

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-817

MEDICAL REVIEW(S)

Medical Team Leader Memo

Sumathi Nambiar MD MPH

Application: NDA 50-817, Cefepime for Injection

Date of Submission: February 01, 2008

Classification: Class 2 resubmission

PDUFA Goal Date: August 5, 2008

Applicant: Baxter Healthcare Corporation

Drug Class: Cephalosporins

Recommendation on Regulatory Action

The issue of increased mortality with cefepime compared to other beta-lactams is still under review by the Division and the reasons for this finding have not yet been delineated. In a memo dated November 20, 2007, I had recommended an approvable action for this NDA based in part on concerns regarding the ongoing safety review by the Division. On further reflection and clarification and given that the reference listed drug MAXIPIME[®] and generic versions of cefepime are still on the market, I am recommending that this NDA be approved. This new pre-mixed formulation of cefepime in a GALAXY container does not pose any additional safety concerns beyond what is already known for cefepime. Following completion of the ongoing safety review by the Division, if any labeling changes are made to the MAXIPIME[®] label, similar changes will need to be made to this product's label.

Background

The Applicant had submitted NDA 50-817 on February 28, 2007, under Section 505(b)(2) of the FD&C Act. The reference listed drug (RLD) for this application is MAXIPIME[®]. The Applicant is seeking approval to market Cefepime injection in GALAXY container as 1 gram in 50 mL container and 2 grams in 100 mL container. These pre-mixed products are packaged in GALAXY flexible plastic containers and are stored frozen at -20°C and are for intravenous use only.

On December 21, 2007, the Agency had issued an approvable letter citing the following deficiencies:

1. Identify the equipment to be used for _____ of the drug product and its location within the manufacturing facility. **b(4)**
2. Provide the methodology and acceptance criteria for filter integrity testing.
3. The microbiology deficiencies identified during the review of DMF_____ should be addressed. **b(4)**

The Applicant responded to the approvable letter on February 01, 2008. On April 29, 2008, the Division had requested the Applicant to submit a safety update that covered the period from the last safety report dated November 30, 2007 to present. A response was submitted by the Applicant was received by the Agency on May 27, 2008.

Based on the review of the literature, the Applicant is of the opinion that the labeling for cefepime needs further assessment. The Applicant stated that as the data available to them were limited to those available in the public domain, the Agency's ongoing review of cefepime will be able to provide evidence for any labeling changes. They also state that their product does not present any additional safety concerns beyond what already exists for the approved cefepime products. The Division is currently evaluating the

finding of increased mortality with cefepime compared to other beta-lactams that was reported in a meta-analysis published in May 2007.¹

Indications

In this NDA, the Applicant is seeking approval of Cefepime for injection in GALAXY container for the same indications as MAXIPIME®. MAXIPIME® is currently approved for the following indications:

- Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.
- Empiric Therapy for Febrile Neutropenic Patients. Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
- Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.
- Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.
- Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, *viridans group streptococci*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides fragilis*.

Safety Update

The Applicant has identified nine relevant publications that had not been included in the previous safety update. For a detailed review of these publications, please refer to the review by Dr. Alma Davidson MD, Medical Officer. No new safety information was provided from these studies. One retrospective study evaluated clinical outcomes in patients with Gram-negative bacteremia treated with cefepime.² This study suggested that the breakpoints for cefepime for Gram-negative bacteria may need to be revised, as MIC of ≥ 8 mcg/ml was identified as an independent risk factor for mortality. Based on the

¹Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007 May;7(5):338-48.

²Bhat VS, Peleg AS, Lodise TP et al. Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by Gram-negative organisms. *Antimicrob Agents Chemother* 2007;51:4390-4395

current breakpoints, an isolate with MIC \leq 8 mcg/ml is considered susceptible. The potential need for revising the breakpoints of cefepime is currently under review by the Division. Two additional articles were identified in the literature pertaining to safety of cefepime since the cut off date for the safety update.^{3,4}

Product Quality Microbiology Review:

Dr. Stephen Langille, Ph.D. has reviewed the Applicant's response and found them acceptable. He has recommended approval of this product from a product quality microbiology standpoint.

Labeling

The Applicant has submitted the product label in the PLR format, while the MAXIPIME[®] label is not in PLR format. As such, the formatting will be different compared to the MAXIPIME[®] label. The content changes proposed by the Applicant are primarily based on the difference in formulation such as deletion of reference to intramuscular use, deletion of steps in reconstitution, including directions for use of the frozen product, and including contraindication regarding corn allergy as the product contains dextrose. These changes are acceptable.

The Applicant has also modified the DOSAGE and ADMINISTRATION section and the Pediatric use subsection of PRECAUTIONS section to state that Cefepime Injection in GALAXY Container should be used only in pediatric patients who require the entire 1 or 2 g dose and not any fraction thereof. This is consistent with the label of other cephalosporins administered in a duplex container which also delivers a fixed dose of the product (NDA 50-796, Ceftriaxone and Dextrose in Duplex Container, NDA 50-779, cefazolin and dextrose).

The label has also been updated with regards to *C. difficile* associated disease. This is consistent with a recent labeling change to the RLD label. Changes to the Clinical Pharmacology section are also acceptable.

Conclusions

The issue of increased mortality with cefepime compared to other beta-lactams is still under review by the Division. This new pre-mixed formulation of cefepime in a GALAXY container does not pose any additional safety concerns beyond what is already known for cefepime. No new safety information that merits a label change was noted in the safety update submitted by the Applicant. Following completion of the ongoing safety review by the Division, if any labeling changes are made to the MAXIPIME[®] label, similar changes will need to be made to this product's label.

³ Drago L, De Vecchi E. The safety of cefepime in the treatment of infection. Expert Opin Drug Saf. 2008 Jul;7(4):377-87.

⁴ Hettmer S, Heeney MM. Cefepime-induced neutropenia in a teenager. Pediatr Blood Cancer. 2008 Jul 11

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/s/

Sumathi Nambiar
7/22/2008 09:32:57 AM
MEDICAL OFFICER

**MEDICAL OFFICER'S MEMORANDUM TO FILE
NDA 50-817**

Date: June 30, 2008

Applicant: Baxter Healthcare Corporation
1620 Waukegan Road
McGaw Park, IL 60085

Resubmission date: February 1, 2008

Goal Date: August 5, 2008

Background:

NDA 50-817 was originally submitted on February 28, 2007 and received on March 1, 2007. This submission was granted an approvable action on December 21, 2007 due to microbiology sterility deficiencies identified during the review of Drug Master File (DMF)

— The applicant was requested to submit responses to the deficiencies including a revised draft final printed labeling (FPL) with carton and container labels with recommendations consistent with the Agency letter dated August 24, 2007.

b(4)

Baxter Healthcare Corporation has submitted NDA 50-817 for a new dosage form of cefepime injection (Cefepime Injection in GALAXY Container (PL 2040 Plastic) as a 505(b)(2) application. A 505(b)(2) application may include results of investigations necessary for approval but were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [21 U.S.C. 355(b)(2)]. These applications are regulated under 21 CFR 314.54 which allow an applicant to rely on the Agency's finding of safety and effectiveness for an approved, reference listed drug (RLD) to the extent such reliance would be permitted under the generic drug approval provisions at section 505(J) of the Act. The review of this NDA relies on prior FDA determination of safety and efficacy for the reference listed drug, MAXIPIME® (Cefepime hydrochloride) for Injection. MAXIPIME® by Bristol-Myers Squibb (BMS) was approved for marketing on January 18, 1996.

The clinical review found safety concerns regarding cefepime use based on evidence concerning increased mortality among patients treated with cefepime, as reported in two recent meta-analysis studies by Paul et al and Yahav et al., respectively. The first study by Paul et al. found increased mortality associated with cefepime therapy in febrile neutropenic patients. The second study found the 30-day all-cause mortality to be significantly higher with cefepime in all indications than with other β -lactam antibiotics (Risk ratio of 1.26 and 95% CIs 1.08 -1.49). Based on this safety concern regarding increased mortality with

cefepime the clinical reviewers recommended an approvable action for NDA 50-817 pending completion of the Agency's safety review. In addition, the applicant submitted a safety update information for this NDA in response to the Agency's request letter dated October 25, 2007. The review of this safety update provided new safety information for cefepime regarding increased mortality based on the meta-analysis findings by Yahav et al. This finding of increased mortality is the subject of an on-going safety review by the Agency. The potential impact of this safety issue on cefepime labeling and health care prescribers remains uncertain pending receipt of additional data from BMS and completion of the Agency's safety review.

On February 1, 2008, the Applicant submitted an amendment with complete response to the approvable letter issued December 21, 2007. In this amendment, the chemistry and product quality microbiology reviewer found the Applicant's responses adequate to support approval for NDA 50-817. The chemistry assessment identified no other deficiencies. The submitted draft labeling was reviewed by all disciplines and found to have few revisions.

The literature articles provided some safety information for cefepime use. The adverse reactions in these publications are mentioned in the cefepime label which includes: 1) Clinical adverse reactions: local reactions (rash and discomfort on site of injection); GI (diarrhea, nausea, and vomiting); neurotoxicity (encephalopathy, myoclonus, and convulsions); pruritus, urticaria and anaphylaxis; and 2) Laboratory adverse reactions: increased hepatic transaminases, increased platelet count, and decreased leukocyte count. The literature articles had shortcomings (i.e., lack of details about study design and comparator agents, lack of reporting of adverse event frequency and severity, few details to explain circumstances of death in the case reports, wide range of cefepime dosages used, language translation barriers) which hinder an adequate safety assessment and causality assessment in relation to cefepime administration. The issue of increased mortality cited in the meta-analyses is the critical safety issue whose impact remains to be determined as part of a separate ongoing safety review.

Another safety update information was submitted by the Applicant on May 23, 2008 in response to the Agency's request letter dated April 29, 2008. In that letter, the Agency requested safety information for cefepime that covers the period from the last safety report submission dated November 30, 2007 to the present. It was requested that the safety information should include data from all non-clinical and clinical studies of cefepime regardless of indication, dosage form, or dose level and review of the published literature regarding cefepime regardless of indication, dosage form, or dose level. Of interest, this current safety update provided two recent publications on cefepime. One article described the results of an *in vitro* study measuring the MIC₅₀ and MIC₉₀ of several antibiotics in ESBL-producing strains of *K. pneumoniae* and *E. coli*. In this study, there was larger variability of MIC range (0.125-256) reported for the cefepime study groups as compared to the imipenem, tigecycline and gentamicin study groups. The results of this study appear to provide evidence supporting current Clinical and Laboratory Standards Institute (CLSI)

recommendations for these ESBL-producing isolates. Another article described a retrospective study that evaluated 28-day mortality in patients with bacteremia and infected with Gram-negative organisms treated with cefepime. In this study, the 28-day mortality rate in cefepime-treated patients with Gram-negative organisms reporting an MIC of ≥ 8 mcg/mL was higher (54.8%, 17/31) than in patients infected with similar organisms reporting a cefepime MIC of < 8 mcg/mL (24.1%, 35/145). The investigators found that the current cefepime breakpoint failed to predict clinical outcomes of bacteremia caused by Gram-negative organisms. (*Note: Please see Attachment for the new safety update review.*)

Conclusion and Recommendation:

This safety update has identified two publications of interest, first the results of the *in vitro* study appear to provide evidence supporting current CLSI recommendations for cefepime's antimicrobial activity against ESBL-producing isolates of *K. pneumoniae* and *E. coli*; and second the clinical microbiologic study evaluated the outcome of patients who received cefepime empirically for the treatment of gram-negative bacteremia and found that the 28-day mortality of patients was higher if organisms had an MIC of 8 mcg/mL than in patients infected with organisms with lower cefepime MICs. In a letter dated January 6, 2008, the Agency has requested to update the *in vitro* susceptibility test interpretive criteria (i.e., breakpoints) and quality control parameters of organisms listed in the MAXIPIME[®] label. The response from BMS is currently being reviewed by the Agency. From the clinical perspective, the major safety issue of mortality imbalance in cefepime treated patients noted in the meta-analysis remains unresolved. To date, the Agency is continuing to review safety data for cefepime. Therefore, pending completion of the Agency's ongoing safety review for the drug cefepime, the medical reviewer recommends an approvable action for NDA 50-817.

Attachment

Review of an Amendment - Safety Update #2

NDA 50-817

Drug Name: Cefepime Injection in GALAXY Container

Applicant: Baxter Healthcare Corporation

Date of submission: May 23, 2008

Date received by CDER: May 27, 2008

Date received by MO: June 4, 2008

Materials submitted and reviewed: The materials consisted of two volumes in paper format:

- Cover letter dated May 23, 2008
- Completed Form FDA 356h
- Completed Form FDA 3574
- Copy of Agency's letter dated April 29, 2008
- Table of contents
- Safety Information in MAXIPIME[®] label (Updated information)
- Review of literature (Updated information)
- Copies of literature references

Purpose of submission:

The Applicant submitted this safety update information for NDA 50-817 in response to the Agency's request letter dated April 29, 2008. In that letter, the Agency requested safety information for cefepime that covers the period from the last safety report submission dated November 30, 2007 to the present.

Review of submitted material:

The Applicant has conducted a new literature search to obtain recent safety information on cefepime. The search covered the period from November 30, 2007 to present. According to their search, 232 publications were found. Literature articles that were excluded from their review included those in which cefepime was not the primary focus of the article, any review articles summarizing previously published literature (with exception to meta-analyses), and any publications that were already evaluated in the original submission for NDA 50-817, submitted February 28, 2007 or of the safety update submitted November 30,

2007. The Applicant cited the currently approved MAXIPIME® package insert as one of the references, which describes neurotoxic events that have been reported with cefepime use. In addition, the Agency's CDER-Early Communication publication (dated November 14, 2007) was also cited regarding an ongoing safety review for the drug cefepime.

The Applicant reports that nine relevant publications were identified as reporting cefepime safety data. Three publications reported some safety data from prospective randomized controlled clinical studies evaluating safety and efficacy of cefepime. Two publications were postmarketing case reports from a total of eleven patients with renal failure administered cefepime who experienced a variety of neurological toxicities, including decreased consciousness, confusion, agitation, global aphasia, myoclonus, hyperexcitability, choreoathetosis, convulsions, and coma.

One publication provided report from the SENTRY Antimicrobial Surveillance Program from 1998 through 2004. In this report, the antimicrobial activity of cefepime was tested against ceftazidime-resistant Gram-negative clinical isolates from North American Hospitals. A follow-up publication by the same authors was just an erratum to correct an error made in a table in the former publication displaying antimicrobial activity and susceptibility rates for cefepime and other broad-spectrum agents tested against ceftazidime-resistant Gram-negative bacteria.

One article described the results of a prospective evaluation of the incidence of resistance and factors related to the emergence of antibiotic resistance for infections caused by *Enterobacter* spp., *S. marcescens*, *C. freundii*, and *M. morgani*. Of the 732 patient cases assessed, only 14 (1.9%) patients received cefepime monotherapy, and only 4 (0.5%) patients received cefepime in combination with another antibiotic. While there were no reported cases of bacterial resistance to cefepime therapy, the total identified cases was too small to make any clinically significant conclusions specific to cefepime therapy.

One publication described the results of *in vitro* activity of several antimicrobial agents, alone or in combination, against extended-spectrum β -lactamase (ESBL)-producing strains of *Klebsiella pneumoniae* and *Escherichia coli*.

A separate publication described a retrospective study of a clinical microbiology database to identify patients with gram-negative bacteremia who received cefepime as primary treatment. In this study, the investigators found that the current cefepime breakpoints failed to predict clinical outcomes of bacteremia caused by gram-negative organisms.

The Applicant also evaluated the current published standards for antimicrobial susceptibility as defined by Clinical Laboratory Standards Institute (CLSI). According to their evaluation, it appears that the existing MAXIPIME® label does not reflect the current CLSI recommendations as provided in these documents.

The medical reviewer summarizes the submitted literature publications below:
(MO Note: The brief summary of the literature articles is focused on the safety profile of cefepime. Please refer to the particular publication for other information.)

1. Literature review:

- Ahmed SM, Choudhary J, Ahmed M, et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam and amikacin vs cefepime and levofloxacin: a randomized prospective study. *Indian J Crit Care Med.* 2007;11(3):117-21.

This article describes a prospective observational cohort study of 879 patients admitted in the ICU during April 1, 2004 to March 31, 2005. The study objectives were to compare the survival benefits and cost effectiveness of cefepime-levofloxacin (C-L) as an alternative empirical antibiotic for ventilator associated pneumonia (VAP) with combination of piperacillin-tazobactam and amikacin (P-T-A). Out of the 879 patients admitted in the ICU, 93 patients (C-L, n= 46 and P-T-A, n=47) were clinically suspected to develop early-onset VAP. Treatment outcome was compared between the treatment groups including ICU mortality, duration of mechanical ventilation, duration of ICU stay and total cost incurred on antibiotics. The results of this study showed that the epidemiological characteristics including mean age and APACHE II score were comparable between the two treatment groups. Nine patients (4 in the C-L group and 5 in the P-T-A group) in the study developed acute renal failure and were excluded from the study. Eight patients were found to be receiving inappropriate antibiotics since the organism isolated from the endotracheal aspirate were resistant to the empirical regimen and were excluded from the study. The organisms isolated from the patients included *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *E. coli*, *Acinetobacter*, *Klebsiella* and *Streptococcus species*. The total observed mortality was 37.3% (35% in C-L group; 39.7% in P-T-A group). Patient factors associated with high mortality in both groups included hepatic failure (4 patients died in the C-L group and 4 patients died in the P-T-A group), immunocompromised state (2 patients died in C-L group and 2 patients died in P-T-A group); and APACHE II score of >20 (1 patient died in C-L group and 1 died in the P-T-A group). The authors concluded that combination of C-L is an effective alternative to P-T-A, a widely accepted antibiotic regimen for the treatment of VAP. They further noted that the major limitation in their study was failure to investigate the causative factors associated with early onset VAP and secondly, analysis of the number of days required to make the culture negative for previously isolated organisms was not performed.

