

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-821**

**MEDICAL REVIEW(S)**

NDA 50821

Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container

B. Braun Medical Inc.

Complete Response Submission

November 6, 2009

### **Clinical Team Leader Memo**

#### **Background**

B. Braun Medical Inc. submitted NDA 50821 to the Agency on September 26, 2008 as a 505(b)(2) application. The NDA is for a new drug delivery system for cefepime injection, Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container, in a 1 g and 2 g strength. The review of this NDA relies on the Agency's prior determination of safety and efficacy for the reference listed drug (RLD), Maxipime<sup>®</sup> (NDA 50679, Cefepime for Injection manufactured by Bristol-Myers Squibb) which was approved for marketing on January 18, 1996.

Cefepime is a fourth-generation cephalosporin antibacterial agent indicated for use in the treatment of pneumonia, chemotherapy-induced febrile neutropenia, urinary tract infections, uncomplicated skin infections, and complicated intra-abdominal infections.

The Duplex<sup>®</sup> container is a novel drug delivery system which contains both drug substance (cefepime) and diluent (dextrose) in a sterile, single use, dual-chamber bag. The chambers are separated by a peelable seal which is removed activated prior to constitution of the drug substance with the diluent.

During the first review cycle, Milton Sloan, PhD, Chemistry, Manufacturing, and Controls (CMC) reviewer, indicated that the drug product, Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container, when constituted, had the same quality and stability as that of Maxipime<sup>®</sup> (the RLD). Additionally, interaction between the drug product and the container system had not adversely impacted the identity, purity, potency, safety, strength, efficacy, or stability of the product. However, the application was not recommended for approval from a CMC standpoint due to violations of good manufacturing practices (GMP) noted at the drug substance manufacturing facility, (b) (4) by the Office of Compliance.

There were no pharmacology/toxicology issues which required review for this application.

A request for a bioequivalence/bioavailability waiver in accordance with 21 CFR 320.22(b)(1)(i-ii) was requested with the original submission. The waiver was acceptable to the Clinical Pharmacology reviewer, Aryun Kim, PharmD, since the Cefepime Duplex<sup>®</sup> product contained the same active (cefepime hydrochloride) and inactive (L-Arginine) ingredients in the same concentration as the RLD.

Indications, route of administration, and dosing regimen (frequency and duration) for B. Braun's Cefepime for Injection and Dextrose for Injection in Duplex<sup>®</sup> container will also be identical to BMS's Maxipime<sup>®</sup> in ADD-Vantage vials when reconstituted with 5% dextrose for intravenous administration.

No microbiology data was submitted with the application, however a comment was provided by clinical microbiology prior to a planned pre-NDA meeting with B. Braun, Inc. and the Agency, scheduled for July 14, 2008; the meeting was subsequently cancelled due to satisfactory pre-meeting correspondence. The issue concerned the proposed label's presentation of interpretive criteria and quality control parameters not matching the current Clinical and Laboratory Standards Institute (CLSI) document for the interpretation of in vitro susceptibility testing with cefepime<sup>1</sup>. Proposed labeling for the Cefepime Duplex<sup>®</sup> product would need to be revised to be consistent with what is in the CLSI document. The revision would also need to be incorporated into the RLD (Maxipime<sup>®</sup>) label.

Clinical safety issues related to cefepime were reviewed by Alma Davidson, MD and additional details may be found in her review. The safety information provided with the application contained a 120 day safety update with recent literature articles pertaining to cefepime; these included articles describing isolation techniques, bacterial strain epidemiology, and the pharmacokinetics/pharmacodynamics of cefepime. The clinical safety issues B. Braun was asked to address in this application did not include review of the Yahav meta-analysis<sup>2</sup>, which had suggested an increase in 30-day mortality in patients with fever and neutropenia treated with cefepime versus other beta-lactam antibiotics, since extensive review of this issue by the Agency was ongoing. The safety issues identified in the literature review had previously been included in the product label with the exception of "nonconvulsive status epilepticus" which was included as an adverse drug reaction.

A pediatric study waiver for all pediatric age groups was submitted by the Applicant on January 1, 2009. The basis for the waiver request was that the product does not represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients. The decision was made that the drug product did not require review by the Pediatric Review Committee (PeRC) since the Duplex<sup>®</sup> delivery system was considered to represent a new container for the drug product and not a change in formulation.

