plasma protein binding of ceftaroline is approximately 20% in humans and decreases minimally with increasing concentration. The cytochrome P450 system does not appear to be a significant metabolic pathway for

ceftaroline. Ceftaroline and accompanying metabolites are primarily eliminated through renal excretion.

- The PK of ceftaroline was evaluated in healthy elderly subjects ≥ 65 years of age versus healthy young adults and the results demonstrated that no dose adjustment is necessary based on age. Nor is a dose adjustment necessary based on gender.
- The applicant conducted a single-dose PK study in adolescent subjects (12-17 years of age) and based on these data, it appears that the fixed adult dose of 600 mg would be appropriate for adolescent patients.
- Dose adjustments are recommended for patients with moderate and severe renal impairment, and in patients with ESRD on intermittent HD. These regimens were derived using data from Phase 1 renal impairment studies and will be described in the product labeling.
- *In vitro* studies indicate that ceftaroline is not an inhibitor or inducer of major CYP450 isoenzymes, and thus *in vivo* drug interaction studies are unlikely. In an exploratory population PK analysis of Phase 2/3 patients, no clinically significant differences in ceftaroline C_{max} or AUC_{tau} were observed with concomitant medication use including substrates, inhibitors, or inducers of major CYP450 isoenzymes, anionic or cationic drugs known to undergo active renal secretion, or vasodilator or vasoconstrictor drugs that may alter renal blood flow.
- No significant QT prolongation effect of ceftaroline 1500 mg was detected in the thorough QT study. The largest upper bounds of the two-sided 90% CI for the mean difference between ceftaroline 1500 mg and placebo were below 10 msec. The largest lower bound of the two-sided 90% CI for the ΔΔQTcIb (individual subject correction formula based on the baseline QT-rr slope) for moxifloxacin was greater than 5 msec, and the moxifloxacin profile over time was adequately demonstrated, indicating that assay sensitivity was established.

The conclusions of Drs. Kim and Zhang are that the application is acceptable from a clinical pharmacology perspective and can be approved. There are no recommended Phase 4 commitments.

6.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Dr. Avery Goodwin, has recommended the approval of this application, based on his review of the clinical microbiology data. He has recommended changes to the package insert that have been incorporated by the applicant, and has recommended a post-marketing requirement to monitor for the development of resistance to ceftaroline, which will be incorporated into the action letter. Key findings from his review include:

- Data from large prospective surveillance studies and other investigator studies support the applicant's assertion that ceftaroline demonstrates *in vitro* activity against pathogens associated with ABSSSI and CABP.

Surveillance studies included *S. aureus* from Europe and the USA and isolates that tested positive for the Panton-valentine leukocidin (PVL) gene, heterogenenous vancomycin-intermediate (hVISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), quinupristin/dalfopristin non-susceptible, tetracycline resistant, mupirocin-resistant, linezolid-resistant, daptomycin non-susceptible, and fluoroquinolone-resistant isolates. The MIC_{90} values from these studies ranged from 0.12-2 mcg/mL against all staphylococci tested. Against MRSA, the ceftaroline MIC_{90} was reported to be 1 mcg/mL for US isolates while against coagulase-negative staphylococci, the MIC_{90} values were 0.5 mcg/mL for US isolates and 1 mcg/mL for European isolates.

- Ceftaroline is also active *in vitro* against *S. pneumoniae* with MIC_{90} values ranging from 0.004-0.025 mcg/mL and $\leq$ 0.016 for some β-hemolytic streptococcal isolates. Against viridans streptococci, the MIC_{90} values were 1 mcg/mL.
- For Enterobacteriaceae, the MICs ranged from $\leq$ 0.016 to > 32 mcg/mL. Drastically decreased activity was observed against AmpC and ESBL producers, and ceftazidime non-susceptible Enterobacteriaceae isolates such as *Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Enterobacter cloacae,* and *Enterobacter aerogenes.*
- The applicant submitted data demonstrating the propensity for ceftaroline to induce AmpC, which may complicate its use for treatment of infections caused by members of the Enterobacteriaceae.
- Ceftaroline is expected to have a post-antibiotic effect ranging from 0.8 to 7.2 hours. The duration is species specific and the bactericidal activity was observed at $\geq$ 2X the MIC with bactericidal effects ($\geq$ 3 $\log_{10}$ killing) occurring at 8 to 24 hours.
- No antagonism was demonstrated when ceftaroline was tested and compared with other antimicrobial agents.
- Data from a variety of animal models supports the activity of ceftaroline against Gram-positive and -negative organisms. These animal studies included the mouse neutropenic thigh model, murine subcutaneous infection model, endocarditis infection model, pneumonia infection model, bacteremia infection model, and meningitis infection model.