MO Comment: *This article provided limited information including dosing, duration of the antibiotic use and other adverse events in the study. Although mortality was reported, the direct causes of deaths and causative pathogens isolated from the cultures in those who died were not mentioned in this article.*

- Shahid SK. Efficacy and safety of cefepime in late-onset ventilator-associated pneumonia in infants: a pilot randomized and controlled study. *An Trop Med Parasitol.* 2008; 1 02(1):63-71.

This is a pilot, randomized, and controlled study to evaluate the efficacy and safety of cefepime in late-onset VAP in infants at the Duchess of Kent Hospital in Sandakan, Sabah, Malaysia during the period of April 1, 2004 to August 31, 2005. Thirty children aged <one year with late-onset VAP (i.e., VAP occurring 5 or more days after intubation) met the entry criteria and were randomized to receive cefepime (15 cases) or ceftazidime (15 cases). The clinical responses and microbiological clearance of tracheal aspirates were evaluated in each treatment arm. Ten of the 15 children administered cefepime and 5 children tested with ceftazidime showed a satisfactory clinical response. One infant in the cefepime arm who had a negative tracheal aspirate culture (at day-0) was cured but two of the three infants in the ceftazidime arm who had negative cultures (at day-0) died. This article reported that no other serious adverse events that had occurred in either treatment arm.

The study reported that the frequencies of clinical cure by each treatment arm were similar for each pathogen encountered (*Pseudomonas*, *Klebsiella*, *Acinetobacter*, and *Proteus*) except *E. coli*. Late-onset VAP caused by *E. coli* was much more likely to show clinical cure with cefepime than ceftazidime (100% v 0%). Among the 9 infants with polymicrobial cultures (7 in cefepime arm and 2 in the ceftazidime arm), cefepime was more likely to eradicate the organism than ceftazidime (86% v. 0%). Eight patients (four with *Pseudomonas*, two with *Klebsiella*, and two with *E. coli*) had persistent infections in spite of therapy. Superinfection was seen in seven (23%) of the infants (five given ceftazidime and two given cefepime). The organisms in four of the infants with superinfection were *E. coli* and *Acinetobacter*.

The authors concluded that results of their study indicate that cefepime monotherapy appears to be at least effective and safe as ceftazidime monotherapy and with better microbiological clearance. The study had some limitations including a small sample size, and the presence of other pathogens (i.e., anaerobes and fungi) was not checked from the tracheal aspirates.

MO Comment: In this study of late-onset VAP, there were no reported fatalities in the cefepime arm but three infants died in the ceftazidime arm. The causes of deaths and other details surrounding the deaths of the infants were not mentioned in this paper. The study reports no other serious adverse events observed in either treatment groups. Information about non-serious AEs was not reported.

- Kwon KT, Cheong HS, Rhee J-Y, et al. Panipenem versus cefepime as empirical monotherapy in adult cancer patients with febrile neutropenia: a prospective

randomized trial. *Jpn J Clin Oncol* 2008;38(1):49-55.

This article describes a prospective, randomized, open-label comparative trial which was conducted from April 2004 to June 2005 in a tertiary teaching hospital in Seoul, South Korea. The study objective was to compare the efficacy and safety of panipenem/betamipron with cefepime as empirical monotherapy for adult cancer patients with febrile neutropenia. All enrolled patients were randomly assigned either panipenem or cefepime. Panipenem/betamipron was administered as 0.5/0.5g intravenously every 8 hours and cefepime, 2 g intravenously every 12 hours. In addition, vancomycin 1 g I.V. every 12 hours was given to patients who presented with prior colonization with MRSA, obvious catheter-related infection, or a positive blood culture for Gram-positive organisms. All febrile episodes were classified as microbiologically defined infection (MDI), clinically defined infection (CDI) or unexplained fever (UF). Clinical responses to antibiotic therapy were defined as success, initial response but regimen modified or failure. The results of the study showed that a total of 116 patients were enrolled: 55 patients in the panipenem group and 61 patients in the cefepime group. Demographic and clinical characteristics were similar in the two groups. In the final evaluation, the success rate for the panipenem group (89.1 %) was similar to that of the cefepime group (91.8%). Of the 18 bacterial isolates, nine (50%) were Gram-positive and nine (50%) were Gram-negative. *Escherichia coli* (four strains) were the most common isolate, followed by MRSA (3). Except for two methicillin-resistant *Staphylococci* and one *Stenotrophomonas maltophilia*, 15 isolates were susceptible to both panipenem and cefepime.

A total of 27 adverse events related to the use of the test drugs were observed in 25 patients: 13 events (23.6%) in the panipenem and 14 (23.0%) in the cefepime group. Gastrointestinal dysfunction such as nausea or vomiting was the most frequent events in the panipenem group (10.9%) than in the cefepime group (1.6%) and liver dysfunction was the most frequent event in the cefepime group (14.8%) than in the panipenem group (7.3%). According to this article, all of these adverse events spontaneously resolved after completion of treatment. There were no severe adverse events that required withdrawal from this study.

Two deaths occurred in the panipenem group due to septic shock and adult respiratory distress syndrome associated with pathologically confirmed adenoviral pneumonia. In the cefepime group, five cases showed clinical failure including one death due to biliary sepsis.

The authors concluded that although the study was small, panipenem appeared to be as effective and safe as cefepime for empirical monotherapy in the treatment of adult cancer patients with febrile neutropenia.

MO Comment: The reported adverse reactions in the cefepime group including GI events and liver dysfunction are reflected in the cefepime label. However, the specific liver abnormality was not reported. There was no other information provided regarding the death in the cefepime group.

- Parotte MC, Krzesinski JM. Le cas clinique du mois. Antibiotiques et patient dialyse: Trois cas de toxicité neurologique du cefepime. Rev Med Liege. 2008;63(3):119-21.

***(Note: English translation) Clinical Case of the Month
Antibiotics and Dialyzed Patients: Three Cases of Neurological Toxicity with Cefepime***

This paper describes three clinical cases of neurological toxicity from the use of cefepime in dialyzed patients:

1. The first case is a 79-year-old woman with diabetes, who had received peritoneal dialysis for several years following renovascular kidney failure. She had been prescribed 500 mg of cefepime IV for 24 hours to treat a multi-resistant bacterial urinary tract infection. On the third day of administration, the patient developed myoclonic twitches in her face, upper limbs, and then her lower limbs. An electroencephalogram (EEG) revealed broad-based metabolic encephalopathy without epileptic origin. Her brain scan was normal for her age. The twitching ceased after the medication was stopped.
2. The second case was a 63-year-old male patient with history of hypertension and unilateral nephrectomy due to kidney stones and recurrent urinary tract infection. In addition, the patient had a history of poliomyelitis leading to neurogenic bladder and placement of an indwelling catheter. The patient was on the verge of dialysis as a consequence of a failing single kidney due to recurrent UTI. He was prescribed 500 mg of cefepime IV for 24 hours for a multi-resistant bacterial urinary tract infection. In the morning of the fifth day of treatment, he became confused, followed by aphasia, sudden right hemiplegia and twitching. The electroencephalogram revealed a large number of slow, poorly structured, with theta and delta waves. After a brain scan, which ruled out cerebral hemorrhage, the clinical situation improved with three hours of hemodialysis, after which the patient gradually regained the ability to speak and move. Cefepime was stopped.
3. The third case was a 72-year-old female, who had been undergoing hemodialysis for a few months following acute kidney failure with myeloma. Cefepime (500 mg, IV) was prescribed for 24 hours to treat a hospital-acquired pulmonary infection. After three days of treatment, she experienced an acute state of confusion with neck stiffness. Both the brain scan and the lumbar puncture were negative, and

the symptoms improved after three hours of hemodialysis and stopping cefepime. The authors concluded that these cases should remind health care professionals and patients of the importance of dosage adjustment with cefepime when prescribed to patients with varying degrees of renal impairment. Early recognition of neurotoxic signs and symptoms during cefepime therapy is important for prompt diagnosis and appropriate treatment.

MO Comment: This article published in the French language was translated to English. Baxter provided the English translation of the article as requested by the reviewer. These cases demonstrate the neurotoxic reactions to cefepime particularly in renal patients on dialysis.

- Sonck J, Laureys G, Verbeelen D. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant.* 2008;23(3):966-70.

This is a retrospective review of eight patients admitted in the University hospital of Brussels, Belgium between June 1999 and October 2006. These patients with renal insufficiency developed neurological symptoms during treatment with cefepime. All these renal patients had fatal outcomes. The characteristics of the eight patients are summarized in the following table:

Table 1: Patient characteristics of Eight Patients with Cefepime-induced neurotoxicity

Copyright

b(4)

According to this publication, Patient A died after ventricular tachycardia and unsuccessful

CPR. Patient B died shortly after starting comfort care. Patient C died after cardio-respiratory arrest. The cause of death of patients D and E was unclear. Autopsy of patient F suggested that the patient died of cardiorespiratory failure due to severe atherosclerosis and emphysematous-anthracosilicotic lung disease with tracheitis, bronchitis and bronchopneumonia. The autopsy findings in patient G suggested that the patient died of myocardial infarction with heart failure, pulmonary edema and bilateral pneumonia. Autopsy of patient H suggested that the patient died of *E. coli* pneumonia.

The authors concluded that their findings confirm the neurotoxicity to cefepime treatment for serious infections in patients with renal insufficiency.

MO Comment: Neurotoxicity is a known adverse reaction associated with cefepime use particularly in patients with renal impairment, which could lead to life-threatening or fatal outcomes. Likewise, these neurological events including encephalopathy have also been reported in patients with normal renal function. It is of great importance that in patients with renal disease, cefepime should be used with caution, dose be adjusted accordingly and patients be monitored for neurotoxicity. These neurotoxic adverse reactions are reflected in the cefepime label.

- Pfaller MA, Sader HS, Fritsche TR, et al. Antimicrobial activity of cefepime tested against ceftazidime-resistant gram-negative clinical strains from North American hospitals: report from the SENTRY antimicrobial surveillance program (1998-2004) (Diagnostic Microbiology and Infectious Disease 56, 63-68, 2006). *Diagn Microbiol Infect Dis.* 2007;57(4):471.

This publication was an erratum to correct an error made in Table 2, page 66 of the above 2006 article by the same authors. The table showed the antimicrobial activity and susceptibility rates for cefepime and other broad-spectrum antibiotic agents tested against 3030 ceftazidime-resistant GNB isolated in North American hospitals.

MO Comment: The correction made in this table was the percentage under the "Susceptible" category for Piperacillin/tazobactam (from 12.0 to 41.3) for Pseudomonas aeruginosa. This erratum did not change the antimicrobial activity of cefepime previously reported for P. aeruginosa.

- Choi S-H, Lee JE, Park SJ, et al. Emergence of antibiotic resistance during therapy for infections caused by Enterobacteriaceae producing AmpC β -lactamase: implications for antibiotic use. *Antimicrob Agents Chemother.* 2008;52(3):995-1000.

This publication described an observational study evaluating the results of prospectively collected data from all patients admitted to the Asian Medical Center, a tertiary-care affiliated teaching hospital in Seoul, Korea from January 2005 to June 2006. The objective of this study was to determine the incidences of the emergence

of resistance during antimicrobial therapy for infections caused by Enterobacteriaceae producing AmpC β -lactamase. A total of 732 patients with infections were included for analysis. Of the 732 cases, 14 (1.9%) patients received cefepime monotherapy and 4 (0.5%) patients received cefepime in combination with an aminoglycoside. The emergence of resistance to broad-spectrum cephalosporins occurred more often in *Enterobacter* spp. (8.3%, 10/121) than in *C. freundii* (2.6%, 1/39), *S. marcescens* (0%, 0/37%) and *M. organii* (0%, 0/21). It was noted in this study that biliary tract infection associated with malignant bile duct invasion was significantly associated with the emergence of resistance to broad-spectrum cephalosporins (including cefotaxime, ceftriaxone and ceftazidime). Of the 218 patients who received broad-spectrum cephalosporin therapy, 9.1% (1/11) of the patients in whom the therapy was associated with the emergence of resistance died, whereas 1.0% (2/207) of the patients in whom the treatment was not associated with the emergence of resistance died. The authors concluded that the emergence of resistance during antimicrobial therapy for infections caused by organisms producing the AmpC β -lactamase was mainly confined to *Enterobacter* spp. They found a low rate of mortality among patients in whom resistance emerged during antimicrobial therapy. However, the study was limited to a small population to reach a reliable conclusion.

MO Comment: Interestingly, this study showed no reported case of bacterial resistance to cefepime therapy. The broad-spectrum cephalosporins mentioned in the study excluded cefepime. Regarding mortality the exact cephalosporin used was not provided. Information regarding adverse events was not provided.

- Cha R. In vitro activity of cefepime, imipenem, tigecycline, and gentamicin, alone and in combination, against extended spectrum β -lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*. *Pharmacotherapy*. 2008;28(3):295-300.

This article describes in vitro susceptibility of several antimicrobial agents alone or in combination against extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli* isolates. Minimum inhibitory concentration (MIC) testing was performed at 5.5 and 7.0 log₁₀ colony-forming units (cfu)/mL. Time-kill studies were performed over 24 hours with high inoculum of 7.0 log₁₀ cfu/mL for cefepime, imipenem, tigecycline, and gentamicin at 1 times MIC. For all antimicrobial agents tested, the MIC values for 50% and 90% of the tested strains were dependent upon the inoculum concentration being used. Combination studies were tested for cefepime plus tigecycline. For cefepime therapy, the following table summarizes the susceptibility results:

Table 1: Cefepime's Susceptibility results for 10 Clinical strains each of *K. pneumoniae* and *E.coli* at two different inocula

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For susceptibility results of Imipenem, Tigecycline and Gentamicin, the following table summarizes the results:

Table 2: Imipenem, Tigecycline and Gentamicin's Susceptibility results for 10 Clinical strains each of *K. pneumoniae* and *E.coli* at two different inocula

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According to the investigators, the results of the study demonstrated that there was a large range of cefepime MICs observed from clinical strains of *K. pneumoniae* and *E. coli*. Furthermore, the observed MICs were within cefepime susceptibility categories and well below concentrations achieved in humans with traditional doses. The investigators concluded that cefepime exhibited bactericidal activity but did not correlate to clinical outcome. Tigecycline exhibited predictable bacteriostatic activity and synergy in combination against a subset of study isolates. Imipenem exhibited predictable bactericidal activity against all isolates. Therefore, they further conclude that intricate studies of the relationships of ESBL genotypes to the predictability of microbiologic or clinical outcome would be helpful in evaluating the appropriateness of specific antimicrobial therapies in ESBL-related infections.

MO Comment: *The reviewer concurs with the investigators that further studies would be helpful in evaluating the appropriateness of specific antimicrobial therapies in ESBL-related infections.*

- Bhat SV, Peleg A Y, Lodise TP, et al. Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by gram-negative organisms. *Antimicrob Agents Chemother.* 2007;51(12):4390-5.

This publication describes a retrospective study of a hospital's clinical microbiology database to identify patients with gram-negative bacteremia. Patients identified were those who received cefepime (1 to 2 g every 12 hours) as the primary mode of therapy and patients who received monotherapy and those who received cefepime as part of combination therapy. A total of 284 episodes of bacteremia from 269 patients were treated with cefepime. The investigators excluded 43 episodes from patients who lacked MIC data, leaving them with 241 episodes from 229 patients. In addition, all episodes of patients who had concomitant bloodstream infection with a gram-positive organism or fungus were excluded from the study. The remaining episodes was 204 episodes from 197 patients with gram-negative bacteremia. Seven patients had two episodes of bacteremia so that a total of 204 episodes were analyzed. Patients treated with cefepime were infected predominantly with *Pseudomonas aeruginosa* (n=50), *E. coli* (n=40), *K. pneumoniae* (n=26), *Serratia marcescens* (n=24) and *Enterobacter cloacae* (n=21).

The following table summarizes the rate of mortality stratified by cefepime MIC of the pathogen:

Table 1: Mortality rate stratified by Cefepime MIC of pathogen

MIC	Number of patients who died n/N(%)
≤1 mcg/mL	27/116 (23.3%)
2 mcg/mL	5/18 (27.8%)
4 mcg/mL	3/11 (27.3%)
8 mcg/mL	9/16 (56.3%)
≥16 mcg/mL	8/15 (53.3%)

The results of the cefepime MIC breakpoint (as derived from the classification and regression tree, CART) analysis indicated that patients with cefepime MICs ≥8 mcg/mL had a twofold or greater increase in 28-day mortality over that of patients with MICs <8 mcg/mL (54.8% and 24.1%). The investigators also conducted a multivariable analysis to determine independent predictors of adverse clinical outcomes (i.e., 28-day mortality) in which they identified the following risk factors:

- Use of cefepime against an isolate with an MIC ≥8 mcg/mL
- An APACHE-II score ≥25

- Creatinine clearance rate < 60 mL/min
- Use of continuous renal replacement therapy.
- Central venous line as the source of bacteremia
- An infection with *Pseudomonas aeruginosa*

In addition, the investigators performed a secondary analysis in order to determine whether an organism with an MIC 8 mcg/mL is in itself a marker for poorer clinical outcome. They compared the results of this study to 19 additional patients with Gram-negative bacteremia who reported a cefepime MIC of 8 mcg/mL and treated with another antibiotic. When comparing the rates of 28-day mortality, the cefepime subgroup had a higher rate of mortality than the subgroup of patients treated with other antibiotics, but not statistically significant (56.3% and 38.9%, respectively; p=0.31; OR, 2.0; 95% CI 0.5-7.9). The investigators concluded that the weight of these data appear to support a change to lower the cefepime breakpoint. Gram-negative bacteria reporting a cefepime MIC of 8 mcg/mL are no longer considered as “susceptible”, particularly in countries where the licensed dosage regimen of cefepime in severe infections is 1-2 gm every 12 hours. The investigators noted limitations of their study including limited sample size, a retrospective study design, and arbitrary outcome measures.