A complete response letter was issued by the Agency for NDA 50821 on July 21, 2009. The deficiencies cited in the complete response letter included the findings

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<sup>1</sup> Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 19th Informational Supplement. CLSI document M100-S19, CLSI 940 West Valley Rd., Suite 1400, Wayne, PA 19087-1898, 2009.

<sup>2</sup> Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and metaanalysis. *Lancet Infect Dis.* 2007 May;7(5):338-48.

of significant deviations from current Good Manufacturing Practice (GMP) regulations at the (b) (4) and that DMF (b) (4) was found to be inadequate to support NDA 050821. Final discussions regarding the content of the label were not complete at the time the complete response letter was issued.

### **Complete Response Submission**

On November 6, 2009, the Applicant submitted a complete response to the letter issued by the Agency on July 21, 2009.

The complete response included an updated letter of authorization for DMF (b) (4). The Applicant also stated that they had been informed by (b) (4), that responses submitted by (b) (4) to the FDA Warning Letter were acceptable and that a reinspection request had been submitted to the Agency by (b) (4).

The response also included updated labeling based on changes which had been made to the Maxipime<sup>®</sup> label in the interim.

The safety update contained the results of a PubMed search for cefepime citations from February 10, 2009 to October 2009. Eighty six citations were identified and complete copies of articles obtained for abstracts suggesting any reference to human safety. The majority of publications involved isolation techniques, in vitro testing, antibacterial efficacy, and information regarding the pharmacokinetics/pharmacodynamics of cefepime. Six of the eight clinically relevant articles involved discussion of the observations from the Yahav meta-analysis which had reported an increased mortality rate associated with use of cefepime. The articles were based on either re-analysis of studies included in the Yahav paper or presentation of additional studies conducted. Two articles discussed neurologic adverse reactions (encephalopathy and nonconvulsive status epilepticus). The articles with relevance to clinical safety were reviewed by Alma Davidson, MD, and additional details can be found in her review.

The label for the B. Braun product was provided in PLR format and was based on that of the RLD, Maxipime<sup>®</sup>. The PLR format of the Cefepime for Injection USP and Dextrose for Injection USP in the Duplex<sup>®</sup> Container was reviewed by all disciplines and appropriate changes were made. The Agency and the Applicant are nearing completion of the final label at this time.

Although the Applicant has requested a full waiver of pediatric studies for this application, data on the safety and efficacy of cefepime in all indications approved for adults (except complicated intra-abdominal infection) are approved for all pediatric patients with the exception of infants and neonates < 2 months of age. A partial waiver is granted for this pediatric subgroup. Language will also be included in the pediatric use section to advise that the cefepime Duplex<sup>®</sup> product

be used only in those pediatric patients who require the full 1 or 2 g dose of cefepime.

**Conclusions and Recommendations on Regulatory Action**

Based on a review of the original application and complete response, this application is recommended for approval.

Approval is contingent, however upon a satisfactory outcome from the re-inspection of the drug substance manufacturer, (b) (4).

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-50821

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B BRAUN MEDICAL CEFEPIME  
INC

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JANICE K POHLMAN  
05/03/2010

**NDA 50-821**  
**Cefepime for Injection and Dextrose for Injection in the Duplex Container**  
**TEAM LEADER MEMO**

**Regulatory History:**

B. Braun Medical, Inc. submitted NDA 50-821, Cefepime for Injection and Dextrose for Injection in the Duplex Container on September 25, 2008. The application was submitted in accordance with the 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The reference listed drug (RLD) (NDA 50-679, Maxipime) is approved for the following indications: pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, empiric therapy for febrile neutropenic patients, and complicated intra-abdominal infections.

Prior to submission, a Type B teleconference was requested by the Applicant on May 9, 2008, to discuss whether the application could be submitted as a 505(b)(2) application using Bristol-Myers Squibb's Maxipime as the RLD. A question regarding requirement for USP designation was also raised because the sample preparation method for this product differed from that for USP methodology. Discussion was also requested regarding possible implications of the FDA's ongoing review of a published meta-analysis by Yahav, et al.<sup>1</sup>, reporting an increase in all-cause mortality associated with use of cefepime relative to other beta-lactam antibacterial agents.

The Agency responded to the Applicant's questions with an e-mail correspondence on July 11, 2008. Based on the comments provided, the teleconference was cancelled. The FDA agreed that Maxipime was an appropriate RLD. The FDA review of the cefepime mortality meta-analysis was ongoing and the Applicant was advised that any updates relating to cefepime safety would apply to their product as well. The Applicant was advised that the USP designation is not required so long as the alternative compendial testing is better than or equivalent to USP methodology and the tested product would reasonably be expected to comply with the compendial test standards.