The following table illustrates the susceptibility interpretive criteria that have been agreed to by the review team and the applicant to be included in the package insert.

Table 1: Susceptibility Interpretive Criteria for Ceftaroline

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
*Staphylococcus aureus (*includes methicillin-resistant isolates - skin isolates only)-See **NOTE** below	≤1[a]	—	—	≥24	—	—
Streptococcus agalactiae [a] (skin isolates only*)*	≤0.03	—	—	≥26	—	—
Streptococcus pyogenes [a] (skin isolates only)	≤0.015	—	—	≥24	—	—
Streptococcus pneumoniae [a] (CABP isolates only)	≤0.25	—	—	≥27	—	—
Haemophilus influenzae (CABP isolates only)	≤0.12	—	—	≥33	—	—
Enterobacteriaceae[b] (CABP and skin isolates)	≤0.5	1	≥2	≥23	20-22	≤19

S = susceptible, I = intermediate, R = resistant

NOTE: Clinical efficacy of Teflaro to treat lower respiratory infections such as community-acquired bacterial pneumonia due to MRSA has not been studied in adequate and well controlled trials (See “Clinical Trials” section 14)

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than “Susceptible” should be submitted to a reference laboratory for further testing.

[b] Clinical efficacy was shown for the following *Enterobacteriaceae: Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.*

7.0 Summary of Clinical Efficacy: CABP

For additional details regarding the efficacy of ceftaroline for CABP, please refer to the biometrics review of Dr. Daniel Rubin and the clinical efficacy review of Dr. Ariel Porcalla. Cerexa submitted two randomized, double-blind, multicenter, multinational, noninferiority trials of subjects for CABP. Subjects enrolled had to have pneumonia as confirmed by chest x-ray, as well as certain signs and symptoms of disease. In addition, the inclusion criteria required subjects to have PORT (Pneumonia Outcomes Research Trial) scores of either III or IV. Subjects with, or likely to be infected with, MRSA were not permitted to be enrolled because the comparator agent ceftriaxone is not active against this organism. The trials were designed to evaluate whether ceftaroline was noninferior to ceftriaxone using an endpoint of clinical cure at the test-of-cure visit with an NI

margin of 10%. However, the applicant did not provide an adequate justification for the margin of 10% for a clinical response endpoint at TOC. Nor has the Agency been able to find adequate historical evidence for the treatment effect of antibacterial drugs using a clinical response endpoint at the test-of-cure visit. However, the review team was able to find historical evidence for the treatment effect of antibacterial drugs on signs and symptoms of pneumonia for a clinical response endpoint on Days 3-5 during the antibacterial treatment course and conducted an analysis accordingly. The validity of this approach has been presented, discussed, and agreed to by the AIDAC in December of 2009. In order to be considered a responder by Day 4, a subject had to meet the criteria for stability as described in the consensus treatment guidelines of the Infectious Disease Society of America and the American Thoracic Society[1]. The subject also had to show improvement from baseline values for at least one of the following four symptoms, with no worsening in any of these symptoms: cough, dyspnea, pleuritic chest pain, and sputum production. The review team's responder analysis included only subjects that had microbiologically confirmed bacterial pneumonia. The results of this analysis are demonstrated in Table 2 below.

Table 2: Response Rates at Study Day 4 (72-96 hours) From Two Phase 3 CABP Trials

	Teflaro n/N (%)	**Ceftriaxone n/N (%)**	**Treatment Difference (2-sided 95% CI)**
CABP Trial 1	48/69 (69.6%)	42/72 (58.3%)	11.2(-4.6,26.5)
CABP Trial 2	58/84(69.0%)	51/83 (61.4%)	7.6 (-6.8,21.8)

The results of this analysis demonstrate the noninferiority of ceftaroline to ceftriaxone when using an NI margin of -10% and numerically favor ceftaroline for both trials.

Although there is no data to support the use of clinical response at test-of-cure (TOC) as a primary endpoint for a noninferiority trial, these endpoints still provide important clinical information regarding the course of pneumonia in patients, and results of these analyses for the clinically evaluable and modified intent-to-treat populations are depicted in Table 3 below.

[1]Mandell LA et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases.* 2007;44:S27-72.