MO Comment: The detail information about the deaths in this study was not reported in this paper. The reviewer believes that the results of this study appear to support revising the cefepime breakpoints for gram-negative bacteria with an MIC of 8 mcg/mL as being non-susceptible.

- Pfaller MA, Sader HS, Fritsche TR, et al. Antimicrobial activity of cefepime tested against ceftazidime-resistant gram-negative clinical strains from North American Hospitals: report from the SENTRY Antimicrobial Surveillance Program (1998-2004)

This article reports the results of the SENTRY antimicrobial surveillance program of the antimicrobial activity of cefepime tested against ceftazidime-resistant Gram-negative clinical strains from North American Hospitals from 1998 to 2004. According to this report in order to assess the effect of ceftazidime resistance on the activity of other antimicrobial agents, 3030 ceftazidime-resistant Gram-negative bacilli (GNB) isolates (of a total of 42,061 clinical GNB isolates) were tested against a panel of more than 30 antibiotic agents. Ceftazidime resistance was observed in 40.3% of *Acinetobacter* spp., 16.9% of *Pseudomonas aeruginosa*, and 5.7 % Enterobacteriaceae isolates.

MO Comment: This antimicrobial surveillance program provides a useful method to assess and monitor for emerging resistance in antibiotics.

- Clinical and Laboratory Standards Institute (CLSI). CLSI document M7-A7, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard. 7th ed. Wayne, PA: CLSI; January 2006.
- Clinical and Laboratory Standards Institute (CLSI). CLSI document M2-A9, Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard. 9th ed. Wayne, PA: CLSI; January 2006.
- Clinical and Laboratory Standards Institute (CLSI). CLSI document M100-S18, Performance Standards for Antimicrobial Susceptibility Testing. 18th Informational Supplement. Wayne, PA: CLSI; January 2008.

MO Comment: The above three published CLSI documents provide information regarding performance standards for antimicrobial susceptibility tests for all antibiotics including cefepime. The cefepime breakpoints in the MAXIPIME[®] label do not reflect the current CLSI standards recommendations. According to CLSI Document M100-S18 under Enterobacteriaceae: "Strains of Klebsiella spp., E.coli and P. mirabilis that produce ESBLs may be clinically resistant to therapy with penicillins, cephalosporins, or aztreonam, despite apparent in vitro susceptibility to some of these agents." Furthermore, this document states that for all confirmed ESBL-producing strains, the test interpretation should be reported as resistant for the above antimicrobial class or subclass including cefepime. (Note: The clinical reviewer defers to the microbiology review by Dr. Avery Goodwin and Dr. Frederick Marsik for further comments regarding revisions of cefepime breakpoints as recommended by CLSI.)

2. U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Early communication about an ongoing safety review- cefepime (marketed as Maxipime). Available at: http://www.fda.gov/cder/drg/early_commcefepime.htm. Accessed November 14, 2007.

The Agency's early communication informs the public about an ongoing safety review of cefepime. An article in a recent issue of *The Lancet Infectious Diseases* describing a higher all cause mortality in patients treated with cefepime compared to other beta-lactam antibiotics led to further safety evaluation by the Agency.

MO Comment: This is the first communication issued by the Agency dated November 14, 2007 to inform the public about its ongoing safety review of cefepime. A follow-up to this communication issued May 14, 2008 by the Agency stated that the review of safety data for cefepime was continuing. The Agency also stated that pending completion of review for all requested data from the manufacturer (BMS) of MAXIPIME[®], the Agency cannot

reach a definitive conclusion as to the cause of increased mortality seen with cefepime compared to other beta-lactam antibiotics.

3. MAXIPIME® (package insert). Princeton (NJ): Bristol Myers Squibb Company; revised January 2007, approved per NDA 50-679/S-028, 09/14/2007).

This package insert for MAXIPIME® (Cefepime hydrochloride, USP) for Injection (revised January 2007) incorporates the new text for *Clostridium difficile* associated diarrhea (CDAD) as provided by the Agency in a letter dated September 14, 2006 to all Sponsors with approved antimicrobial agents.

MO Comment: These new revisions to the MAXIPIME® label were approved for NDA 50-679/SLR-028 on September 14, 2007. No new additional safety information was included in this labeling supplement.

MO Conclusion:

The review of this safety update provided new safety information for cefepime from two recent literature articles of interest. The first article described the results of an *in vitro* study by Cha R. measuring the MIC₅₀ and MIC₉₀ of various antimicrobial agents in ESBL-producing strains of *K. pneumoniae* and *E. coli*. In this study, the larger variability in MIC range was reported for the cefepime study groups as compared to imipenem, tigecycline and gentamicin study groups. The reviewer concurs with the applicant's assessment that the results of this *in vitro* study appear to provide evidence supporting current CLSI (CLSI document M100-S18) recommendations that ESBL-producing *K. pneumoniae*, *K. oxytoca*, *E. coli*, and *P. mirabilis* should not be reported as being susceptible to penicillins, cephalosporins, and aztreonam. Thus, cefepime may not be a clinically effective antibiotic agent in treating ESBL-producing isolates of *K. pneumoniae* and *E. coli*.

The second article by Bhat et al described a retrospective study, which sought to provide data in support of lowering the current cefepime breakpoints. In this study, the clinical outcome of almost 200 patients who were administered cefepime empirically for the treatment of gram-negative bacteremia was evaluated. It was found that the 28-day mortality rate in cefepime-treated patients whose organisms had an MIC of 8 µg/mL approximated that of patients with MICs outside of the susceptible range. Furthermore, the 28-day mortality rate in cefepime-treated patients with gram-negative bacteremia due to organisms with MICs ≥8 µg/mL was higher (54.8%) than in patients infected with similar organisms with cefepime MICs of ≤8 µg/mL (24.1%).

In addition, some of the literature articles provided safety information for cefepime use regarding adverse reactions that are mentioned in the cefepime label including: GI (nausea,

vomiting, and liver dysfunction); and neurotoxicity including fatalities (decreased consciousness, myoclonus, agitation, convulsions and coma).

The literature articles had limitations (i.e., in vitro study, analysis of a retrospective data, small sample size, arbitrary outcome measures, lack of reporting of adverse event frequency and severity, few details to explain circumstances of deaths), which hinder an adequate safety assessment and causality assessment in relation to cefepime administration.

The issue of increased mortality cited in the meta-analyses is the critical safety issue whose impact remains to be determined as part of a separate and continuing safety review. The potential impact of this safety issue on cefepime labeling and health care prescribers remains uncertain pending completion of the Agency's safety review.

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/s/

Alma Davidson
7/21/2008 04:56:36 PM
MEDICAL OFFICER

Sumathi Nambiar
7/22/2008 09:30:31 AM
MEDICAL OFFICER

MO Review of an Amendment - Safety Update

NDA 50-817

Drug Name: Cefepime Injection in GALAXY Container

Applicant: Baxter Healthcare Corporation

Date submitted by Baxter: November 30, 2007

Date received by CDER CDR: December 3, 2007

Date received by Project Manager: December 7, 2007

Date received by MO: December 10, 2007

Materials submitted and reviewed: The materials consisted of two volumes in paper format:

- Cover letter dated Nov. 30, 2007
- Completed Form FDA 356h
- Copy of Agency's letter dated October 25, 2007
- Table of contents
- Safety Information in MAXIPIME[®] label (Updated information)
- Review of literature (Updated information)
- Copies of literature references

Purpose of submission: The applicant submitted this safety update information for NDA 50-817 in response to the Agency's request letter dated October 25, 2007.

Brief review of Applicant's responses to the following Agency's requested information:

1. Describe in detail any significant changes or findings in the safety profile of cefepime.

According to the Applicant, they are relying on the Agency's previous finding of safety and effectiveness of the Reference Listed Drug (RLD, MAXIPIME[®]) to support its 505(b)(2) application for Cefepime Injection. The Applicant conducted a new literature search to obtain recent safety information on cefepime by providing the recently revised RLD label (NDA 50-679/SLR-028, approved September 14, 2007). In this revised MAXIPIME label, it provided the changes to WARNINGS and INFORMATION FOR PATIENTS sections pertaining to the *Clostridium difficile* associated diarrhea (CDAD) language.

2. Provide a summary of worldwide experience on the safety of cefepime.

In response to #2 request, the Applicant states that they do not currently market cefepime in any country and has no worldwide experience on the safety of cefepime. However, they added that the literature search provided in their original submission (dated February 28, 2007) and this new additional literature search should reflect the worldwide experience on the safety of cefepime.

3. Provide English translations of current approved foreign labeling for cefepime.

The Applicant states that they do not currently market cefepime in any country and has no foreign labeling under their control.

Review of Submitted Literature Publications

The Applicant has conducted a new literature search in response to the Agency's request for information on October 25, 2007. The search covered the period from January 1, 2006 to October 31, 2007. According to their search, 104 publications were found. Literature articles that were excluded from their review included those in which cefepime was not the primary focus of the article, any review articles summarizing previously published literature (with exception to meta-analyses), and any publications that were already evaluated in the original submission for NDA 50-817, submitted February 28, 2007.

The Applicant reports that seven publications (six prospective trials and one retrospective study) were identified as reporting cefepime safety data from clinical studies evaluating cefepime's efficacy and safety. Six publications are post-marketing reports. Of the six, four articles reported patients who experienced neurological events including encephalopathy, myoclonus, and convulsions. One article reports a case of selective immediate hypersensitivity to cefepime. Lastly, the recent publication by Yahav et al described the results of a systematic review and meta-analysis of cefepime.

The medical reviewer summarizes the submitted literature publications below:

(MO Note: The brief summary of the literature articles is focused on the safety profile of cefepime. Please refer to the particular literature reference for other information in the article.)

1. MAXIPIME® (package insert). Princeton (NJ): Bristol Myers Squibb Company; revised January 2007, approved per NDA 50-679/S-028, 09/14/2007).

This package insert for MAXIPIME® (Cefepime hydrochloride, USP) for Injection (revised January 2007) incorporates the new text for *Clostridium difficile* associated

diarrhea (CDAD) as provided by the Agency in a letter dated September 14, 2006 to all Sponsors with approved antimicrobial agents.

MO Comment: These new revisions to the MAXIPIME® label was approved for NDA 50- 679/SLR-028 on September 14, 2007. No new additional safety information was included in this labeling supplement.

2. Ariffin H, Ai C-L, Lee C-L, Abdullah W-A. Cefepime monotherapy for treatment of febrile neutropenia in children. *J Pediatr Child Health.* 2006;42(12):781-4.

This is a prospective study in children aged 16 years and younger with underlying malignancies who presented with febrile neutropenia to the Pediatric Oncology Unit, University of Malaya Medical Center, Kuala Lumpur. In this study, 79 children with 133 episodes of febrile neutropenia were studied between August 2004 and August 2005. Cefepime was given intravenously at a dose of 50 mg/kg/dose every 12 hours as a single-agent. Treatment with cefepime was changed to another antibiotic if fever persisted after 72 hours or if a resistant bacterial isolate was identified. Patients were analyzed for clinical outcome, documented infections and side-effects of cefepime. A microbiologically documented infection was seen in 26 episodes. Success was defined as clinical improvement without treatment modification. Death or any change to the empirical antibiotic was considered as failure. The reported success rate of cefepime was 60%. The rate of survival through neutropenia (with or without modification) was 98%.

There were two deaths in the study. One patient with newly diagnosed relapsed acute myeloid leukemia who apparently developed septic shock (blood culture negative) and died 24 hours after admission. The second patient had macrophage-activation syndrome who remained febrile throughout his stay and died of apparent multi-organ failure after two months in hospital. The study reports that no patients developed adverse effects from the study drug.

MO Comment: This study did not report other adverse events. The exact causes of death and causality assessments in the two patients were not reported in this article.

3. Legout L, Senneville E, Stern R, Yazdanpanah Y, Savage C, Roussel-Delvallez M, et al. Treatment of bone and joint infections caused by gram-negative bacilli with a cefepime-fluoroquinolone combination. *Clin Microbiol Infect.* 2006;12(10):1030-3.

This is a 3-year retrospective study that evaluated the efficacy and safety of cefepime combined with a fluoroquinolone (ofloxacin or ciprofloxacin) for treatment of bone and joint infections caused by Gram-negative bacilli in 28 patients. The medical charts of patients treated by the Orthopedic Surgery Service, Lille, France from January 1999 to December 2001 were reviewed. Cefepime was administered intravenously twice daily at

2 G every 12h for a total of 4 weeks and adjusted according to renal function. A fluoroquinolone was administered intravenously for the first 5 days, followed by oral administration. Intraoperative cultures yielded primarily *Pseudomonas* spp. and *Enterobacter cloacae*. Cure was observed in 79% of patients. Cure was defined as an absence of clinical, biological and radiological evidence of infection following all postoperative treatment. Failure was defined as any other outcome. Erythema or pain at site of injection, alteration of taste and diarrhea were reported by four patients. However, no patients discontinued the treatment. Failure was observed in five patients at a mean of 8 months (range 1-16) following surgery. Each of these patients underwent further surgery and additional treatment because of recurrent sepsis. One patient with infected hip prosthesis who underwent debridement died apparently of myocardial infarction and reported as unrelated to antibiotic treatment.

MO Comment: The information regarding this single death in the study was limited. The other adverse effects reported including diarrhea, erythema or pain at site of injection are mentioned in the Cefepime label. Alteration of taste has been reported with use of fluoroquinolones and other antibiotics.

4. Liu Y-B, Lu X-J, Zong Z-Y, Yu R-J, Lu J-X, Zhang W, et al. A multicenter, double-blind, randomized clinical trial of parenteral cefepime in the treatment of acute bacterial infections. *Chin J Antibiot.* 2007;32(6):367-70,376.

This study is a multicenter, double blind, randomized study comparing the efficacy and safety of domestic injectable cefepime with “Maxipime” for the treatment of acute bacterial infections. Cefepime was administered intravenously at a dose of 1-2 g twice daily for 7 to 14 days. A total of 211 patients were enrolled in the study. The report states that at the end of treatment, the cure rate was 42.30% and effective rate was 84.61% in the trial group; while the cure rate was 48.59% and 79.43% in the control group (Maxipime®). The bacterial eradication rates were 91.3% and 86.7%, respectively. Adverse reactions reported in the study include skin rash, temporary acidophilia, and mild elevated transaminases.

MO Comment: The information provided in this paper was limited to the English translated clinical abstract. Please note that this study was performed in China and the text of the article was mainly in the Chinese language. The information provided was not clear as to the study design and study drugs.. It appears in the abstract that the “domestic injectable” cefepime was the primary test drug and Maxipime® (cefepime hydrochloride) was the control drug. There is no mention of other antibiotics in the abstract. The adverse reactions (skin rash and elevated transaminases) are mentioned in the cefepime label. Acidophilia was not defined in the abstract.

5. Paladino JA, Eubanks DA, Adelman MH, Schentag n. Once-daily cefepime versus ceftriaxone for nursing home-acquired pneumonia. JAm Geriatr Soc. 2007;55(5):651-7.

This is a prospective randomized, double-blind study comparing once daily intramuscular (IM) cefepime with ceftriaxone conducted in 6 skilled nursing facilities. The study objective was to assess and compare the efficacy, safety, and pharmacoeconomics of once-daily IM cefepime with those of ceftriaxone for the treatment of elderly long-term care facility residents with nursing home-acquired pneumonia (NHAP). The patients were residents aged 60 years and older with NHAP and not amenable to oral treatment but not requiring hospitalization. Patients were randomized to receive 1 g IM every 24 hours of cefepime or ceftriaxone. After 3 days, patients with objective evidence of improvement could be switched to oral antibiotics to complete a 10 to 14-day course. Sixty-nine patients were randomized; 61 were evaluable: (32 to cefepime, 29 to ceftriaxone). Clinical success rate was 78% in the cefepime-treated group and 66% in the ceftriaxone-treated group. Adverse reactions reported include mild discomfort at site of injection for both cefepime and ceftriaxone. Seven patients (11.5%) were hospitalized: two cefepime-treated patients (6.2%) for 10 days and five ceftriaxone-treated patients (17.2%) for 25 days. Five patients (8%) died in the study: two cefepime-treated patients (6.2%) and three ceftriaxone-treated patients (10.3%). Pneumonia or its sequelae was reported as the cause of death.

MO Comment: Discomfort at site of injection is a local reaction commonly reported with cefepime use. The details of the deaths in this study were not reported in this article. Patients who died of pneumonia were considered clinical failures.

6. Yakovlev SV, Stratchounski LS, Woods GL, Adeyi B, McCarroll KA, Ginanni JA, et al. Ertapenem versus cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit. Eur J Clin Microbiol Infect Dis. 2006 ;25(10):633-41.

This was a prospective, double-blind, multicenter, international study, conducted from April 1999 through April 2002. The study compared the efficacy and safety of ertapenem and cefepime as initial treatment for adults with pneumonia acquired in skilled-care facilities or in hospital environments outside the intensive care unit. Patients ≥ 18 years of age were eligible for the study if they were diagnosed with hospital/healthcare-associated pneumonia (HHCAP). Ertapenem 1 g once a day or cefepime 2 g every 12 h were administered intravenously. The primary efficacy outcome was the clinical response rate in the clinically evaluable patients at the test-of-cure (TOC) visit (7-14 days after completion of study therapy). At the TOC assessment, favorable response rate was 87.3% in the ertapenem-treated group and 86% in the cefepime-treated group.