**Product History:**

Cefepime is a fourth generation cephalosporin antibacterial agent with broad spectrum activity against Gram positive and Gram negative aerobic bacteria. Cefepime was initially approved in 1996 for the treatment of pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), and uncomplicated skin and skin structure infections.

A meta-analysis by Yahav, et al. in *Lancet Infectious Diseases*, May 2007, described a higher rate of all-cause mortality in patients treated with cefepime compared to other  $\beta$ -lactam antibacterial agents, particularly in the subgroup of patients with fever and neutropenia. Cefepime is the only drug approved by the FDA for empiric treatment of patients with fever and neutropenia. FDA issued an Early Communication on November

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<sup>1</sup> Yahav D, Paul M, Fraser A et al. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7: 338-348.

Cefepime Duplex, B. Braun

14, 2007, and an update on May 14, 2008, indicating that it was working with the Bristol-Myers Squibb, the manufacturer of Maxipime, to further evaluate the risk of death in patients treated with cefepime.

B. Braun Medical Inc. received initial approval for the use of the Duplex Container system with Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container in July 2000. The Duplex Container system is a dual chamber bag filled with powder (drug substance) and diluent (dextrose) in separate chambers. Pressure is applied to the diluent chamber which breaks the seal between chambers, allowing the powder to be reconstituted with the diluent. The system is designed for single use administration. According to the Applicant, the advantages of this system include decreased potential for admixture errors or contamination of the drug product and decreased risk of needle stick injuries with the needle-free system. The Cefepime for Injection and Dextrose for Injection in the Duplex Container application is the seventh cephalosporin duplex container application submitted to the FDA.

**Summary of Discipline Reviews:**

A Pharmacology/Toxicology review was not necessary for this application since the product contained no new impurities or degradation products needing to be qualified via nonclinical testing.

The Clinical Microbiology review by Avery Goodwin, PhD, noted that the in vitro susceptibility test interpretive criteria and quality control parameters for this product needed to be revised to be consistent with the Clinical Laboratory Standards Institute (CLSI) document. However, the revision must first be addressed by Bristol-Myers Squibb, the RLD manufacturer, before such changes could be incorporated into the B. Braun product label for cefepime.

The Clinical Pharmacology reviewer, Aryun Kim, Pharm.D, concluded that the Applicant met the requirements for waiver of evidence of in vivo bioavailability, based on the criteria listed in 21 CFR 320.22(b).

A Statistics review of the application was not required since the application did not contain any new clinical data.

The application was not recommended for approval by the Chemistry, Manufacturing, and Controls (CMC) reviewer, Milton Sloan, PhD. This recommendation was based on the Office of Compliance finding the drug substance manufacturing facility, (b) (4) unacceptable. Therefore the supporting DMF (b) (4) has a deficient status for this NDA.

**Clinical Review:**

NDA 50-821 was submitted as a 505(b)(2) application relying on the FDA's previous finding of the safety and efficacy of cefepime for treatment of the previously noted indications. Therefore no clinical data was included with the application. A safety update

for cefepime was provided by the Applicant in the form of literature review in response to the Agency's request. The Clinical Review was conducted by Alma Davidson, MD.

One new potential safety issue identified was a review of case reports from the literature describing cases of non-convulsive status epilepticus.

#### Non-convulsive Status Epilepticus (NCSE)

The Applicant provided a review article that identified 25 published cases of NCSE associated with the use of cefepime. As noted by Dr. Davidson, most cases occurred in adults, with a mean age of 60 years (range 15-86). The symptoms were reported 1-15 days (mean of 6 days) after initiating cefepime therapy. All reported patients except one had renal impairment. The NCSE resolved with discontinuation of cefepime and initiation of anticonvulsant treatment. Four patients had fatal outcomes due to underlying medical illness. The product label for the RLD contains information in the WARNINGS section of the label about life-threatening or fatal occurrences of encephalopathy, myoclonus, and seizures. The Applicant would like to include NCSE in the Warnings and Precautions, and Adverse Reactions, Postmarketing Experience sections of the product label.

Literature was included in this application, as it has been in past applications regarding the potential for allergic or hypersensitivity type reactions with ingestion or infusion of dextrose or corn sugar.