Table 3: Clinical Cure Rates at TOC from Two Phase 3 CABP Trials

	Teflaro n/N (%)	Ceftriaxone n/N (%)	Treatment Difference (2-sided 95% CI)
CABP Trial 1			
CE	194/224 (86.6%)	183/234 (78.2%)	8.4 (1.4, 15.4)
MITTE	244/291 (83.8%)	233/300 (77.7%)	6.2 (-0.2, 12.6)
CABP Trial 2			
CE	191/232 (82.3%)	165/214 (77.1%)	5.2 (-2.2, 12.8)
MITTE	231/284 (81.3%)	203/269 (75.5%)	5.9 (-1.0, 12.8)

It is notable that despite the enrollment of subjects with PORT scores of III and IV at baseline, 30 day all-cause mortality rates were low at approximately 2%. Also among the 42 subjects with baseline bacteremia, none died. In the historical literature, subjects aged 50 years or greater and with bacteremia had the highest mortality rates.

The biometrics reviewer, Dr. Daniel Rubin, performed multiple sensitivity analyses to evaluate the robustness of the study results, and these analyses continued to find results in favor of the ceftaroline-treated subjects. Based on their reviews, Drs. Rubin and Porcalla conclude that the applicant has demonstrated the efficacy of ceftaroline for CABP. The CDTL, Dr. Janice Pohlman, concurs with this conclusion.

A meeting of the Anti-infective Drugs' Advisory Committee was convened on September 7, 2010, to discuss this application, and the committee members voted unanimously that the applicant had demonstrated the efficacy of ceftaroline for the treatment of CABP.

8.0 Summary of Efficacy: ABSSSI

For additional information regarding the efficacy of ceftaroline for ABSSSI, please refer to the biometrics review of Dr. Christopher Kadoorie and the clinical efficacy review of Dr. Neil Rellosa. Cerexa submitted two Phase 3 trials (studies 06 and 07) to support the safety and efficacy of ceftaroline for the treatment of ABSSSI. The trials were Phase 3, multicenter, randomized, double-blind, comparative trials of the safety and efficacy of ceftaroline compared to vancomycin plus aztreonam in subjects with ABSSSI. The prespecified co-primary endpoints were the per-subject clinical cure rate at the TOC visit in the CE and MITT populations. The prespecified noninferiority margin for clinical cure at TOC was 10%. However, the applicant provided insufficient justification for the historical evidence of treatment effect of antibacterial drugs for clinical cure at the TOC visit. Nor has the Agency been able to find adequate historical evidence for the treatment effect of antibacterial drugs at the TOC visit either. However, there is data to support an NI margin for a clinical response endpoint at an earlier

timepoint of 48-72 hours, as described in the draft Guidance for Industry titled "Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment" that was issued in August 2010.

This analysis is based on the cessation of spread of the lesion with absence of fever on Day 3 (48-72 hours) in a modified analysis population excluding subjects with lesions sizes of < 75 cm^2 at baseline, patients with major abscesses with < 5 cm of surrounding erythema, and patients with infection types of "ulcer" or "other". The results of this analysis are shown in Table 4 below.

Table 4: Clinical Responders at Study Day 3 From Two Phase 3 ABSSSI Trials

	Teflaro n/N (%)	Vancomycin/ Aztreonam n/N (%)	Treatment Difference (2-sided 95% CI)
ABSSSI Trial 1	148/200 (74.0)	135/209 (64.6)	9.4 (0.4, 18.2)
ABSSSI Trial 2	148/200 (74.0)	128/188 (68.1)	5.9 (-3.1, 14.9)

Limitations to this analysis included uncertainties about the reliability of lesion measurement, NI margin justification from historical studies, the post-hoc nature of testing, interpretations of findings and the types of patients symptoms addressed. Despite these limitations, this analysis demonstrates the noninferiority of ceftaroline to vancomycin plus aztreonam and meets an NI margin well above -10%. Dr. Kadoorie also conducted numerous other analyses to evaluate the robustness of study results, and these analyses consistently demonstrated the same finding as that of the Day 3 cessation of spread analysis.

Although the NI margin for the prespecified analysis cannot be justified, outcomes at the TOC visit are still important to understand the clinical course of disease for subjects receiving ceftaroline and vancomycin plus aztreonam. These results are depicted in Table 5 below.

Table 5: Clinical Cure Rates at TOC from Two Phase 3 ABSSSI Trials

	Teflaro n/N (%)	Vancomycin/ Aztreonam n/N (%)	Treatment Difference (2-sided 95% CI)
Trial 1			
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)
Trial 2			
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4., 4.5)
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)

Based on their reviews, Drs. Kadoorie and Rellosa conclude that the applicant has demonstrated the efficacy of ceftaroline for the treatment of ABSSSI. The CDTL, Dr. Janice Pohlman, also agrees with this conclusion.