Commonly reported drug-related clinical and laboratory adverse experiences in this study included: For Ertapenem treatment group (n=148): oral candidiasis (4.1%), nausea (2.7%), infusion-site complication (2.0%), diarrhea (2.0%), rash (2%); increased ALT (1.5%),

increased AST (3.0%), increased alkaline phosphatase (3.7%); and increased platelet count (7.0%). For Cefepime treatment group (n=150): oral candidiasis (2.0%), nausea (0.7%), infusion-site complication (2.0%), diarrhea (1.3%), rash (2%); increased ALT (2.9%), increased AST (2.2%), increased alkaline phosphatase (2.9%); and increased platelet count (4.2%).

The deaths in the study were: 21 (14.2%) patients in the ertapenem group and 20 (13.3%) in the cefepime-treated group. Ten of 21 (48%) patients (ertapenem group) and 12 of 20 patients (cefepime group) who died during the study had APACHE scores >15. The article states that no death was judged to be drug-related.

MO Comment: The adverse reactions experienced by patients in the study are mentioned in the cefepime label. Detailed information regarding the deaths in this study were not provided in this article.

7. Yan X-R, Jia L-N, Gui B-S, Wang T, Sun X-Z, Lan Y, et al. A multicenter randomized control clinical trial of cefepime hydrochloride injection in the treatment of acute bacterial infections. *Chin J Antibiot.* 2007;32(1) :33-6.

This was a multi-center, single-blind, randomized controlled study of cefepime hydrochloride versus cefepime in the treatment of moderate and serious acute bacterial infections. A total of 241 patients were enrolled in this study; 121 patients were treated with cefepime hydrochloride and 120 patients in the control group (cefepime). The reported cure rate for the cefepime hydrochloride treated-group was 54.39% and 54.21% in the cefepime-treated group. The adverse reactions reported included: GI events (primarily digestive reactions), occasional rash, elevation of hepatic enzymes, and decrease of leukocyte and hemoglobin. No deaths were reported.

MO Comment: The information provided in this article was limited to the English translated clinical abstract. It was not clear in the abstract whether the control drug was another form of cefepime. Please note that this study was performed in China and the text of the article was mainly in the Chinese language. No specific details regarding gastrointestinal adverse events . But were described as “digestive” reactions. The adverse reactions reported in this study are probably cefepime-related.

8. Zhu C-Q, Dong S-X, Chen Y, Gui Q, Pan H. Efficacy of cefepime on the treatment of senile with lower respiratory infections. *Chin J New Drugs.* 2006;15(13):1104-6.

This was a study to evaluate the efficacy and safety of cefepime in the treatment of lower respiratory infections (LRTI) probably in (?) elderly patients. The abstract reports that 80 patients with LRTI were treated with cefepime 4 g per day intravenously. The response rate of cefepime-treated patients was 75% and bacterial eradication rate was 69.3%. No side-effects were observed in this study.

MO Comment: The information provided in this article was limited to the English translated clinical abstract. The study design was not provided in the abstract. Please note that this study was performed in China and the text of the article was mainly in the Chinese language. No adverse events reported in this study.

9. Capparell FJ, Diaz MF, Hlavnika A, Wainsztein NA, Leiguarda R, Del Castillo ME. Cefepime-and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology*. 2005;65:1840.

This is a case report of an 85-year-old man who was admitted to the ICU because of sepsis and abdominal pain. The patient had a history of hypertension, obesity, a coronary artery bypass graft, colon cancer surgically treated with remission, abdominal aneurysm surgically corrected, and deep venous thrombosis on oral anticoagulation. He experienced an acute confusional syndrome during a previous admission due to an epididymitis treated with a cephalosporin (not specified). The initial workup suggested an acute urinary tract infection. His APACHE II score was 13. His serum creatinine level was 0.8 mg/dL. He was started on cefepime 1 g IV BID and amikacin 1 g IV per day. After 48 hours, he continued only with cefepime 2 g IV BID, as blood and urinary cultures were positive for *E. coli*. Twenty hours later, he developed acute delirium, which was treated with IV haloperidol (2.5 mg) and oral olanzapine (2.5 mg) with partial success. Brain CT was normal. His neurologic condition further deteriorated; he was stuporous, pupils were symmetric and reactive to light, ocular fundus was normal; extraocular movements were full; no deficits were found in the remainder of the cranial nerves. There were no meningeal signs, and neither focal motor nor sensory deficits were present. Deep tendon reflexes and plantar responses were normal. He had no hemodynamic alteration, and temperature was normal. He was intubated. He had normal arterial blood gases, blood cell count, serum chemistry test, and ammonium level. His creatinine level was 0.8 mg/dL and his 24-hour measured creatinine clearance was 75 mL/min that day. He had repeat negative blood, urinary, and bronchial lavage cultures. He had a normal CSF examination. An EEG showed slow symmetric 4- to 7-Hz wave activity but no evidence of epileptic discharges. Because of the possibility of drug-induced encephalopathy, psychotropic drugs and cefepime were stopped, and the antibiotic was changed to piperacillin/tazobactam. One day after withdrawal of cefepime, his neurologic status markedly improved, and the patient was extubated. After 7 days of IV antibiotic therapy, the patient received cefixime 400 mg/day PO. Thirty-six hours later, his conscious state gradually deteriorated, with delirium and stupor leading again to the need for tracheal intubation. His renal function remained normal (creatinine 0.7 mg/dL). Despite exhaustive workup, no etiology other than cefixime was found to explain the encephalopathy. The antibiotic was changed, and the patient fully recovered in less than 36 hours. He completed treatment and was discharged with a normal neurologic status. The authors stated that the temporal association of the encephalopathy induction and resolution with the cefepime and cefixime administration and withdrawal makes the

two drugs highly likely to be responsible for the encephalopathy.

MO Comment: (Note: This case report has been previously summarized in the Clinical review for the original submission of NDA 50-817.) This patient with normal renal function developed encephalopathy induced by cefepime or cefixime. Neurotoxicity associated with cephalosporins has been reported in patients with renal failure or overdose but rarely in patients with normal renal status. The reviewer concurs with the authors' assessment that the two antibiotics likely caused the encephalopathy.

10. De Silva DA, Pan A B-S, Lim S-H. Cefepime-induced encephalopathy with triphasic waves in three Asian patients. *Ann Acad Med Singapore*. 2007;36(6):450-1.

This is a case report of three Asian patients who developed encephalopathy and documented triphasic waves on electroencephalogram (EEG) while on treatment with cefepime.

Patient 1: A 77-year-old Chinese male patient with end-stage renal failure on hemodialysis presented with acute pancreatitis. He was started on intravenous ceftriaxone for 6 days before the antibiotic coverage was changed to intravenous cefepime at 2 g twice a day. After 4 days of cefepime, he became confused and developed myoclonus. The initial EEG showed semi-periodic, generalized but predominantly bifronto-central triphasic waves at 1 to 2 Hz. Other abnormalities included abnormal liver function tests: bilirubin 9 umol/L, alkaline phosphatase (ALP) 319 U/L, alanine aminotransferase (ALT) 76 U/L, and aspartate aminotransferase (AST) 38 U/L. The ammonia level was normal (17 umol/L). His renal function did not deteriorate: (baseline serum urea was 8.4 mmol/L and creatinine 371 mmol/L while serum urea was 7.8 mmol/L and creatinine 276 mmol/L when he was encephalopathic). He continued to receive regular hemodialysis when he was encephalopathic. Three days after the cessation of cefepime, he was less confused. A repeat EEG was normal.

Patient 2: A 71-year-old Indian male patient with alcohol-related liver cirrhosis was admitted for otitis media. He was started on intravenous ceftriaxone and ciprofloxacin for 2 weeks before being given cefepime at 2 g twice a day intravenously. After 3 days of cefepime, he became confused and developed asterixis. The initial EEG showed periodic generalized triphasic waves at 1 to 2 Hz, localized maximally over the fronto-central regions. His liver function did not deteriorate: baseline serum bilirubin was 11 umol/L, similar to the level of 10 umol/L while encephalopathic. The ammonia level (22 umol/L) and renal function (serum urea 4.4 mmol/L, creatinine 129 mmol/L) were normal. Two days after cefepime cessation, the confusion and asterixis resolved. A repeat EEG showed disappearance of triphasic waves.

Patient 3: A 59-year-old Chinese female patient with end-stage renal failure on hemodialysis presented with infected gangrene of the right big toe. She was started on intravenous vancomycin. He also developed a right big toe disarticulation. Due to ascending cellulitis, a right below-knee amputation was subsequently performed. After 2 weeks of vancomycin, the antibiotic was changed to cefepime 1 g once a day, adjusted for her renal function. After 2 days of cefepime, she became drowsy and confused with myoclonic jerks of both upper limbs. Her initial EEG showed periodic triphasic waves. Liver function tests were normal: bilirubin 7 $\mu\text{mol/L}$, ALP 98 U/L, ALT 15 U/L, and AST 19 U/L. Her renal function did not deteriorate and she was continued on regular hemodialysis. The baseline serum urea was 25.5 mmol/L and creatinine 662 mmol/L , while urea was 19.1 mmol/L and creatinine 602 mmol/L when she was encephalopathic. Four days after discontinuation of cefepime, she was alert and orientated. Her myoclonus resolved. A repeat EEG 7 days later showed no triphasic wave.

MO Comment: Neurotoxicity is a known adverse effect of cephalosporins including cefepime and manifested as encephalopathy, myoclonus and asterixis as demonstrated in these three patients.

11. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic consideration, and literature review. *Pharmacotherapy*. 2006;26(8):1169-74.

This is a case report of a 67-year-old woman with multiple medical histories, including diabetes mellitus, chronic renal insufficiency, hypertension, asthma, anemia of chronic disease, breast cancer with mastectomy, and recurrent urinary tract infections. The patient was admitted to the hospital because of lethargy and confusion and found to have *E. coli* UTI. The patient was initially administered linezolid 600 mg bid I.V. and cefepime 1 g/d. A urine culture revealed sensitivity to cefepime and linezolid was discontinued on day 2. The patient remained lethargic and confused. Cefepime was increased to 2 g/day. On day 5, the patient apparently became alert and could answer simple questions. However on day 8, her lethargy and confusion recurred and developed myoclonus in her extremities and occasionally in the trunk. Blood cultures showed no growth and her urine culture grew less than 1000 colonies/mL. Her BUN was 50 mg/dl and serum creatinine was 2.1 mg/dl. Liver and thyroid function tests were within normal limits. Cefepime-induced neurotoxicity was suspected. Cefepime was discontinued on day 8. Clonazepam and levetiracetam were administered for seizure prophylaxis. MRI and computed tomography scan performed on admission revealed no acute infarct. Electroencephalogram (EEG) obtained on day 10 revealed generalized background slowing and multiphasic sharp waves. The patient's serum cefepime level measured on day 8, 24 hours after the last dose was 39 $\mu\text{g/mL}$. The level declined 18 hours later (day 9) to 10 $\mu\text{g/mL}$ and was below 5 $\mu\text{g/mL}$ at day 10. On day 10, the patient's condition improved except the myoclonic jerks in the right arm which stopped by day 12. Clonazepam was discontinued on day 11 and levetiracetam on day 13. The report states that the patient's mental status returned to

baseline by day 17.

MO Comment: Neurotoxicity is a known adverse event associated with cefepime but most probably underreported in patients with renal impairment who receive relatively excessive doses. In some cases, it has been reported that with drug cessation, neurotoxicity resolves. Other cases have been reported that required hemodialysis to resolve the neurotoxicity. It is of great importance that in patients with renal disease, the maintenance dose of cefepime should be reduced and patients should be monitored for neurotoxicity. (Note: This case report has been summarized in the Clinical review for the original submission of NDA 50-817.)

12. Lin C-M, Chen Y-M, Po HL, Hseuh I-H. Acute neurological deficits caused by cefepime: a case report and review of literature. *Acta Neurol Taiwan*. 2006;15(4):269-72.

This is a case report of a 91-year old woman without other medical history except right hip fracture who was admitted because of high fever and right flank pain. A UTI was suspected and empirical therapy of cefepime 2 g q 8h by intravenous drip was administered. On the 9th day, the patient developed stupor. An emergency brain CT scan showed no abnormalities. Her blood chemistry results showed no abnormalities. Two hours later, the patient went into respiratory failure and was intubated and transferred to the ICU. Her urine culture was positive for *Pseudomonas aeruginosa*. But no blood cultures were obtained. She then developed convulsions and was treated with phenytoin. Cefepime was discontinued on the 14th day of cefepime treatment because the UTI was resolved. Four days later, her convulsions and myoclonus resolved. She was extubated and discharged from the ICU without neurological deficits. She was discharged home on the 36th day after discontinuation of cefepime.

MO Comment: It appears in this case that cefepime use in the elderly patients in good health might be a contributing factor to the neurotoxicity. Physicians should be aware of the potential risk of developing neurological events with cefepime use in the elderly patients using high dose.

13. Moreno E, Davila I, Laffond E, Macias E, Isidoro M, Ruiz A, et al. Selective immediate hypersensitivity to cefepime. *J Investig Allergol Clin Immunol*. 2007;17(1):52-4.

This is a report of a 61-year old man with multiple myeloma who was admitted to the hospital due to a 2-week long fever. He was given treated initially with ciprofloxacin and amoxicillin/clavulanic acid without response. He was then given cefepime 2 g q d intravenously. Five minutes after the first dose, the patient presented with generalized pruritus, urticaria, dyspnea and wheezing. He was treated with methylprednisolone

and dexchlorphenamine intravenously. This patient had apparently tolerated cefepime two years before this event and he has no history of allergy or atopy. The patient underwent prick and intradermal skin testing with penicillin and cephalosporin reagents. The skin tests were positive to cefepime and negative to other beta-lactam antibiotics. Controlled administration of amoxicillin/clavulanate and ceftazidime was well tolerated by the patient.

MO Comment: This report appears to be a selective hypersensitivity to cefepime as demonstrated by skin and challenge tests. The literature reports that cases of hypersensitivity to cefepime is rare. Given the clinical presentation and history of this patient including his previous exposure to cefepime and positive intradermal test, strongly suggest an IgE-mediated reaction (type-I allergic reaction). The patient experienced initial symptoms of pruritus, urticaria, dyspnea and bronchospasm. But there was no report of hypotension, tachypnea and tachycardia progressing to anaphylaxis. Urticaria is mentioned in the cefepime label. However, bronchospasm is not mentioned in the cefepime label.

14. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007;7(5):338-48.

This meta-analysis evaluated 57 randomized controlled trials that compared cefepime with a different β -lactam antibiotic. This study identified a higher incidence of all-cause mortality in patients treated with cefepime compared to other β -lactam antibiotics (risk ratio 1.26 [95% CI 1.08-1.49]). Among subcategories of patients with febrile neutropenia, increased mortality with cefepime was seen (RR 1.42 [95% CI 1.09-1.84]). In this study, the authors did not describe the incidence of breakthrough bacteremia and microbiologically identifiable infections in the cefepime-treated patients who died compared to the comparator-treated patients. The authors offered two possible explanations for the increased risk of all-cause mortality: 1.) Undiagnosed cases of encephalopathy or non-convulsive status epilepticus, or 2.) Inadequate antimicrobial efficacy in vivo. The authors concluded that the main limitation of this meta-analysis review was the lack of complete mortality data.

MO Comment: This is the second of two meta-analysis studies performed by Yahav, et al. concerning increased mortality in patients treated with cefepime. This was a well-designed systematic review using methods to assess heterogeneity and bias. The Agency is currently reviewing the mortality data information provided by Bristol-Myers Squibb (BMS) Company. (Note: This article has been previously summarized in the Clinical review for the original submission of NDA 50-817.)

15. U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Early communication about an ongoing safety review-cefepime (marketed as Maxipime). November 14, 2007.

MO Comment: This early communication publication is in keeping with FDA's commitment to inform the public about its ongoing safety review of cefepime.

MO Conclusion:

The review of this safety update provided a new safety information for cefepime regarding increased mortality based on the meta-analysis findings by Yahav et al. This finding of increased mortality is the subject of an on-going safety review by the Agency. The potential impact of this safety issue on cefepime labeling and health care prescribers remains uncertain pending receipt of additional data from BMS and completion of the Agency's safety review.

The literature articles provided some safety information for cefepime use. The adverse reactions in these publications are mentioned in the cefepime label which include: 1) Clinical adverse reactions: local reactions (rash and discomfort on site of injection); GI (diarrhea, nausea, and vomiting); neurotoxicity (encephalopathy, myoclonus, and convulsions); pruritus, urticaria and anaphylaxis); and 2) Laboratory adverse reactions: increased hepatic transaminases, increased platelet count, and decreased leukocyte count. The literature articles had shortcomings (i.e., lack of details about study design and comparator agents, lack of reporting of adverse event frequency and severity, few details to explain circumstances of death in the case reports, wide range of cefepime dosages used, language translation barriers) which hinder an adequate safety assessment and causality assessment in relation to cefepime administration. The issue of increased mortality cited in the meta-analyses is the critical safety issue whose impact remains to be determined as part of a separate ongoing safety review.

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/s/

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CLINICAL REVIEW

Application Type	NDA
Submission Number	50-817
Submission Code	N-000
Letter Date	01-March-2007
Stamp Date	02-March-2007
PDUFA Goal Date	01-January-2008
Reviewer Name	Alma C. Davidson
Review Completion Date	November 14, 2007
Established Name	Cefepime Injection in GALAXY Container
(Proposed) trade name	Cefepime Injection in GALAXY Container
Therapeutic Class	Cephalosporin
Applicant	Baxter Healthcare Corporation
Priority Designation	S
Formulation	Solution, injection
Dosing Regimen	1 to 2 grams q8h or 12h
Indication	To treat infections that are proven or strongly suspected to be caused by susceptible bacteria
Intended Population	Adult and Pediatric patients

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(MO Note: Some of the sections in this clinical review template has been removed since there are no clinical studies conducted in this 505(b)(2) application and no information available for the particular section or subsection.)