#### Allergic or Hypersensitivity Reactions to Dextrose

The Applicant provided five literature articles reporting on potential allergic and hypersensitivity reactions to dextrose. Manifestations of these reactions have included: urticaria, pruritis, dermatitis, myalgias, and gastrointestinal symptoms. The label for this and other cephalosporin/dextrose products in the Duplex Container include a contraindication to use in patients with hypersensitivity to corn products.

During the course of this NDA review, the FDA meta-analysis, both on a trial-level and patient-level was completed.

#### Cefepime Mortality Meta-Analysis

On June 17, 2009, an FDA Alert titled "Information for Healthcare Professionals: Cefepime" was issued. This alert reported on the results of the FDA meta-analysis of mortality associated with cefepime, including data from 88 clinical trials (38 trials contained in the Yahav meta-analysis and 50 additional clinical trials), in which a total of 9,467 patients were treated with cefepime and 8,288 treated with comparators. There was no statistically significant difference in mortality observed between cefepime and comparators. An additional patient-level meta-analysis performed by FDA included data from 35 comparative clinical trials and also demonstrated no statistically significant difference in mortality.

The FDA, through the Office of Surveillance and Epidemiology and in conjunction with the Premier Healthcare Informatics data base will be performing a post-marketing analysis of mortality associated with cefepime versus comparable agents.

#### **CLINICAL REVIEW CONCLUSIONS**

Based on the clinical review, the application is recommended for approval by the clinical reviewer, contingent upon conclusions of other disciplines and formal review of the Applicant's proposed label.

However, this application is not recommended for approval from a Chemistry, Manufacturing, and Controls perspective. The Office of Compliance has issued a withhold recommendation on this NDA due to the potential of pending action against the contracted drug substance facility, (b) (4)

Labeling discussions were not conducted with the Applicant during this review cycle. A formal review of the proposed label will be performed when a Complete Response is submitted.

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**M E M O R A N D U M**

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

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**DATE:** 07-21-09

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

**TO:** Division File

**SUBJECT:** Deputy Division Director's Decisional Memo for NDA 50-821  
cefepime and dextrose for injection in the Duplex® III Container, 1  
g in 50 mL and 2 g in 50 mL

**1.0 Background**

Cefepime is an injectable, semi-synthetic cephalosporin in the  $\beta$ -lactam class of antibacterial agents. Its mechanism of action is bactericidal via inhibition of cell wall synthesis by binding to penicillin-binding proteins found in the bacterial cell wall of both Gram-positive and Gram-negative bacteria. The applicant, B. Braun Medical Inc., has submitted NDA 50-821 in support of cefepime and dextrose for injection in the Duplex Container. This application is submitted under Section 505(b)(2) of the FD&C Act, contains no new clinical studies, and relies on the Agency's previous finding of safety and effectiveness for the reference listed drug (RLD) product, cefepime hydrochloride (MAXIPIME™, NDA 50-679, approved 1/18/96). Six other Duplex products by B. Braun have been approved by the Agency for other antimicrobial products.

The indications for which the applicant is seeking approval are identical to those approved for MAXIPIME and are:

- treatment of pneumonia caused by *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species
- empiric therapy for febrile neutropenic patients
- uncomplicated and complicated urinary tract infection (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 pneumonia*, *Enterobacter* species, or *Bacteroides fragilis*

This memo will summarize elements of all reviews by discipline. For detailed discussions, please refer to the respective CMC, product quality microbiology, pharmacology/toxicology, microbiology, clinical pharmacology, clinical, and biometrics reviews.

## 2.0 Summary of Chemistry, Manufacturing, and Controls

Cefepime for Injection, USP (sterile bulk) manufactured by (b) (4) is a sterile mixture of cefepime hydrochloride USP and L-arginine USP. The drug product, Cefepime for Injection USP and Dextrose for Injection USP in the Duplex III container is sterile, nonpyrogenic, and packaged in a single use, dual chamber container. The two chambers are separated by a foil seal that is peeled off prior to use. A second seal is then activated between the drug chamber and forward compartment containing the administration port. Cefepime for Injection USP is then mixed and dissolved in the diluent (dextrose) in a closed and sterile system. Data from studies demonstrated that the drug product, stored at recommended conditions, met all chemical, microbiological, and particulate matter requirements. Stability indicators demonstrate that the integrity of the product will be maintained throughout its shelf life.