At the AIDAC meeting on September 7, 2010, the committee voted unanimously that the applicant had demonstrated the efficacy of ceftaroline for the treatment of ABSSSI.

9.0 Summary of Safety

Dr. Ariel Porcalla's medical officer review provides further discussion of the safety of ceftaroline. The safety database for this NDA includes 1740 subjects who received ceftaroline in the ten clinical pharmacology studies, two Phase 2 trials, and four Phase 3 trials. Of these, 1441 received the to-be-marketed dose of 600 mg IV q 12 h for 5-14 days.

Patients in the pooled Phase 3 safety population were predominantly male, white, non-Hispanic, with a mean body mass index (BMI) of 27 kg/m^2, a mean age of 54 years, and normal renal function. Demographic characteristics (e.g. age, gender, height, weight, BMI, ethnicity, race, and creatinine clearance [CrCl]) were similar between the ceftaroline- and comparator-treated groups. In particular, the elderly, overweight, and patients with mild and moderate renal impairment were well-represented in the safety population.

In both the ABSSSI Phase 3 trials, the incidence of treatment-emergent adverse events (TEAEs) (44.7% [309/692] vs 47.5% [326/686]), severe adverse events (SAEs) (4.3% [30/692] vs 4.1% [28/686]), premature discontinuations because of TEAEs (3.0% [21/692] vs 4.8% [33/686]), and deaths (0.4% [3/692] vs 0) were similar between the ceftaroline-treated groups compared to the vancomycin plus aztreonam-treated group, respectively. For both CABP trials, the incidence of treatment-emergent adverse events (TEAEs) (46.5% [283/608] vs 45.5% [278/611]), severe adverse events (SAEs) (11.0% [67/608] vs 11.7% [72/611]), premature discontinuations because of TEAEs (4.3% [26/608] vs 4.1% [25/611]), and deaths (2.4% [15/608] vs 2.0% [12/611]) were similar between the ceftaroline-treated groups compared to the ceftriaxone-treated group, respectively.

A total of 30 deaths were reported before the LFU visit, 18 were subjects treated with ceftaroline (15 from the CABP trials and 3 from ABSSSI) and 12 were treated with the comparators. After the LFU visit, 5 more deaths in the ceftaroline group and 8 more deaths in the comparator group were reported. One patient’s sudden death from an unknown etiology may potentially be related to ceftaroline. One death caused by hepatic failure and subsequent multi-organ dysfunction syndrome was potentially related to ceftriaxone. Lastly, insufficient therapeutic

effect by ceftaroline may have caused a patient to die of septic shock. All in all, the incidence of mortalities was low and similar between the two treatment groups. Deaths were from cardiac, respiratory, neoplastic, and infectious etiologies. The variety of etiologies suggested that it was relatively unlikely that ceftaroline use was associated with an increased risk of death.

The incidences of SAEs were low and similar between the two treatment groups. Most SAEs were categorized under the System Organ Class (SOC) Infections (pneumonia, pyothorax, and cellulitis), Respiratory Disorders (pulmonary embolism, pleural effusion, respiratory failure), and Cardiac Disorders (cardiac failure congestive, cardiopulmonary failure). Most SAEs appeared to be either from complications of the primary indications of the trials or from chronic underlying comorbidities of the patients.

The most frequently reported adverse drug reactions (ADRs) experienced by the ceftaroline-treated group in the Phase 3 trials for both indications were: diarrhea (5%), nausea (4%), rash (3%), and constipation, vomiting, increased transaminases, hypokalemia, and phlebitis (2%). ADRs reported in the pooled safety population were consistent with ADRs expected in the cephalosporin class of antibacterials.

Potentially clinically significant changes (PCS) in laboratory parameters such as hematology, coagulation, clinical chemistry, and urinalysis occurred infrequently and similarly between the two treatment groups in the pooled Phase 3 trial population. The only exception is the higher incidence of Coombs' test seroconversion in the ceftaroline group compared to the comparator group (10.7% vs 4.4%). Its clinical relevance is unknown since the incidence of anemia was low and similar between the two groups (1.2% and 1.3%) and no case of drug-induced hemolytic anemia was reported. Information regarding the Coombs' test seroconversion and monitoring for drug-induced anemia will be included in the Warnings and Precautions section of the ceftaroline package insert.