1 EXECUTIVE SUMMARY

Cefepime is a cephalosporin antibiotic marketed as MAXIPIME[®], the reference listed product by Bristol-Myers Squibb Company. MAXIPIME[®] had been in the market worldwide since its approval on January 18, 1996. This new drug application, NDA 50-817 is a product by Baxter Healthcare Corporation. The product is Cefepime Injection in Galaxy Container and submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. A 505(b)(2) application may include results of investigations necessary for approval but were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [21 U.S.C. 355(b)(2)]. These applications are regulated under 21 CFR 314.54 which allow an applicant to rely on the Agency's finding of safety and effectiveness for an approved, reference listed drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(J) of the Act.

NDA 50-817 is submitted to support the use of a new delivery system (Galaxy plastic container) for cefepime injection. The review of this NDA relies on prior FDA determination of safety and effectiveness for the reference listed drug, MAXIPIME[®] (Cefepime hydrochloride) for Injection.

1.1 Recommendation on Regulatory Action

Based on evidence concerning increased mortality among patients treated with cefepime, as reported in two recent meta-analysis studies by Yahav, et al., the clinical reviewer has safety concerns regarding cefepime use. Therefore, from the clinical perspective, the clinical reviewer is recommending an approvable action. The applicant needs to provide safety update information of cefepime or data verifying that the findings of these meta-analysis studies are accurate. These data should be reviewed and obtained from published and unpublished clinical studies for cefepime. The first study by Yahav, et al¹, found increased mortality associated with cefepime therapy in febrile neutropenic patients. The second study was a follow-up by the same investigators who found a 30-day all-cause mortality to be significantly higher with cefepime than with other β -lactam antibiotics (Risk ratios of 1.26 and 95% CIs 1.08 -1.49).²

The MO's recommendations for changes to the Cefepime Injection in GALAXY Container label are as follows:

- Addition of a statement in the Pediatric Use subsection as follows:

“Cefepime injection in Galaxy container should not be used in pediatric patients who require more than the recommended adult dose in order to prevent unintentional overdose.”

- Addition of new proposed statements in the “Patient Counseling information” section regarding adverse events of cefepime-related neurotoxicity. The statements are as follows:

“Patients should be advised of neurological adverse events that could occur with cefepime use. Patients should inform their healthcare provider at once of any neurological signs and symptoms to include encephalopathy (disturbance of consciousness, including confusion, hallucinations, stupor, and coma), myoclonus and seizures for immediate treatment, dosage adjustment, or discontinuation of cefepime.”

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity.

The clinical reviewer recommends that the following adverse events should be monitored as part of post-marketing surveillance program for cefepime:

- Encephalopathy (including confusion, disorientation, hallucinations, agitation, stupor, coma and related events)
- Seizures (convulsion, non-convulsive status epilepticus, myoclonus and related events)
- Fatal outcomes (including causes of deaths and causality assessments)

1.2.2 Required Phase 4 Commitments

The clinical reviewer recommends that the sponsor should develop a post-marketing patient registry to study patients treated with cefepime who develop neurotoxicities (i.e., encephalopathy and seizures), fatal events including causes of deaths, microbiologic data of patients at the time of death, and other rare adverse events that may arise during cefepime therapy.

1.3 Summary of Clinical Findings

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Cefepime Injection in GALAXY Container.

1.3.1 Safety

The safety of this product is supported by the clinical studies performed by Bristol-Myers Squibb using the reference listed drug, MAXIPIME[®] for Injection. The reviewer searched the safety database of the reference-listed drug for any additional safety information.

1.3.2 Dosing Regimen and Administration

Cefepime for Injection in GALAXY[®] Container, 1 g and 2 g is intended for intravenous use only.

2 INTRODUCTION AND BACKGROUND

Cefepime is a semi-synthetic, broad spectrum cephalosporin antibiotic classified within the fourth generation class. It has enhanced activity *in vitro* against Gram-positive and Gram-negative bacteria. Cefepime has been marketed in the U.S. for over a decade. The NDA for Cefepime (MAXIPIME[®] for Injection, NDA 50-679) was initially approved on January 18, 1996 for the following indications: Pneumonia (moderate to severe); Uncomplicated and

complicated urinary tract infections (including pyelonephritis); and Uncomplicated skin and skin structure infections. Subsequent approved indications include Empiric therapy for febrile neutropenic patients (May 16, 1997) and Complicated intra-abdominal infections (January 30, 1998). Both the reference listed drug substance and drug product, MAXIPIME[®] (Cefepime Hydrochloride) for Injection are currently manufactured by Bristol-Myers Squibb Company. The drug substance, cefepime hydrochloride, USP for this application, NDA 50-817 is currently manufactured by _____ in _____
_____ The drug product for NDA 50-817 is manufactured by Baxter Healthcare Corporation. The Applicant is seeking approval for Cefepime Injection in GALAXY Container (PL 2040 Plastic) for the same indications approved for MAXIPIME[®] for Injection related to intravenous use.

b(4)

2.1 Product Information

- Description of the product:

Cefepime Injection is a premixed liquid preparation (1g/50 mL and 2 g/100 mL) designed to be comparable to 1 g and 2 g MAXIPIME[®] (Cefepime for Injection) doses when the 1 g and 2 g MAXIPIME strengths are reconstituted with 50 mL and 100 mL of 5% Dextrose Injection, respectively.

Baxter's "ready-to-use" Cefepime Injection products requires no reconstitution prior to use. Baxter states that their drug product is consistent with MAXIPIME[®] and the USP monograph for Cefepime for Injection. Cefepime for Injection will be a mixture of Cefepime Hydrochloride, USP and L-Arginine, USP. The L-Arginine, at an approximate concentration of 725 mg/g of cefepime, is added to adjust the pH of the solution to 4.0 – 6.0, consistent with reconstituted MAXIPIME. Hydrochloric acid and/or additional L-Arginine may be used to adjust the solution pH, and approximately 2.06% dextrose will be added to render the formulation iso-osmotic. Baxter's premixed Cefepime Injection products will be packaged in GALAXY flexible plastic containers and stored frozen (-20°C) for long-term storage and is thawed prior to intravenous administration.

Cefepime for Injection, USP

Chemical Name: 1-[[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamidol]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7²-(Z)- (O-methyloxime), monohydrochloride, monohydrate

Chemical structure:

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Chemical formula: $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$

Molecular weight: 571.50

Dosage Strength: 1 g or 2 g

- Established Name: Cefepime Injection
in GALAXY Container
- Proposed trade name: Cefepime Injection
in GALAXY Container
- Chemical class: antibiotic
- Pharmacological class: cephalosporins
- Applicant's proposed indications, dosing regimens, age groups

Cefepime Injection in GALAXY Container has the same indications and dosing regimens as the reference listed drug, MAXIPIME[®] related to intravenous use only.

2.2 Currently Available Treatment for Indications

There are numerous antibiotics in the market that are approved for the same indications as Cefepime Hydrochloride, USP for Injection with the exception of "Empiric therapy for Febrile Neutropenic Patients" indication.

2.2 Availability of Proposed Active Ingredient in the United States

The active ingredient, Cefepime hydrochloride is marketed as MAXIPIME® for injection in the U.S. MAXIPIME® has been available in the U.S. market since 1996.

2.4 Important Issues With Pharmacologically Related Products

There are no safety or effectiveness concerns with pharmacologically related products. Recent labeling changes with other cephalosporins were made which included changes to the WARNINGS section and PRECAUTIONS/Information for Patients subsection regarding *Clostridium difficile* associated diarrhea (CDAD) as requested by the Agency in a letter to Sponsors dated September 29, 2006.

2.5 Presubmission Regulatory Activity

- On February 10, 2006, the Applicant submitted a letter of request to the Agency regarding their proposed NDA submission as a 505(b)(2) application for Baxter's premixed formulation of Cefepime injection.
- On March 22, 2006, the Applicant sent a letter to the Agency under PIND 73,452 regarding the submission of information package for Pre-NDA Type B Meeting for April 24, 2006.
- On April 24, 2006, the Applicant and the Agency had a pre-NDA meeting by teleconference regarding the proposed 505(b)(2) NDA for Cefepime for Injection in Galaxy Container. The purpose of the pre-NDA meeting was to address the proposed content of the 505(b)(2) application for the Baxter premixed formulation of Cefepime injection and obtain the Agency's input on the Applicant's development strategy. In that meeting, the Agency agreed that no additional clinical studies of efficacy and safety were required.

2.6 Other Relevant Background Information

The Applicant does not have any marketing history with cefepime injection in Galaxy container.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The reader is referred to the CMC review by the chemistry reviewer, Milton Sloan for detailed descriptions of the drug product and manufacturing process. For microbiology findings, please refer to the microbiology review by Avery Goodwin.

3.2 Animal Pharmacology/Toxicology

There were no additional toxicity studies required in this application. However, studies were undertaken by the Applicant to qualify the safety of the impurity profile of Baxter's pre-mixed cefepime formulation. The studies include: A 14-day repeat-dose general toxicity study in rats; an *in vitro* mouse lymphoma assay; an *in vitro* human peripheral lymphocyte assay; and an intravenous *in vivo* mouse micronucleus assay. (Note: The reader is referred to the pharmacology/toxicology review by Dr. Amy Ellis, for details.)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The applicant relies on the Agency's finding of safety and effectiveness for the approved, reference listed drug, MAXIPIME® (cefepime hydrochloride, USP) for Injection.

4.2 Financial Disclosures

Since there are no new clinical studies performed by the applicant for this submission, therefore financial disclosure of clinical investigators is not applicable.

5 CLINICAL PHARMACOLOGY

There are no new clinical pharmacology data submitted with this application. Cefepime for Injection in Galaxy Container contains the same active ingredient as the reference listed drug, MAXIPIME® (cefepime hydrochloride, USP) for Injection by Bristol-Myers Squibb. Baxter has requested a waiver for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence of Cefepime for Injection in Galaxy Container in accordance with 21 CFR 320.22(b)(1). The waiver was granted. (Note: The reader is referred to the clinical pharmacology review of Jeffrey Tworzyanski, Pharm. D. for details.)

5.1 Pharmacokinetics

The pharmacokinetics data are the same as the reference listed drug, MAXIPIME® (cefepime hydrochloride, USP) for Injection.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Cefepime Injection in Galaxy Container. The review of this NDA relies on prior FDA determination of effectiveness for the reference listed drug, MAXIPIME®.

6.1 Indication

The indications for this product are similar to the reference listed drug, MAXIPIME® (cefepime hydrochloride) for Injection.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Literature Review

The Applicant stated that a review of the published literature on Cefepime hydrochloride to identify and assess any new clinical safety information was performed. In addition, the Applicant also reviewed the package insert for MAXIPIME® (December 2003). According to the Applicant, based on the review of the cefepime literature, there are no changes regarding safety needed to the currently approved MAXIPIME® label.

The reviewer summarizes the submitted 20 published literature articles on cefepime safety information. In addition, the reviewer performed a literature search using PubMed, Embase, search of relevant cases in FDA-Adverse Events Reporting System DataMart and review of the recent annual report for MAXIPIME®.

A. This review of the literature focuses on the safety profile of cefepime. The submitted articles are summarized as follows:

1. Badaro R, et al. A Multicenter Comparative Study of Cefepime versus Broad-Spectrum Antibacterial Therapy in Moderate to Severe Bacterial Infections. *Brazilian Journal of Infectious Dis* 2002; 6(5):206-218.

This article reports an open-label, multi-center clinical study evaluating the safety and efficacy of cefepime empiric monotherapy compared with standard broad-spectrum combination therapy for hospitalized adult patients with moderate to severe community-acquired bacterial infections.

In this trial, 84 (53%) cefepime and 81 (51%) comparator-treated patients reported at least 1 treatment-emergent event. Twenty-five (16%) cefepime and 30 (19%) comparator-treated patients had at least 1 adverse event considered to be drug-related. For cefepime injection, injection site reactions, phlebitis, diarrhea, and abdominal pain were the most common drug-related adverse events reported. For the comparator regimens, phlebitis, fever, nausea, rash, and tachycardia represented the most frequently reported drug-related adverse events. A total of 27 (9%) patients died during the study (17 cefepime, 10 comparator). The article reports that the majority of deaths (86%) occurred in patients diagnosed with CAP prior to start of antibiotic therapy. Deaths were apparently not treatment related, but were due to underlying disease and comorbidity.

MO Comment: The adverse events (AEs) for cefepime noted in this trial include injection site reactions, phlebitis, diarrhea, and abdominal pain. These AEs are mentioned in the RLD label except abdominal pain. Seventeen patients died in the cefepime treated group versus 10 patients in the comparator group. The authors stated that mortality was apparently not treatment related but patient's underlying disease and comorbidity have caused their deaths.

2. Huang C-K, Chen Y-S, Lee SS-J, et al. Safety and efficacy of cefepime versus ceftazidime in the treatment of severe infections. *J Microbiol Immunol Infect.* 2002;35(3):159-67.

This article reports a clinical trial describing an open-label randomized study to evaluate the safety and efficacy of cefepime versus ceftazidime as initial therapy in the treatment of hospitalized patients with severe bacterial infections, including septicemia, UTI, bacterial bronchitis, bacterial pneumonia and intraabdominal infection. Fifty-two patients with severe infections were eligible and prospectively randomized to receive cefepime (26 patients) or ceftazidime (26 patients) during a 15-month period.

Two patients treated with cefepime died, one from superinfection and one from suspected paraneoplastic syndrome. The most common AEs were hyperkalemia, impaired liver chemistry, diarrhea and hypoalbuminemia in both treatment groups. Two patients in cefepime group and 3 in ceftazidime group reported local intolerance at the injection site, but all continued treatment. Other AEs occurring during treatment included femoral neck fracture secondary to accidental fall (1 patient), upper airway viral infection (1 patient), and disturbed consciousness as complication of hypercalcemia (1 patient) in the cefepime group.

MO Comment: The adverse reactions noted in this trial including hyperkalemia, impaired liver chemistry, diarrhea, local intolerance at injection site and disturbance of consciousness are mentioned in the cefepime label.

3. Cherif H, Bjorkholm M, Engervall P, Johansson P, Ljungman P, Hast R, et al. A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. *Scand J Infect Dis.* 2004;36(8):593-600.

This article describes a prospective open-label, randomized, multicenter study comparing the efficacy and safety of cefepime with that of imipenem-cilastatin for management of febrile neutropenia in adult patients with hematological malignancies. Between September 1996 and December 1998, 180 patients with 207 episodes of febrile neutropenia were randomized (105 to cefepime and 102 to imipenem-cilastatin) in 7 major hematology departments in Sweden. At final evaluation 1-2 weeks after completion of antibiotic therapy, cefepime success rate was 40% and 51% in the imipenem-cilastatin treated group. The 4-week overall mortality rate was 5% by treatment group. Three (2%) of the cefepime treated patients and 4 (3%) of imipenem-cilastatin treated patients died as a result of infections. AEs occurring during or 1-2 weeks after cessation of therapy included nausea/vomiting, 8 (7%), diarrhea 8 (7%), skin rash or pruritus 6 (5%), and headache 1 episode in the cefepime group.

MO Comment: The adverse reactions noted in this trial related to cefepime use are mentioned in the cefepime label.

4. Tamura K, Imajo K, et al and the Japan Febrile Neutropenia Study Group. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis.* 2004;39(suppl 1):S15-24.

This article describes a prospective open-label, randomized, multicenter study comparing cefepime or cefepime in combination with amikacin in treating febrile neutropenia in patients with hematological malignancies. The report states that this study was conducted according to the Evidence-based recommendations on Antimicrobial Use in Febrile Neutropenia in Japan as proposed at the Miyazaki meeting (February 1998). Between May 1, 2000 and February 1, 2002, there were 201 patients enrolled from 30 centers in this study and randomized to receive cefepime monotherapy (n=100) or cefepime/amikacin combination therapy (n=101). Twelve patients were not evaluable for the efficacy of therapy because of inclusion criteria violations. Among the 189 evaluable patients, 5.8% had microbiologically and 10.6% had clinically documented infections. At day 3, 31 patients (32.6%) treated with cefepime monotherapy and 43 patients (45.7%) treated with combination therapy achieved complete defervescence.

Seven early deaths occurred (days 5, 6 [2 patients], 7, 11, 22, and 23) in the monotherapy arm. Five early deaths occurred (days 8, 18 [2 patients], 22, and 24) in the combination-therapy arm. Of the 4 patients who died within 7 days of therapy in the monotherapy arm, 1 died of septic shock on day 5 and another died of progression of leukemia and infection on day 6. Adverse events possibly related to therapy occurred in 5 patients in the monotherapy arm and in 4 in the combination-therapy arm. These events including skin rash in 3 patients, renal dysfunction in 1, and elevation of liver function test results in 5 were mild and did not require cessation of treatment with the study drug, except for 1 patient receiving combination therapy who had skin rash.

MO Comment: The adverse reactions noted in this trial are mentioned in the cefepime label. Seven patients died in the cefepime monotherapy group and 5 died in the combination group. The type of infections as causes of deaths was not mentioned in this paper.

5. Konstantinou K, Baddam K, Lanka A, Reddy K, Zervos M. Cefepime versus ceftazidime for treatment of pneumonia. *J Int Med Res.* 2004; 32(1):84-93.

This article describes a retrospective, observational study conducted at the William Beaumont Hospital, Royal Oak, Michigan over a 3-year period between May 1997 and May 2000 which compared patients with pneumonia (community and hospital-acquired), with and without sepsis treated with cefepime (n=66) or ceftazidime (n=132). Clinical and microbiologic cure occurred in 63.6% and 58.3% of the cefepime and 56.1% and 45.5% of the ceftazidime-treated patients, respectively.