This application is not recommended for approval by the CMC reviewer, Milton Sloan, PhD because the Office of Compliance has issued a withhold recommendation for this NDA because the manufacturing sites are not in compliance with current Good Manufacturing Practices (cGMP). There is the potential for pending action against the contracted drug substance manufacturing facility, (b) (4). The site was issued a 483 after inspection that listed violations that rise to the level of a potential Warning Letter. Also, the supporting DMF (b) (4) currently has a deficient status.

## 3.0 Summary of Product Quality Microbiology

The sterility assurance reviewer, Robert Mello, PhD, has recommended approval of the product. The manufacturing process involves an (b) (4) sterile powder fill and an (b) (4) filtration/fill of dextrose diluent into a presterilized, two-compartment Duplex III flexible IV bag. However, the reviewer has two comments to be transmitted to the applicant regarding ongoing stability program commitments and container/closure part number inconsistencies.

#### **4.0 Summary of Pharmacology/Toxicology**

This NDA did not require a pharmacology toxicology review because the applicant did not conduct any additional nonclinical toxicology studies. The Division had agreed that no additional studies were necessary as long as there are no impurities or degradation products that exceed the ICH qualification threshold levels or the levels in the comparable marketed products such as Maxipime®. According to the CMC reviewer, there are no impurities or degradation products in the current product that require qualification via nonclinical testing.

#### **5.0 Summary of Clinical Pharmacology**

This application is found to be acceptable for approval by the clinical pharmacology reviewer, Aryun Kim, PharmD. The applicant meets the requirements for waiver of evidence of bioavailability, based on the listed criteria in 21 CFR 320.2(b). The cefepime Duplex product contains the same active and inactive ingredients as the RLD. Indications, route of administration, and dosing regimen for B. Braun's Cefepime for Injection and Dextrose for Injection in Duplex III container will be identical to Maxipime in ADD-Vantage vials when reconstituted with 5% dextrose for intravenous administration.

#### **6.0 Summary of Clinical Microbiology**

There are no new microbiology data contained in this application. However, the clinical microbiology reviewer notes that the interpretive criteria and the quality control parameters of the cefepime label do not match what is in the current Clinical and Laboratory Standards Institute document for the interpretation of in vitro susceptibility testing with cefepime. However, the label of the RLD, Maxipime, will need to be updated first before B. Braun can change the package insert for the cefepime in Duplex container.

#### **7.0 Summary of Efficacy**

No new clinical trial information is submitted to support the efficacy of this application. B. Braun references NDA 50-679 in support of the efficacy of this application.

#### **8.0 Summary of Safety**

The safety update was reviewed by the medical officer, Alma Davidson, who recommends approval of the application from a clinical standpoint. Recent published literature noted non-convulsive status epilepticus which is not specifically mentioned in the RLD label. However, encephalopathy, a related

condition, is described and therefore an update to the RLD package insert is not necessary at this time. No other safety concerns were identified.

On June 17, 2009, the Agency issued an Update to a Safety Review of Cefepime and Information for Health Care Professionals regarding the Agency's results of a meta-analysis undertaken to address a meta-analysis by Yahav et al. in *Lancet Infectious Diseases*, May 2007, that appeared to demonstrate a higher rate of all-cause mortality in patients treated with cefepime compared to other  $\beta$ -lactam antibacterial agents, particularly in the subgroup of patients with fever and neutropenia. In the FDA analyses of both patient-level and trial-level data, no statistically significant increase in mortality was seen in cefepime-treated patients compared to comparator-treated patients. Based on these results, we have determined that cefepime remains an appropriate therapy for its approved indications.

### **8.0 Recommendation**

Due to the aforementioned CMC deficiencies, the application cannot be approved in its present form. Therefore, a complete response letter will be issued to the applicant, outlining the deficiencies and the information necessary to respond to them.

Katherine A. Laessig, MD

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Kathrine Laessig  
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## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	50-821
Priority or Standard	S
Submit Date(s)	September 25, 2008
Received Date(s)	September 26, 2008
PDUFA Goal Date	July 25, 2009
Division / Office	DAIOP/OAP
Reviewer Name(s)	Alma C. Davidson
Review Completion Date	May 22, 2009
Established Name	Cefepime for Injection and Dextrose Injection in Duplex Container
(Proposed) Trade Name	Cefepime for Injection and Dextrose Injection in Duplex® Container
Therapeutic Class	Cephalosporin
Applicant	B. Braun Medical, Inc.
Formulation(s)	Solution, injection
Dosing Regimen	1 to 2 grams q8h or 12h
Indication(s)	To treat infections that are proven or strongly suspected to be caused by susceptible bacteria
Intended Population(s)	Adult and Pediatric patients