At the AIDAC meeting on September 7, 2010, the AC members voted unanimously that the applicant had demonstrated the safety of ceftaroline for the treatment of ABSSSI and CABP. Drs. Porcalla and Pohlman conclude that given the benefit of ceftaroline for the treatment of CABP and ABSSSI, the safety profile is acceptable and the application should be approved.

10.0 Summary of Other Regulatory Issues

The Division of Scientific Investigations conducted audits of eight clinical investigators who enrolled subjects in any of the four Phase 3 trials. The classification for seven of the sites was NAI, and for one site was VAI. The inspection of the applicant, Cerexa, revealed no issues.

The Agency received a follow-up report from Cerexa regarding an investigator from India who had participated in the CABP Trial 09 on August 13, 2010. This investigator had been reported on the internet to have allegedly committed fraud in another company's clinical trial. In a follow-up site inspection, Cerexa was unable to locate source material or documents. Data from the 7 patients enrolled at this site were excluded from FDA analyses based on recommendations from the Division of Scientific Investigations. Additionally, the Office of Antimicrobial Products chose to exclude two additional sites from India (one patient enrolled per site) from the analysis since DSI could not ensure reliability of the data because they had been monitored by the same CRO. This CRO was not involved in the monitoring for any other clinical trial sites.

OSE has reviewed the labeling, carton, and container labeling and provided comments that have been conveyed to the applicant. DMEPA has conducted a proprietary name, label, and labeling review and has no objection to the proposed proprietary name of Teflaro.

The proposed pediatric plan was submitted to the IND 71371 on August 15, 2009. A pediatric plan and deferral request was submitted to the NDA on February 2, 2010. The deferral was requested for all pediatric age ranges from birth to age < 18 years as pediatric studies are not completed and the drug is ready for approval in adults. The plan was presented to the PeRC on October 20, 2010. As pediatric trials are required under PREA, the following required pediatric studies will be included in the action letter:

1692-001: Single dose pharmacokinetic trial

Perform a trial in pediatric patients being treated concomitantly with antibacterial agent(s) to evaluate single dose pharmacokinetic parameters and assess safety of Teflaro (ceftaroline fosamil) in all pediatric age groups. Five age cohorts must be studied as follows:

- Group 1: children from 6 to < 12 years
- Group 2: children from 24 months to <6 years
- Group 3: young infants/toddlers from 28 days to < 24 months
- Group 4: term neonates < 28 days (stratification within the group: 0-14 days; from 14 days to < 28 days)
- Group 5: pre-term neonates < 28 days (stratification within the group: 0-14 days; from 14 days to < 28 days)

There must be a minimum of 8 evaluable subjects per cohort. In group 3, there will be an equal representation of patients aged 28 days to < 12 months and $\geq$ 12 months to < 24 months.

Final Protocol Submission: 11/2010
Trial Completion Date: 01/2014
Final Report Submission: 07/2014

1692-002: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with CABP utilizing an enrichment strategy for enrollment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Pediatric patients under 17 years of age with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

1692-003: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with ABSSSI including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients under 17 years of age with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

1692-004: Cerebrospinal Fluid (CSF) Concentration Trial

Perform a trial assessing the CSF concentration profile of Teflaro (ceftaroline fosamil) in infants < 2 months of age. A minimum of 12 infants < 2 months receiving antibacterials for treatment of late-onset neonatal sepsis must be studied.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

1692-005: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in infants < 2 months of age with ABSSSI and CABP including patients with infection suspected or demonstrated to be caused by MRSA.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

11.0 Recommendation

I concur with the conclusions and recommendation of the review team that the applicant has demonstrated substantial evidence of the efficacy and safety of

ceftaroline for the treatment of CABP and ABSSSI caused by susceptible isolates of designated microorganisms. Although noninferiority margins for the prespecified endpoints and timepoints for the Phase 3 trials for both indications could not be justified, the exhaustive and thorough efforts of the review team in conducting extensive sensitivity analyses using endpoints and timepoints for which there is historical evidence of treatment effect of antibacterial drugs, provided robust evidence for the treatment effect of ceftaroline for the requested indications. In addition, the safety profile is reasonably similar to other approved cephalosporins with no major safety concerns identified. Ceftaroline will represent an important new antibacterial agent for the treatment of ABSSSI and CABP, particularly since it has activity against MRSA, as well as against *S. pneumoniae* and some members of the Enterobacteriaceae. Therefore, I recommend approval of this application.

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
10/29/2010