Deaths occurred in 31.8% and 34.8% of the cefepime and ceftazidime-treated patients, respectively. Adverse events including gastrointestinal events occurred in 7.6% and 9.1% of the cefepime and ceftazidime-treated patients) and allergy occurred in 4.5% of the

ceftazidime treated group and 0.0% of the cefepime treated group.

MO Comment: The adverse events mentioned in this article are noted in the cefepime label. The cause of deaths was not reported in this article.

6. Tamura K et al, and Kyushu Hematology Organization for Treatment (K-HOT) Study Group
Cefepime or carbapenem treatment for febrile neutropenia as a single agent is as effective as a combination of 4th-generation cephalosporin + aminoglycosides: Comparative study. *Am J Hematol.* 2002;71(4):248-55.

This article describes the study conducted by Kyushu Hematology Organization for Treatment (K-HOT) Study Group in order to validate the practice guidelines for antimicrobial use in patients with febrile neutropenia (FN) as proposed at the Miyazaki meeting (Feb. 1998). The K-HOT study group consists of 18 participating university-affiliated medical institutions, but 17 enrolled the patients into the study. Patient accrual was initiated in May 1999 and study period was extended to August 2000 due to delayed IRB approval in other hospitals. One hundred sixty-five patients with febrile neutropenia were enrolled and randomized as follows: 42 to cefepime; 41 to a carbapenem; and 82 to receive a combination of cefepime and an aminoglycoside. Of the 165, 153 were evaluated for primary efficacy. The study states that each treatment arm achieved complete defervescence in more than 60% of the patients within 3 days.

Deaths occurred early in 3 patients at days 9, 16, and 19 after initiation of antibiotics for FN in patients treated with a single antibiotic; and 3 in the combination regimen group at days 14, 15, and 20, respectively. Two patients died of infection. The first patient had MRSA cellulitis after bone marrow transplantation complicated with severe veno-occlusive disease. The second patient had possible sepsis complicated with painful pyoderma gangrenosum. Other causes of death include acute renal failure in 1 patient, CHF in 1 patient, subdural hematoma in 1, and disease progression of acute adult T-cell leukemia (ATL) in 1. The article reports that adverse events possibly related to cefepime, a carbapenem, and a combination was found in 9, 11, and 12 patients, respectively. It further reports that a (grade 3) diarrhea was seen in one patient on carbapenem and (grade 2) serum alkaline phosphatase elevation while on combination therapy. The AEs in other patients were generally mild (grade 1) and required no specific treatment. cefepime, a carbapenem, and a combination were found in 9, 11, and 12 patients, respectively. It further reports that a (grade 3) diarrhea was seen in one patient on carbapenem and (grade 2) serum alkaline phosphatase elevation while on combination therapy. The AEs in other patients were generally mild (grade 1) and required no specific treatment.

MO Comment: The adverse events reported in this article are mentioned in the cefepime label. However, the AEs experienced by some patients in the cefepime monotherapy group were not reported in this article. Two of the deaths occurred in patients with serious infections including MRSA and sepsis (etiology unclear).

7. Moschovitis G, Gallen St, Bernasconi E, Cerny A, Lugano and the Swiss Cefepime Study Group. Cefepime is a safe and effective empiric treatment of moderate to severe bacterial infections in the elderly. *Chemother J.* 2002;11(5):183-7.

This article describes a prospective, open-label, non-randomized, multicenter study in Switzerland between May 1996 and December 1997. The types of infection included in this study were pneumonia, febrile neutropenia, sepsis syndrome, intraabdominal infections, urinary tract infections, and skin and soft tissue infections. Cefepime 2 g was administered intravenously every 12 h (and every 8 h in patients with febrile neutropenia). The dose was adjusted to patient's renal function according to manufacturer's recommendations.

The article reports that microbiological data were obtained only when clinically indicated. A total of 473 patients were recruited. Three patients were excluded. Of the 470 patients, 49 could not be assessed for clinical response because there was no clinical assessment made by the physician. Of the 421 patients, clinical cure occurred in 249 (59.1%) and clinical improvement in 135 (32.1%), treatment failure in 31 (7.4%) and relapse in 6 (1.4%).

Twenty-seven patients died during the course of the study (9 with moderate and 18 with severe infections). The report states that none of the deaths was related to the study drug. Adverse reactions were observed in 38/470 (8.1%) of the patients. The AEs observed in the study include: allergic skin reactions (exanthema, eczema, maculo-papular rash, pruritus, flushing) and gastrointestinal symptoms (diarrhea, nausea, abdominal pain, taste perversion) were observed 12 times for both skin and GI adverse events. Laboratory abnormalities (increase of ALT or alkaline phosphatase) were found in only seven cases. These laboratory abnormalities were possibly related to cefepime as judged by the treating physician. Leucopenia (mild) possibly related to cefepime was observed in two patients. In both cases, study drug was not discontinued and the patients were apparently cured. One case of thrombocytopenia was found in an elderly patient with moderate infection and normal renal function. The treating physician assessed this thrombocytopenia as unrelated to study drug. In patients <65 years old, 8/224 (3.6%) patients were prematurely withdrawn from therapy due to 9 AEs (5-allergic reactions, 3-diarrhea and one coma). In the group of >65 years, 8/246 (3.3%) had to be withdrawn from therapy due to 11 AEs (4-allergic reactions, one diarrhea, one nausea, one pruritus, one thrombocytopenia, 3 severe CNS effects-dystonia, psychosis, confusion). In these CNS events, a relationship to the study drug has not been confirmed.

MO Comment: The adverse events reported in this article are mentioned in the cefepime label. The cause of the reported deaths that occurred in 27 patients was not stated in the article. However, the authors stated that the deaths were not related to the study drug.

8. Sanz MA, Lopez J, Lahuerta JJ, et al and the Spanish PETHEMA Group. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia: results of an open, randomized, multicenter trial. *J Antimicrob Chemother.* 2002;50(1):79-88.

This article reports an open-label, comparative, randomized, multicenter study conducted in 18 Spanish Institutions. From May 1998 to April 2000, a total of 984 episodes of febrile neutropenia occurring in 969 adult patients were randomized into the study. Patients received either intravenous cefepime 2 g every 8 h or piperacillin/tazobactam (pip/taz) 4g/500 mg q 6 h and each patient received intravenous amikacin as a single daily dose of 20 mg/kg body weight (to a maximum of 1.5 g). Clinical response was determined at 72 h and at completion of therapy. Eight hundred and sixty-seven episodes were assessable for efficacy (432 cefepime, 435 piperacillin/tazobactam). This article reports that frequency of success without modification of the empirical therapy was nearly identical for cefepime plus amikacin (49%) compared with piperacillin/ tazobactam plus amikacin (51%). For microbiologically documented infections, success rates of 40% versus 39%, respectively, were found.

The overall rate of AEs considered related or probably related to study medications was similar in the two treatment groups: 10% for the cefepime group and 11% for the piperacillin/tazobactam group. The AEs included: nephrotoxicity (moderate to severe, probably attributable to aminoglycoside, 7 episodes in cefepime group and 6 in the pip/taz group; mild nephrotoxicity observed in 12 additional episodes); cutaneous allergic reaction (14 cefepime and 8 pip/taz); drug-induced hypokalemia (12 in cefepime and 13 pip/taz). The article states that hepatotoxicity, gastrointestinal intolerance and other intercurrent side effects were rarely associated with either of the study antibiotic.

Overall mortality rates at day 10 and at day 30 were 1.2% and 5.3%, respectively. The article states that mortality due to infection (presenting or secondary infection) occurred in a total of 10 patients: 4 patients died before day 10 (one cefepime and 3 pip/taz) and 6 additional patients at day 30 (one cefepime and 5 pip/taz). An additional 36 patients died of non-infectious causes, including underlying disease progression (n=14), fatal hemorrhage (n=11) and other causes (n=11).

MO Comment: The adverse events reported in this article are mentioned in the cefepime label. The type of infections that caused the deaths of ten patients were not mentioned in this article.

9. Fleming DR, Ziegler C, Baize T, Mudd L, Goldsmith GH, Herzig RH. Cefepime versus ticarcillin and clavulanate potassium and aztreonam for febrile neutropenia therapy in high-dose chemotherapy patients. *Amer J Clin Oncol.* 2003;26(3):285-8.

This article describes an open-label, randomized study comparing the efficacy and cost of empirical treatment with cefepime as monotherapy versus combination therapy consisting of ticarcillin/clavulanate and aztreonam in febrile neutropenic patients following high-dose chemotherapy, with or without radiation, and with or without peripheral blood stem cell

support. Treatment consisted of cefepime 2 g intravenously every 8 h or a combination of ticarcillin/clavulanate potassium 3.1 g intravenously every 6 h and aztreonam 1 g intravenously every 8 hours. The treatment evaluation was based on the following parameters: resolution of fever at 72 hours, incidence of diarrhea, the need to add vancomycin for Gram-positive organisms identified in blood cultures, the need to alter gram-negative antimicrobial coverage, death due to presumed sepsis during the study treatment, and the addition of amphotericin for additional antifungal coverage.

A total of 126 patients were entered into the study over a 28-month period (75 patients received cefepime and 51 patients received ticarcillin/clavulanate potassium and aztreonam). The article reports that using afebrile status following 3 days of therapy as primary endpoint, both regimens produced comparable clinical response rates (cefepime= 55% versus ticarcillin/clavulanate potassium + aztreonam=61%). The primary organisms in both groups were Gram-positive organisms requiring the addition of vancomycin therapy. Death due to infectious causes was reported as 3 (4%) in the cefepime group and 2 (4%) in the ticarcillin/clavulanate +aztreonam group.

MO Comment: Only infection-related mortality was reported in this study. The type of infection was not mentioned. No other AEs were reported in this study.

10. Bow EJ, Rotstein C, Noskin GA, Laverdiere M, Schwarer AP, Segal BH, et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis.* 2006;43(4):447-59.

This article reports a randomized, open-label, controlled, multicenter, non-inferiority clinical trial study among high-risk patients from 34 university-affiliated tertiary care medical centers in the United States, Canada and Australia. The patients had leukemia or undergoing hematopoietic stem cell transplantation and were hospitalized for empirical treatment of febrile neutropenia. Patients received piperacillin- tazobactam (pip/taz) 4.5 g every 6 h or cefepime 2 g every 8 h intravenously. For the 528 patients treated (265 received pip/taz and 263 received cefepime) success rates were 26.8% and 20.5%, respectively at the test-of-cure visit. There were 8 deaths (3%) in the pip/taz group and 15 (5.7%) in the cefepime group. The causes of death in the pip/taz group included pneumonia and respiratory failure in 4 multi-organ system failure in 1, sepsis syndrome in 1, intracranial hemorrhage in 1, and cardiac failure in 1. The causes of death in the cefepime group included pneumonia and respiratory failure in 9 patients, shock in 2, sepsis syndrome in 1, myocardial infarction in 1, pulmonary hemorrhage in 1, and cardiac failure in 1.

Reported adverse events included skin/mucous membranes, cardiorespiratory, gastrointestinal, CNS, and laboratory abnormalities. This study reports that more cefepime-treated patients discontinued the study drug before TOC than in the pip/taz treated patients (64 patients vs. 43 patients), mostly due to adverse events (cefepime: 30 patients vs. pip/taz: 19 patients). Rashes and diarrhea were reported frequently in both treatment groups (pip/taz: 29.4%, 34.3%; cefepime: 22.1%, 30.4%), respectively. *C. difficile* associated diarrhea was observed more often among cefepime recipients (6.8%) than among piperacillin-

tazobactam recipients (2.3%).

MO Comment: Death due to infectious causes in both treatment groups could be expected in these high-risk patients with febrile neutropenia. The AES occurring in the cefepime group are mentioned in the label.

11. Diekema DJ, Coffman SL, Marshall SA, Beach ML, Rolston KV, Jones RN. Comparison of activities of broad spectrum β -lactam compounds against 1,128 Gram-positive cocci recently isolated in cancer treatment centers. *Antimicrob Agents Chemother.* 1999; 43(4):940-3.

This article reports a surveillance *in vitro* study of 1,128 Gram-positive organisms isolated from 10 cancer treatment centers in the United States. The study states that cefepime and imipenem provide wider empiric coverage than widely used expanded-spectrum cephalosporins (i.e., ceftazidime and ceftriaxone) against these organisms.

MO Comment: The applicant provided this article but there is no safety information for cefepime reported in this article.

12. Paul M, Yahav D, Fraser A, et al. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2006;57(2):176-89.

This article describes a systematic review and meta-analysis of randomized controlled trials comparing antibiotics with anti-Gram positive spectrum to control or placebo, in addition to the same baseline antibiotic regimen in both treatment arms. Thirty-three trials fulfilled the inclusion criteria. Cefepime was assessed in 17 trials, comparing it with ceftazidime in 8 trials, imipenem in 4, piperacillin/tazobactam in 3 and meropenem in two. Data regarding all-cause mortality were obtained for all studies. The primary outcome assessed was all-cause mortality, 30 days following end of treatment. Secondary outcomes included treatment failure, infection-related mortality, treatment modification, microbiological failure, superinfection, and adverse events. The authors found that cefepime was associated with higher all-cause mortality at 30 days than other beta-lactams (RR 1.44, 95% CI 1.06-1.94). Infection-related mortality, bacterial superinfections and discontinuation of the allocated treatment were more common with cefepime, whereas no differences were observed regarding other secondary outcomes.

Adverse events requiring discontinuation occurred more frequently with cefepime. More patients in the cefepime arm discontinued treatment due to infections. Discontinuation due to treatment failure was not assessed separately.

MO Comment: This is the first of the two studies performed by Yahav, et al concerning increased mortality among patients with febrile neutropenia treated with cefepime. The authors stated that the major limitation of the study is the small number of studies identified and some of these studies did not provide comparative data for all-cause mortality. The cause of deaths among patients with febrile neutropenia in these cefepime trials was not mentioned in this meta-analysis review. The type of infections causing discontinuation of treatment with

cefepime was not reported in this study. Overall, this systematic review is a well performed study by these authors despite its limitation.

13. Baririan N, Chanteux H, Viaene E, Servais H, Tulkens PM. Stability and compatibility study of cefepime in comparison with ceftazidime for potential administration by continuous infusion under conditions pertinent to ambulatory treatment of cystic fibrosis patients and to administration in intensive care units. *J Antimicrob Chemother.* 2003;51(3):651-8.

This article reports a stability and compatibility study of cefepime. Cefepime has been examined for stability, potential liberation of degradation products and compatibility with other drugs under conditions mimicking its potential use by continuous infusion in cystic fibrosis and intensive care patients. Ceftazidime was used as a comparator. This report states that based on a limit of maximum 10% degradation, cefepime can be considered stable for a maximum of 24 h at 25°C but for only ~14 h at 30°C, and for <10 h at 37°C. Cefepime released unidentified degradation products if maintained at >30°C for >12 h as shown from an increase in pH and development of red-purple color. Incompatibilities were observed with erythromycin, propofol, midazolam, phenytoin, piritramide, theophylline, nicardipine, *N*-acetylcysteine and a concentrated solution of dobutamine. The authors concluded that cefepime cannot be used safely by continuous infusion if containers are kept from more than a few hours at 37°C (as will be the case for cystic fibrosis patients if using portable pumps carried under clothes); caution must be exercised in ICU patients if the temperature and co-administration of other drug is not kept under tight control.

MO Comment: Cefepime as shown in this study cannot be used safely by continuous infusion if containers are stored more than a few hours at 37°C.

14. Stein GE. Safety of newer parenteral antibiotics. *Clin Infect Dis.* 2005;41(5):293-302.

This article reviews the safety profiles of newer parenteral antibiotics including carbapenems, cephalosporins, fluoroquinolones, glycylicyclines, lipopeptides, oxazolidinones, and streptogramins. Cefepime is the only cephalosporin discussed in this article. This article reports that approximately 2000 patients with mild to severe bacterial infections were treated with cefepime in comparative clinical studies. According to this review, majority of patients received cefepime 2 g every 12 h by intravenous route and patients with less-severe infections received 0.5-1 g every 12 h. The most common AEs occurred in the digestive system (6.3%), including nausea (1.8%), diarrhea (1.7%), vomiting (1.5%), and constipation (1.2%). The most common AE associated with the use of cefepime use was headache (2.4%). Rash was noted in 1.8% of cefepime-treated patients. The most common laboratory test abnormalities included changes in liver function tests (ALT, 2% and AST, 1.5%). The incidence of seizures in association with the use of cefepime was rare: 11 episodes (0.2%); and only 3 episodes (0.1%) were of probable or unknown relationship to cefepime therapy. Neurotoxicity (e.g., confusion and disorientation) induced by cefepime have also been reported. These neurological changes were often associated with myoclonus and were most frequently encountered in elderly patients and uremic patients.

MO Comment: The neurological adverse events reported in this article are mentioned in the cefepime label.

15. Chow KM, Szeto CC, Hui AC-F, Wong TY-H, Li PK-T. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. *Pharmacotherapy*. 2003;23(3):369-73.