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

Based on the review of the safety update for cefepime injection including the recently completed extensive FDA review of the meta-analysis studies by Yahav et al and febrile neutropenia trials (Note: Safety Review by Peter Kim, MD Maxipime<sup>®</sup> is in DFS-April 7, 2009), the reviewer finds no major safety concerns of cefepime at this time. The safety update review of recent published literature did reveal safety information regarding non convulsive status epilepticus (NCSE) associated with cefepime use. NCSE is not mentioned in Maxipime<sup>®</sup>, the reference-listed drug (RLD) label; however, there is mention of encephalopathy, a related neurological disorder to NCSE. From the clinical standpoint, this application is recommended for approval. However, the overall approval of this application is contingent upon the conclusions of other disciplines, including chemistry, manufacturing, and controls (CMC) review.

### 1.2 Risk Benefit Assessment

The Applicant should be advised of the Agency's risk assessment activities for cefepime based on the recently completed meta-analysis studies and febrile neutropenia trials review, including:

- The Agency, through the Office of Surveillance and Epidemiology (OSE), in conjunction with the Premier Healthcare Informatics database, is poised to perform a postmarketing analysis of mortality associated with the administration of cefepime versus comparable agents.
- The Division of Anti-infective and Ophthalmology Products (DAIOP) may consider changing the dosing recommendations and/or mean inhibitory concentration (MIC) susceptibility breakpoints for *Pseudomonas aeruginosa* and the *Enterobacteriaceae*. This consideration is the subject of an on-going review by the Agency's Clinical Microbiology and Human Biopharmaceutics disciplines.
- The Division may consider providing additional clarification in the INDICATIONS/USAGE section of the label for "Empiric Therapy for Febrile Neutropenic Patients".

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer recommends that B. Braun be advised of the Agency's proposed postmarketing analyses of mortality associated with cefepime versus comparable antimicrobial agents. The results of this analysis may influence any future actions and/or labeling of the B. Braun product.

## 2 Introduction and Regulatory Background

Cefepime is a semi-synthetic, broad spectrum cephalosporin antibiotic classified within the fourth generation cephalosporin 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 the reference listed drug (RLD), MAXIPIME<sup>®</sup> 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). The drug substance, cefepime is also manufactured by BMS Company.

In this submission, the Applicant proposes to manufacture this product as a 505(b)(2) NDA using the BMS product Maxipime in Add-Vantage vials, as the RLD basis of this submission. The Applicant states that there are many similarities between the ADD-Vantage<sup>®</sup> System and the Duplex<sup>®</sup> System, making it the appropriate choice for the RLD. Furthermore, the Applicant contends that both systems have safety features that others do not have, including minimizing admixing errors, standard doses that are in a closed, sterile packaging system, and needle-free system to prevent needlestick injuries. Both systems are easy to use having pre-measured doses with no freezing, thawing or refrigeration required. Both systems can be activated quite easily at the patient bedside with minimal waste. The ADD-vantage<sup>®</sup> System must be mixed with the applicable diluent container that is labeled for use with the ADD-vantage<sup>®</sup> vial. This vial cannot be reconstituted with any other diluent (except for the ADD- vantage<sup>®</sup> diluents) in a sterile manner, and use of other diluents is restricted in the labeling. Any other reconstitution would void the premium aseptic reconstitution system for which it was designed. The same holds true for the Duplex<sup>®</sup> System, a dual chamber bag filled with powder and diluent in separate chambers. When pressure is applied to the diluent chamber, the seal between the chambers breaks allowing the powder

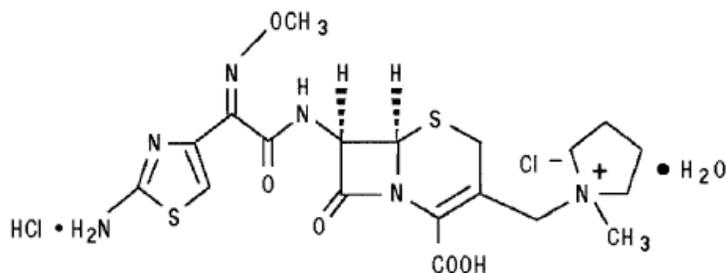
to be reconstituted. The finished product can then be administered to the patient at their bedside. The Add-Vantage vial is administered solely through the intravenous route of administration as is the Duplex finished product. The applicant is seeking approval for Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container for the same indications approved for MAXIPIME<sup>®</sup> for Injection with the exception of administration by the intramuscular route.

## 2.1 Product Information

Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX dual chamber container is supplied for intravenous administration in strengths equivalent to 1 g and 2 g of cefepime. Cefepime for Injection USP and Dextrose Injection USP is supplied as a sterile, nonpyrogenic, single use packaged combination of cefepime hydrochloride with L-arginine (drug chamber) and 50 mL of 5% dextrose injection (diluent) in the DUPLEX sterile container. Cefepime for Injection USP and Dextrose Injection USP contains the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of cefepime (C<sub>19</sub>H<sub>24</sub>N<sub>6</sub>O<sub>5</sub>S<sub>2</sub>). The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the reconstituted solution at 4.0 to 6.0.

The DUPLEX container is a flexible dual chamber container. After removing the peelable foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use. Each 50 mL contains cefepime hydrochloride equivalent to either 1 gram or 2 grams of cefepime. Reconstituted solutions of Cefepime for Injection USP and Dextrose Injection USP range in color from colorless to amber. The DUPLEX Container is latex-free, PVC-free, and Di (2-ethylhexyl) phthalate (DEHP)-free. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

Chemical structure:



Chemical formula: C<sub>19</sub>H<sub>25</sub>ClN<sub>6</sub>O<sub>5</sub>S<sub>2</sub>·HCl·H<sub>2</sub>O

Molecular weight: 571.50

Dosage Strength: 1 g or 2 g

Applicant's proposed indications, dosing regimens, age groups:

Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container has the same indications and dosing regimens as the RLD, MAXIPIME<sup>®</sup> with the exception of administration by the intramuscular route.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

No new proposed indications are included in this application. 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.

## 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, cefepime hydrochloride, is marketed as MAXIPIME<sup>®</sup> for injection in the United States. MAXIPIME<sup>®</sup> has been available on the U.S. market since 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).

## 2.4 Important Safety Issues With Consideration to Related Drugs

Recent safety concern regarding increase in mortality of cefepime use was raised by the Yahav et al meta-analysis studies. The Agency's review of the Yahav meta-analysis and additional studies not included in the meta-analysis did not find an association of their findings. The Agency in conjunction with the Premier Healthcare Informatics database will perform a postmarketing analysis of mortality associated with administration of cefepime versus comparable agents.

There are no safety or effectiveness concerns with pharmacologically related products (i.e., other cefepime 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 Summary of Presubmission Regulatory Activity Related to Submission

The pre-submission regulatory activities between the Sponsor and the Division of Anti-infective and Ophthalmology Drug Products (DAIOP) regarding this application are as follows:

- May 9, 2008 – B. Braun submits a Type B Teleconference Meeting request concerning clarification on the following: 1) Submission as a 505(b)(2) NDA using Bristol Myers-Squibb's Maxipime in the Add-Vantage vials as the RLD. 2) If submission without the USP designation is acceptable due to a different sample preparation method for related compounds. 3) A safety of this product due to a MedWatch alert posted November 20, 2007 pertaining to increase in mortality. A teleconference date suggested was early July 2008.
- May 20, 2008 – FDA response granted the Type B teleconference meeting to discuss the potential NDA 505(b)(2) filing on July 14, 2008. B. Braun is to provide teleconference number and background information for the teleconference with the number of required copies.
- May 30, 2008 – B. Braun submits the response to the May 20, 2008 FDA request by providing the teleconference number. B. Braun states that the May 9, 2008 meeting request contained the background information for this teleconference. Three copies of background materials were forwarded for the pre-NDA 50-821 file as well as 14 desk copies to the Project Manager.
- July 11, 2008 – B. Braun receives an email from the Project Manager (DAIOP) answering the questions in the May 9, 2008 Type B teleconference meeting request. The Agency requests to cancel the July 14, 2008 teleconference if the correspondence sufficiently addresses the questions. B. Braun agreed that the teleconference could be cancelled based on the answers received in this email and emailed the Project Manager concerning the USP preparation for related compounds test pending labeling question for further clarification.
- July 25, 2008 – July 29, 2008 – B. Braun wanted clarification concerning the Agency's proposed labeling statement about the related compounds test. The project manager forwarded the Sponsor's question to the CMC group and scheduled a telephone call between Dr. Schmuff and the B. Braun representatives (Kimberly Ernst and Patricia Smith). Dr. Schmuff was wondering why we wanted this statement in our labeling. Kimberly Ernst explained we had a similar issue during our review of NDA 65-430 because we couldn't meet the specification for the (b) (4). Dr. Schmuff stated that the FD&C Act states that you do not need to perform the USP test. He stated that if the product is tested and if it does comply with the USP no statement is needed on the labeling. Dr.