This article describes a retrospective review of 42 cases of cefepime-induced neurotoxicity and 12 cases of ceftazidime-induced neurotoxicity. The authors performed a retrospective analysis of these cases based on their own experience and literature search. Six of these cases were found in their institution, of which three patients on dialysis developed cefepime induced neurotoxicity and three patients had ceftazidime-induced neurotoxicity. Thirty-nine patients with cefepime-induced neurotoxicity and nine with ceftazidime-induced neurotoxicity were identified from the literature search. Antibiotic neurotoxicity was defined as an adverse CNS reaction in which the antibiotic has been strongly implicated. Common findings were confusion with temporospatial disorientation (96% of patients), myoclonus (33%), and seizures (13%). These neurological findings were frequently encountered in uremic and elderly patients. The risk of delayed diagnosis was greater with cefepime than ceftazidime neurotoxicity. The median interval between symptom onset and diagnosis of cefepime and ceftazidime neurotoxicity was 5 and 3 days, respectively. The authors concluded that the consistent finding that they observed in these cases was that a delay occurred in diagnosing cefepime neurotoxicity. The delay may suggest a lack of clinical awareness of this disease entity versus neurotoxicity from ceftazidime. They added that clinicians' awareness of these potential neurotoxicities with the use of these antibiotics must be increased so that the time between symptom onset and diagnosis can be reduced.

MO Comment: Cefepime-induced neurotoxicity is mentioned under postmarketing experience of the cefepime label. In this article, clinicians are encouraged to be aware about the potential neurotoxicities with the use of these cephalosporins in order to avoid delay in diagnosis and treatment.

16. Chatellier D, Jourdain M, Mangalaboyi J, Ader F, Chopin C, Derambure P, et al. Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. *Intensive Care Med*. 2002;28(2):214-7.

This article reports five cases of life-threatening cefepime-induced neurotoxicity observed in a 2-year period from a university hospital-intensive care unit. According to this report, five patients were treated with cefepime because of severe and prolonged infections. Acute renal failure developed in all of the five patients, probably due to aminoglycoside renal toxicity in two patients, dehydration in one patient, and diabetes mellitus in another. In one patient, a 16-year old male with mucoviscidosis was administered cefepime (9 g/daily) for bronchitis; concomitant medications included tobramycin, trimethoprim-sulfamethoxazole, and azithromycin. The report states that this patient developed renal failure and neurological manifestations (coma with Glasgow coma score of 8, generalized myoclonia). The period between the start of cefepime therapy and onset of neurological findings was 12 days. The renal failure in this patient was attributed to cefepime-induced immunoallergic nephritis, with high IgE serum level and gallium citrate hyperfixation in the area of the kidneys. Cefepime

dose was not adjusted for renal function in any of the five cases. In all cases, the initial neurological symptoms (disorientation, confusion, and depressed consciousness) became progressive leading to facial or multifocal myoclonic movements, and convulsive or non-convulsive status epilepticus. The paper states that four patients were comatose on admission in the ICU. The EEG findings were characteristic of status epilepticus. Cefepime levels were elevated as measured by high performance liquid chromatography. All patients received antiepileptic drugs and hemodialysis. In two patients, mechanical ventilation and thiopental therapy had to be used. The report states that four patients completely recovered and discharged to home. However, one patient, a 73-year old male with history of rheumatoid arthritis and infection of knee prosthesis died. He received cefepime 2 g and amikacin (unknown dose). The patient died of multiorgan failure with refractory status epilepticus and coma. The authors stated that a delayed diagnosis might have significantly contributed to the fatal outcome in this patient.

MO Comment: Given the severity of these neurotoxicity cases, a careful monitoring of renal function is important particularly in patients treated with cefepime for serious infections.

17. Dakdouki GK, al-Awar Ghassan N. Cefepime-induced encephalopathy. *Int J Infect Dis.* 2004;8(1):59-61.

This literature article describes a 60-year-old male patient with diabetes mellitus and end-stage renal disease (on hemodialysis). The patient was admitted because of pneumonia and administered cefepime 2 g empirically. Five days later, the patient started to have neurological manifestations (confusion, visual and auditory hallucinations and agitation without focal deficit). The patient did not improve despite hemodialysis over two days. Cefepime was discontinued. The report states that within one day, the patient started to improve and his mental status returned to baseline level. Apparently, according to the patient's wife, the patient had a history of confusion and hallucination after taking ceftazidime a year ago.

MO Comment: This case report reinforces the necessity for dose adjustment of cefepime in renally impaired patients and potentially avoid the risk of developing neurotoxicity. Based on the wife's recollection of patient's past medical history, this patient had a prior history of neurotoxicity with another cephalosporin (i.e., ceftazidime).

18. Coghill JM, Martinez A, Moll S. Transient drug-induced white blood cell aplasia. *Am J Hematol.* 2006;81(8):639-40.

This article describes a case of a 28-year-old man with no significant past medical history who was admitted because of fever, myalgia and left cervical lymphadenopathy of 3-week duration. His initial blood work revealed a WBC of $32.3 \times 10^9/L$, absolute neutrophil account of $30.3 \times 10^9/L$, hemoglobin of 12.9 g/dL and a platelet count of 755. The peripheral blood film demonstrated a marked left shift with numerous band forms. The patient received empiric antibiotic therapy including doxycycline, levofloxacin, vancomycin, and metronidazole. A bone marrow aspirate and biopsy was performed on hospital day 7 and revealed a hypercellular, left-shifted marrow with no evidence of malignancy or infection.

On day 9, blood cultures were negative and no other infectious source of fever was identified and all antibiotics were discontinued. However, a few days, later (day 13) the patient's condition began to deteriorate. The patient became hypotensive and developed sepsis and transferred to the ICU. He was given empiric therapy including vancomycin, metronidazole, cefepime, and subsequently imipenem. On day 23, the patient's total WBC showed marked leucopenia ($0.4 \times 10^9/L$) and absolute neutrophil count of $0.1 \times 10^9/L$. A follow-up bone marrow sample showed relative erythroid hyperplasia, normal appearing megakaryocytes and absence of myeloid precursors. Drug-induced white cell aplasia was diagnosed. The patient's antibiotics were revised and patient was administered filgastrim injection daily. In addition, granulocyte infusions were administered for 3 days for persistent severe neutropenia. Subsequently, the patient's white cell count started to recover. The patient's fever resolved and was discharged. The authors hypothesized that pure white cell aplasia developed as a result of one of the antibiotics use. According to the authors, they cannot exactly tell which drug was responsible, but the time course of the leucopenia suggests that it could be either cefepime or vancomycin. Both of these antibiotics have been reported to cause white cell aplasia.

MO Comment: Cases of drug-induced neutropenia have been reported in the literature. Decreases in WBC and neutrophils are mentioned in the cefepime label in correlation with clinical trials of cefepime with multiple dosing regimens.

19. Rhomberg, PR, Jones RN, Sader HS, Fritsche TR, and The Mystic Programme Study Group. Antimicrobial resistance rates and clonality results from the meropenem yearly susceptibility test information collection (MYSTIC) programme; report of year five. *Diagn Microbiol Infect Dis.* 2004;49(4):273-81.

This article reports the U.S. meropenem yearly susceptibility test information collection programme. It monitors the spectrum of activity and potency of meropenem within medical centers where carbapenems are used for treatment of serious infections. The antimicrobial activity of 11 broad-spectrum agents was assessed against 2,848 isolates in 2003. The report of MIC showed high potency of meropenem against all monitored pathogens. Against all Gram-negative bacilli tested, the overall rank order of susceptibility was meropenem (96.3%) > imipenem (95.6%) > cefepime (93.7%) > tobramycin (91.9%) > piperacillin/tazobactam (90.2%) > ceftazidime (90.1%) > gentamicin (89.6%) > levofloxacin (82.8%) > ciprofloxacin (82.5%) > aztreonam (81.8%) > ceftriaxone (72.3%).

MO Comment: This surveillance program reports yearly susceptibility test information of meropenem and other antibiotics. This paper reports that cefepime ranked third of susceptibility among the antibiotics tested against all Gram-negative bacilli isolates. (Note: This paper was included with the other articles though without safety information for cefepime.)

20. Saito A, Otsuka M, Kobayashi K, Otsubo K. Clinical efficacy of cefepime in nonresponders to other antibiotics of postmarketing special surveillance. *Jpn J Chemother.* 2002;50(1):29-46.

This article reports a postmarketing surveillance to investigate the clinical efficacy of cefepime in nonresponders to betalactam antibiotics. The production of β -lactamase by pathogens is considered one of the major non-response factors to beta-lactam antibiotics in bacterial infections. Five hundred sixty-three patients were recruited but 423 were analyzed to evaluate clinical efficacy. Efficacy rates of 65.9% was obtained in non-responders to parenteral cephalosporins and 74.0% in nonresponders to parenteral penicillins were obtained when compared against the type of previous treatment. The authors concluded that the extreme stability of cefepime is supported by similar results in efficacy observed in non-responders to previous treatment with betalactam antibiotics where strains detected were either producing or not producing β -lactamase.

MO Comment: This article reports no safety information for cefepime. (Note: This paper was included with the other articles though without safety information for cefepime. This paper is in Japanese and some of the text was translated to English.)

8 ADDITIONAL CLINICAL ISSUES

8.1 Literature Review

- The reviewer performed an additional literature search regarding the safety and efficacy of cefepime. A search in PubMed and Embase was conducted. The following recent and relevant published literature articles were found and briefly summarized here: (Please note that the following articles are not included in the previous section, 7.1 Literature, in this review.)
- Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007 May; 7(5): 338-48.

This is a meta-analysis of randomized controlled trials comparing cefepime to another beta-lactam antibiotic, looking at 30-day all-cause mortality as primary outcome; and secondary outcomes as clinical failure, microbiological failure, bacterial, fungal, and any superinfections and adverse events. In the analysis, the authors found all-cause mortality to be significantly higher with cefepime than with other β -lactams (Risk ratios of 1.26 and 95% CIs 1.08-1.49). The authors offered two possible explanations for the results. The first is an unrecognized adverse event (i.e., neurotoxicity events with cefepime use including encephalopathy and non-convulsive status epilepticus). The second possible explanation is inadequate antimicrobial efficacy in vivo. The authors stated that the main limitation of this study is the lack of complete mortality data. All cause mortality was not reported in all studies they reviewed.

MO Comment: This is the second of two meta-analysis studies² performed by Yahav,

et al. concerning increased mortality in patients treated with cefepime. This study was well-designed systematic review using methods to assess heterogeneity and bias. The Division of Anti-infective and Ophthalmology Products looked closely at this recent meta-analysis study. Given the concerning results of this study, the Division posed questions to the Sponsor (Bristol-Myers Squibb) of the RLD, MAXIPIME® (Cefepime for Injection) about these findings and requested for information including mortality and safety analyses of all cefepime trials both published and unpublished. The reviewer looked at relevant safety literature articles looking at neurotoxicity related to cefepime use. (Note: The mortality and safety analyses of data provided by BMS will be addressed in a separate review.)

- Roberts JA, Webb SAR, Lipman J. Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; 29: 117-128.

This is a review which aimed to identify and analyze the published literature to compare cefepime and ceftazidime and determine which should be preferred as empirical cephalosporin therapy in critically-ill patients with sepsis. The authors performed a systematic literature review of original publications and review articles using Medline in February 2006. Both cefepime and ceftazidime are broad-spectrum cephalosporin antibiotics and commonly selected agents for empirical antibiotic therapy for nosocomial infections in critically-ill patients. This literature review has identified potential advantages of cefepime over ceftazidime with regards to broader-spectrum of activity, reduced association with resistant bacteria and cost effectiveness. The review also found that both antibiotics appear to have similar tolerability, ability to penetrate various body tissues and therapeutic efficacy. This review mentions a recent meta-analysis of randomized controlled trials indicated that cefepime should not be selected as empirical therapy in febrile neutropenia². This finding has been subject to much conjecture in the literature. The authors concluded that a head-to-head study characterizing the clinical relevance of the pharmacodynamic profile in either serum or tissues is lacking. Therefore, further pharmacokinetic/pharmacodynamic and clinical studies are required to quantify these apparent advantages.

MO Comment: This systematic literature review of both cefepime and ceftazidime met its primary objective. However, the safety profile of both antibiotics was not fully explored including other adverse events (the ones not mentioned in this paper), deaths and discontinuations in the studies reviewed. The reviewer agrees that further clinical studies should be done to better determine the cited advantages of both beta-lactam antibiotics.

- Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy*. 2006 Aug;26(8):1169-74

This is a case report of a 67-year-old woman with multiple medical histories including diabetes mellitus, chronic renal insufficiency, hypertension, asthma, anemia of chronic disease, breast cancer with mastectomy and recurrent urinary tract infections. The patient was admitted to the hospital because of lethargy and confusion and found to have *E. coli*

UTI. The patient was initially administered linezolid 600 mg bid I.V. and cefepime 1 g/d. A urine culture revealed sensitivity to cefepime and linezolid was discontinued on day 2. The patient remained lethargic and confused. Cefepime was increased to 2 g/day. On day 5, the patient apparently became alert and could answer simple questions. However on day 8, her lethargy and confusion recurred and developed myoclonus in her extremities and occasionally in the trunk. Blood cultures showed no growth and her urine culture grew less than 1000 colonies/mL. Her BUN was 50 mg/dl and serum creatinine was 2.1 mg/dl. Liver and thyroid function tests were within normal limits. Cefepime-induced neurotoxicity was suspected. Cefepime was discontinued on day 8. Clonazepam and levetiracetam were administered for seizure prophylaxis. MRI and computed tomography scan performed on admission revealed no acute infarct. Electroencephalogram (EEG) obtained on day 10 revealed generalized background slowing and multiphasic sharp waves. The patient's serum cefepime level measured on day 8, 24 hours after the last dose was 39 µg/mL. The level declined 18 hours later (day 9) to 10 µg/mL and was below 5 µg/mL at day 10. On day 10, the patient's condition improved except the myoclonic jerks in the right arm which stopped by day 12. Clonazepam was discontinued on day 11 and levetiracetam on day 13. The report states that the patient's mental status returned to baseline by day 17.

MO Comment: Neurotoxicity is a known adverse event associated with cefepime but most probably underreported in patients with renal impairment who receive relatively excessive doses. In some cases, it has been reported that with drug cessation, neurotoxicity resolves. Other cases have been reported that required hemodialysis to resolve the neurotoxicity. It is of great importance that in patients with renal disease, the maintenance dose of cefepime should be reduced and patients should be monitored for neurotoxicity.

- Capparelli FJ, Diaz MF, Hlavnika A, Wainsztein NA, Leiguarda R., Del Castillo ME. Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology* 2005;65:1840.

This is a case report of an 85-year-old man who was admitted to the ICU because of sepsis and abdominal pain. The patient had a history of hypertension, obesity, a coronary artery bypass graft, colon cancer surgically treated with remission, abdominal aneurysm surgically corrected, and deep venous thrombosis on oral anticoagulation. He experienced an acute confusional syndrome during a previous admission due to an epididymitis treated with a cephalosporin (not specified). The initial workup suggested an acute urinary tract infection. His APACHE II score was 13. His serum creatinine level was 0.8 mg/dL. He was started on cefepime 1 g IV BID and amikacin 1 g IV per day. After 48 hours, he continued only with cefepime 2 g IV BID, as blood and urinary cultures were positive for *E. coli*. Twenty hours later, he developed acute delirium, which was treated with IV haloperidol (2.5 mg) and oral olanzapine (2.5 mg) with partial success. Brain CT was normal. His neurologic condition further deteriorated; he was stuporous, pupils were symmetric and reactive to light, ocular fundus was normal; extraocular movements were full; no deficits were found in the remainder of the cranial nerves. There were no meningeal signs,

and neither focal motor nor sensory deficits were present. Deep tendon reflexes and plantar responses were normal. He had no hemodynamic alteration, and temperature was normal. He was intubated. He had normal arterial blood gases, blood cell count, serum chemistry test, and ammonium level. His creatinine level was 0.8 mg/dL and his 24-hour measured creatinine clearance was 75 mL/min that day. He had repeat negative blood, urinary, and bronchial lavage cultures. He had a normal CSF examination. An EEG showed slow symmetric 4- to 7-Hz wave activity but no evidence of epileptic discharges. Because of the possibility of drug-induced encephalopathy, psychotropic drugs and cefepime were stopped, and the antibiotic was changed to piperacillin-tazobactam. One day after withdrawal of cefepime, his neurologic status markedly improved, and the patient was extubated. After 7 days of IV antibiotic therapy, the patient received cefixime 400 mg/day PO. Thirty-six hours later, his conscious state gradually deteriorated, with delirium and stupor leading again to the need for tracheal intubation. His renal function remained normal (creatinine 0.7 mg/dL). Despite exhaustive workup, no etiology other than cefixime was found to explain the encephalopathy. The antibiotic was changed, and the patient fully recovered in less than 36 hours. He completed treatment and was discharged with a normal neurologic status. The authors state that the temporal association of the encephalopathy induction and resolution with the cefepime and cefixime administration and withdrawal makes the two drugs highly likely to be responsible for the encephalopathy.

MO Comment: This patient with normal renal function developed encephalopathy induced by cefepime or cefixime. Neurotoxicity associated with cephaloporins have been reported in patients with renal failure or overdose but rarely in patients with normal renal status. The reviewer concurs with the authors' assessment that the two drugs likely caused the encephalopathy.

- Maganti R., Jolin D., Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav.* 2006 Feb;8(1):312-4.

This is a case report of a 79-year-old woman with a history of type II diabetes, hypertension, and recurrent UTI due to a chronic indwelling catheter. The patient presented to the hospital with one day history of high fever and found to have UTI with *Pseudomonas* and yeast in her urine culture. She was started on cefepime 2 g q 12 and fluconazole 100 mg bid. On day 2, the patient was found to be confused intermittently. On day 3, she became unresponsive but arousable with irregular jerky movements in her arms intermittently. Her BUN and serum creatinine was normal except for an elevated WBC. Her calculated creatinine clearance was 44.47 ml/kg/min. MRI of the brain revealed mild diffuse cerebral atrophy and mild ischemic changes. Spinal fluid examination was normal. An emergent EEG showed continuous generalized sharp and slow wave discharges and associated with jerky movements of her arms at times. The patient was thought to have non-convulsive status epilepticus (NCSE) and was administered lorazepam 4 mg and valproic acid (loading dose was 30 mg/kg). Apparently the EEG background improved initially; however, over the next hour, the continuous generalized sharp and slow wave activity returned. Cefepime was discontinued after the first EEG. Over the next 3 days, her mental status gradually returned to normal. The

patient became more alert and oriented. On day 5, her EEG normalized. Valproic acid was discontinued. The patient was treated with gentamicin and fluconazole for her UTI and discharged apparently improved without any anticonvulsants.

MO Comment: This case illustrates that NCSE can be a complication of cefepime therapy even at therapeutic doses and in the presence of normal serum creatinine. However, the calculated creatinine clearance was abnormal as reported in this article.

- Ferrara N, Abete, P, Giordano M, Ferrara P, Carnovale V, et al. Neurotoxicity induced by Cefepime in a very old hemodialysis patient. Clin Nephrol 2003 May; 59: 388-90.

This is a case report of an 82-year-old male with end-stage renal disease on chronic hemodialysis who received cefepime 1 g/d for pneumonia in a hospital. The patient developed seizures four days after starting cefepime therapy. Cefepime-induced neurotoxicity was suspected and its administration was discontinued. An urgent hemodialysis was started and an improvement of patient's conscious level was observed. On the following day, after a second dialysis, the patient's neurological event resolved. One week later, the patient was discharged from the hospital in stable clinical condition. The authors speculated that the advanced age of the patient and the metabolic encephalopathy induced by chronic uremia made him more sensitive to the neurotoxicity induced by cefepime.

MO Comment: This elderly patient with chronic uremia developed neurotoxicity despite using low dosing regimen of cefepime. Therefore, caution should be exercised in administering cefepime in the elderly patients with severe renal impairment to avoid developing this serious neurological event.

- Abanades S, Nolla J, Rodriguez-Campello A, et al: Reversible coma secondary to cefepime neurotoxicity. Ann Pharmacother. 2004 Apr;38(4):606-9

This a 66-year-old woman with acute myeloid leukemia had a fever on the third day of the initial chemotherapy cycle. Empiric antibiotic treatment with cefepime 2 g every 8 hours was started; fluconazole and vancomycin were subsequently added due to the persistence of fever. Ten days after initiation of cefepime, the patient developed acute renal failure followed by altered consciousness (Glasgow coma scale 6) associated with nonconvulsive status epilepticus (NCSE). Cefepime was discontinued. Epileptiform activity in the electroencephalogram disappeared with clonazepam treatment. The patient regained consciousness 48 hours after cefepime withdrawal.

MO Comment: This case illustrates that the combination of cefepime treatment and acute renal failure may induce drug-related neurotoxicity. NCSE poses a diagnostic challenge because of its nonspecific clinical manifestations particularly in the elderly with renal impairment. Therefore, it is crucial to recognize NCSE early to ensure appropriate and prompt therapy.

9 OVERALL ASSESSMENT

9.1 Conclusions

This NDA for Cefepime Injection in GALAXY Container is submitted in accordance with Section 505 (b)(2) of the Food, Drug, and Cosmetic Act, as regulated under 21 CFR 314.54. All product contact materials are identical to the approved Galaxy container.

9.2 Recommendation on Regulatory Action

Based on evidence concerning increased mortality among patients treated with cefepime, as reported in two recent meta-analysis studies by Yahav, et al., the clinical reviewer has safety concerns regarding cefepime use. Therefore, from the clinical perspective, the clinical reviewer is recommending an approvable action. The applicant needs to provide safety update information of cefepime or data verifying that the findings of these meta-analysis studies are accurate. These data should be reviewed and obtained from published and unpublished clinical studies for cefepime. The first study by Yahav, et al¹, found increased mortality associated with cefepime therapy in febrile neutropenic patients. The second study was a follow-up by the same investigators who found the 30-day all-cause mortality to be significantly higher with cefepime than with other β -lactam antibiotics (Risk ratios of 1.26 and 95% CIs 1.08 -1.49).²

The MO's recommendations for changes to Cefepime for Injection in GALAXY Container label should be conveyed to the Applicant (as outlined under the EXECUTIVE SUMMARY).

9.3 Recommendation on Postmarketing Actions

The clinical reviewer recommends that the following adverse events should be monitored as part of post-marketing surveillance program for cefepime:

- Encephalopathy (including confusion, disorientation, hallucinations, agitation, stupor, coma and related events)
- Seizures (convulsion, non-convulsive status epilepticus, myoclonus and related events)
- Fatal outcomes (including causes of deaths and causality assessments)

9.4 Required Phase 4 Commitments

The clinical reviewer recommends that the sponsor should develop a post-marketing patient registry to study patients treated with cefepime who develop neurotoxicities (i.e., encephalopathy and seizures), fatal events including causes of deaths, microbiologic data of patients at the time of death, and other rare adverse events that may arise during cefepime therapy.

9.5 Labeling Review

The applicant made the following labeling changes to the Cefepime for Injection in Galaxy Container:

- The Cefepime for Injection in Galaxy Container label has been changed to the new format in accordance with the Final Rule.
- Deletion of Drug/Laboratory test interactions section under Drug Interactions section and relocating it under WARNINGS AND PRECAUTIONS section.
- Addition of statement regarding meningeal seeding in the General Precautions section
- Addition of Directions for Use of Cefepime Injection in GALAXY Container subsection under DOSAGE AND ADMINISTRATION section.
- Deletion of all the text relating to intramuscular use.
- Replacement of reference listed drug's specific information with Baxter's information and product name.

9.6 Comments to Applicant

The MO has recommendations for revisions to the Cefepime for Injection in Galaxy Container label to be conveyed to the applicant including:

- Addition of safety labeling of marketed antimicrobials with regard to *Clostridium difficile* associated disease (CDAD)
- Addition of statements in the DOSAGE AND ADMINISTRATION section/ for pediatric patients. The statements are as follows:

“Cefepime injection in Galaxy container should not be used in pediatric patients who require more than the recommended adult dose in order to prevent unintentional overdose.”

- Addition of new proposed statements in the “Patient Counseling Information” section regarding adverse events of cefepime-related neurotoxicity. The statements are as follows:

“Patients should be advised of neurological adverse events that could occur with cefepime use. Patients should inform their healthcare provider at once of any neurological signs and symptoms to include encephalopathy (disturbance of consciousness, including confusion, hallucinations, stupor, and coma), myoclonus and seizures for immediate treatment, dosage adjustment, or discontinuation of cefepime.”

- Other minor editorial changes to the cefepime label.

10 APPENDICES

10.1 Review of Individual Study Reports

There are no study reports for this application.

10.2 Line-by-Line Labeling Review

MO Comment: The Division of Medication Errors and Technical Support (DMETS) was consulted for a review of the container labels and carton labeling for Cefepime Injection in Galaxy container. According to their review, they have concerns with "Tall Man" lettering for the established name on the proposed container labels and carton labeling. DMETS recommends revisions to the container label and carton labeling to minimize product selection errors within Baxter's Galaxy Container line. The proposed recommendations are as follows:

1. *Tall Man Lettering: Deletion of the use of "Tall Man" lettering on this product and using a standard upper/lower case presentation, e.g. Cefepime Injection.*
2. *Container Label (1g and 2g Bags):*
 - *Baxter's name appears as prominently as the established name on the label. Decrease the font of the of the sponsor's name to increase the prominence of the established name.*
 - *DMETS notes that Baxter's use of a white background behind their name in black print and the established name and product strength in red print on several cephalosporins in the GALAXY™ Container product line. The use of the same color background increases the potential for confusion between cephalosporins in Galaxy™ Containers. DMETS recommends the use of black print for the established name for both strengths of Cefepime for injection to better distinguish this product from the other cephalosporins in Galaxy™ Containers.*
 - *The strengths of Cefepime are differentiated by the use of different color print, black for the 1 g bag and red for the 2 g bag. The 2 g bag will also be larger than the 1 g bag. However, the use of the same color background increases the potential for the strengths to be confused. DMETS recommends continued use of black and red to distinguish the strengths (1 g vs. 2 g) as well as using an additional means such as bolding, boxing, or some other means of differentiating the strength to decrease the potential of confusion between the strengths.*

The reviewers (clinical and chemistry) concurred with DMETS recommendations. These recommendations for changes of the container labels and ~~_____~~ for Cefepime Injection in Galaxy container were conveyed to the company.

b(4)

(MO Note: It should be noted that the current approved RLD, MAXIPIME[®] label is under the old format. The following new labeling format for Cefepime Injection in Galaxy container label has been submitted by Baxter on July 13, 2007 in response to FDA's Information request letter dated June 27, 2007. The letter requested for revision of the of the proposed package insert in accordance with the Final rule, titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products". This is the clean version of Cefepime Injection in Galaxy container label.)

b(4)

b(4)

28 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Medical Team Leader Memo

Sumathi Nambiar MD MPH

Application: NDA 50-817, Cefepime for Injection

Date of Submission: February 28, 2007

PDUFA Goal Date: January 1, 2008

Applicant: Baxter Healthcare Corporation

Drug Class: Cephalosporins

Recommendation on Regulatory Action

In a recently published meta-analysis, increased mortality was seen in patients treated with cefepime. The Division is currently reviewing this meta-analysis and other related data. Until the reason(s) for the observed increased mortality are better delineated, I recommend that this NDA receive an approvable action.

Background

This application was submitted under Section 505(b)(2) of the FD&C Act. The reference listed drug for this product is cefepime hydrochloride (MAXIPIME™, NDA 50-679, approved 01/18/96). The Applicant is seeking approval to market Cefepime injection in GALAXY container as 1 gram in 50 mL container and 2 grams in 100 mL container. These premixed products are packaged in GALAXY flexible plastic containers and are stored frozen at -20°C. This product is for intravenous use only, while MAXIPIME can be administered both intramuscularly and intravenously.

Indications

In the NDA, the Applicant is seeking the approval of cefepime for injection for the same indications as MAXIPIME. MAXIPIME is currently approved for the following indications:

- Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.
- Empiric Therapy for Febrile Neutropenic Patients. Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients.
- Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae*, when the infection is severe, or caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.
- Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes*.
- Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, *viridans group streptococci*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, or *Bacteroides fragilis*.

Clinical Studies

No new clinical data were submitted with this NDA. The Applicant has conducted a literature search from 2002 for clinical studies that focused on the use of cefepime. Based on the review of the medical literature, the Applicant concluded that the safety and effectiveness of Baxter's Cefepime Injection are adequately reflected in the proposed labeling. No new safety issues were identified in these publications submitted by the Applicant. For summaries of these publications, please refer to the Medical Officer review by Dr. Alma Davidson, M.D.

In May 2007, a meta-analysis was published in the *Lancet Infectious Diseases* journal (Yahav D, Paul M, Fraser A, et al. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7: 338-48). In this meta-analysis, all randomized controlled trials in which cefepime monotherapy was compared to another beta-lactam monotherapy were included. The addition of a non- β -lactam drug such as aminoglycoside was allowed as long as the same antibiotic and dose were used in both study groups. The primary outcome assessed was 30-day all-cause mortality. Overall, the all-cause mortality was higher with cefepime than other β -lactams (risk ratio [RR] 1.26 [95% CI 1.08-1.49]) and in patients with febrile neutropenia [RR 1.42 (95% CI 1.09-1.84)]. One of the main limitations of this meta-analysis was the lack of complete mortality data. Of the 57 studies identified, mortality data were missing from 16 of the studies (~38% of the population). No clear cut etiology for the increased mortality could be discerned. The hypotheses provided by the authors include an unrecognized adverse event such as encephalopathy and non-convulsive status epilepticus. They postulate that as non-convulsive status epilepticus can be difficult to recognize in elderly patients, particularly if there is no history of seizures, delay in diagnosis may result in increased morbidity or mortality. The second possibility proposed is inadequate antimicrobial efficacy *in vivo*.

The same authors had published another meta-analysis of randomized controlled trials comparing anti-pseudomonal beta-lactams administered as empirical monotherapy for febrile neutropenia, with or without vancomycin in patients with febrile neutropenia (Yahav D, Paul M, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2006.57(2):176-89). The primary outcome assessed was all-cause mortality. Cefepime was associated with higher all-cause mortality at 30 days compared to other beta-lactams (RR 1.44, 95% CI 1.06-1.94).

This issue of increased mortality with cefepime is currently being reviewed further by the Division. Additional data has been requested from BMS regarding deaths observed in studies of cefepime and neurological adverse reactions with cefepime. Of particular interest is the information from trials for which mortality data were not available to the authors of the meta-analysis. A safety update has also been requested from the Applicant.

Labeling

The Applicant has submitted the product label in the PLR format, while the MAXIPIME

label is not in PLR format. As such, the formatting will be different compared to the MAXIPIME label. The content changes proposed by the Applicant are based on the difference in formulation such as deletion of reference to intramuscular use, deletion of steps in reconstitution, including directions for use of the frozen product, and including contraindication regarding corn allergy as the product contains dextrose. These changes are acceptable.

As cefepime in the GALAXY container can only be administered at doses of either 1 gram or 2 grams, it is not suitable for use in all pediatric patients. Its use should be limited to children of certain weights who would require the entire dose of 1 or 2 grams and not any fraction thereof. It is not advisable to use a burette or other similar infusion devices to administer a fraction of the dose as it is a potential source of overdosing. Other formulations of cefepime are available that are more suitable for pediatric use. The DOSAGE and ADMINISTRATION section and the Pediatric use subsection of PRECAUTIONS section should state that to prevent unintentional overdose, this product should not be used in pediatric patients who require less than the full adult dose of cefepime. This is consistent with the label of other cephalosporins administered in a duplex container which also delivers a fixed dose of the product (NDA 50-796, Ceftriaxone and Dextrose in Duplex Container, NDA 50-779, cefazolin and dextrose).

Since submission of this NDA, the label for MAXIPIME has been updated to include language regarding *Clostridium difficile*. These changes need to be incorporated in the label for this product.

Conclusions

NDA 50-817, Cefepime for Injection was submitted under Section 505(b)(2) of the FD&C Act. As the issue of increased mortality with cefepime is still under review, an approvable action is recommended. A safety update from the Applicant is still pending. In addition to the labeling changes proposed by the Applicant, the limitations for its use in the pediatric population need to be included in the product label.

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this page is the manifestation of the electronic signature.**

/s/

Sumathi Nambiar
11/20/2007 01:32:36 PM
MEDICAL OFFICER

MO Review of Consultation Review

Re: NDA 50-817 (Cefepime Injection in Galaxy™ Container)
Sponsor: Baxter Healthcare Corporation

Subject: Consultation review from Division of Medication Errors and Technical Support (DMETS)

Background:

On May 22, 2007, the Division of Anti-infectives and Ophthalmology Products (DAIOP) requested a consult for a review of the container labels _____ for Cefepime Injection in Galaxy Container. The proposed presentations are 1 g of Cefepime in 50 mL and 2 g of Cefepime in 100 mL. The products are “ready to use” premixed intravenous formulations and are stored frozen. DMETS reviewed the container labels _____ submitted by Baxter to identify possible improvements of the labels in order to reduce the potential for medication errors.

b(4)

b(4)

Review of comments and recommendations from DMETS

DMETS expressed no concerns with the proposed packaging configuration. However, they have concerns with “Tall Man” lettering for the established name on the proposed container labels _____. Baxter has chosen to use “Tall Man” lettering on the container labels _____ of this product. In this case, the sponsor proposed to “Tall Man” the “PIME” portion of Cefepime to distinguish this established name from other cephalosporins. Cephalosporins products are often confused with each other because of similar established names for these products. They are concerned that the choice of “PIME” may not be successful in reducing wrong drug errors as several cephalosporins end with the suffix “-ime,” such as cefuroxime, cefotaxime, ceftizoxime, and ceftazidime.

b(4)

On June 28, 2007, a teleconference was held between Baxter and the Agency wherein the company stated that the “Tall Man” letters were arbitrarily chosen and not the subject of any study. Baxter also stated that they received no practitioner input into the selection of these letters to see if they would in fact help differentiate this product from other cephalosporins in their clinical settings. Because this choice of letters was not tested and many cephalosporin products end with “ime,” DMETS are concerned with allowing this “Tall Man” proposal. DMETS is also concerned that arbitrary use of Tall Man lettering has the potential to decrease its effectiveness to distinguish similar name pairs by using this tool more commonly.

In conclusion, DMETS provided recommendations for revisions of the container label and carton labeling to minimize user error and maximize patient safety. The following recommendations include:

1. Tall Man Lettering: Deletion of the use of "Tall Man" lettering on this product and using a standard upper/lower case presentation, e.g. Cefepime Injection.
2. Container Label (1 g and 2g Bags):
 - Baxter's name appears as prominently as the established name on the label. Decrease the font of the of the sponsor's name to increase the prominence of the established name.
 - DMETS notes that Baxter's use of a white background behind their name in black print and the established name and product strength in red print on several cephalosporins in the GALAXY™ Container product line. The use of the same color background increases the potential for confusion between cephalosporins in Galaxy™ Containers. DMETS recommends the use of black print for the established name for both strengths of Cefepime for injection to better distinguish this product from the other cephalosporins in Galaxy™ Containers.
 - The strengths of Cefepime are differentiated by the use of different color print, black for the 1 g bag and red for the 2 g bag. The 2 g bag will also be larger than the 1 g bag. However, the use of the same color background increases the potential for the strengths to be confused. DMETS recommends continued use of black and red to distinguish the strengths (1 g vs. 2 g) as well as using an additional means such as bolding, boxing, or some other means of differentiating the strength to decrease the potential of confusion between the strengths.

3. ✓

b(4)

MO Comment and Conclusion:

The reviewer concurs with DMETS recommendations. DMETS proposed revisions for the "Tall Man" lettering of Cefepime for injection in Galaxy™ Container, container label (1 g and 2 g Bags) _____ should be conveyed to the applicant.

b(4)