Schmuff said what really mattered was meeting the USP specification for the product as long as there is data to show that the specification is met.

## 2.6 Other Relevant Background Information

The applicant does not have any marketing history with cefepime injection in the Duplex container.

## 3 Ethics and Good Clinical Practices

Not applicable.

### 3.1 Submission Quality and Integrity

Not applicable.

### 3.2 Compliance with Good Clinical Practices

Not applicable

### 3.3 Financial Disclosures

Not applicable. No new clinical studies conducted with this application.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Note: The reader is referred to the CMC review by the chemistry reviewer, Dr. Milton Sloan for detailed descriptions of the drug product and manufacturing process.

### 4.2 Clinical Microbiology

Note: The reader is referred to the microbiology review by the microbiology Reviewer, Dr. Avery Goodwin for details.

#### 4.3 Preclinical Pharmacology/Toxicology

There are no additional nonclinical toxicology studies conducted to support this application. According to the animal pharmacology/toxicology reviewer, Dr. Amy Ellis, she has no objection to the approval of NDA 50-821 for Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> container, provided that the chemistry reviewer agrees with the Applicant's assessment that the product contains no impurities or degradation products that need to be qualified via non-clinical testing.

#### 4.4 Clinical Pharmacology

There are no new clinical pharmacology data submitted with this application. Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container contains the same active ingredient as the reference listed drug, MAXIPIME<sup>®</sup> (cefepime hydrochloride, USP) for Injection by Bristol-Myers Squibb. (Note: The reader is referred to the clinical pharmacology review of Aryun Kim for details.)

##### 4.4.1. Mechanism of Action

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

##### 4.4.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this application.

##### 4.4.3 Pharmacokinetics

The pharmacokinetics data are the same as the RLD, MAXIPIME<sup>®</sup> (cefepime hydrochloride, USP) for Injection.

### 5 Sources of Clinical Data

This 505(b)(2) application has no new clinical studies.

#### 5.1 Tables of Studies/Clinical Trials

There are no clinical studies conducted to support this 505(b)(2) new drug application for Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container.

## 5.2 Review Strategy

Not applicable.

## 5.3 Discussion of Individual Studies/Clinical Trials

Not applicable.

## 6 Review of Efficacy

There are no clinical studies conducted by the applicant to support this 505(b)(2) new drug application for Cefepime for Injection Dextrose Injection in Duplex<sup>®</sup> Container. The review for this NDA relies on prior FDA determination of effectiveness based on studies which were not conducted by or for the Applicant, B. Braun Inc. for the reference listed drug, MAXIPIME<sup>®</sup>.

### **Efficacy Summary**

Not applicable.

#### 6.1 Indication

Not applicable.

##### 6.1.1 Methods

Not applicable.

##### 6.1.2 Demographics

Not applicable.

##### 6.1.3 Subject Disposition

Not applicable.

##### 6.1.4 Analysis of Primary Endpoint(s)

Not applicable.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

## 7 Review of Safety

The Applicant was requested to submit a 120-day safety update of cefepime for this submission. Recent literature publications regarding safety of cefepime were submitted and reviewed by the applicant.

### **Safety Summary**

The safety update for cefepime provided recent literature publications that addressed its safety profile. The publications of Thabet et al provided case reports of cefepime-induced non convulsive status epilepticus (NCSE) in a pediatric patient and summarized a total of 25 published cases of NCSE through Medline review of the literature. The other safety issues for cefepime including encephalopathy, status epilepticus, and related neurotoxicity signs and symptoms and neutropenia are mentioned in this safety update. These adverse events are also mentioned in the cefepime or RLD, Maxipime<sup>®</sup> label. Based on the review of the NCSE cases, it is appropriate to add this adverse reaction associated with cefepime to the drug label. The health care professionals should be aware of these potential neurotoxicities with

cefepime use (i.e., encephalopathy and/or NSCE). The RLD Sponsor should be issued a labeling supplement request for this change. After the change has been made for the RLD, it may be included in the Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container label.

## 7.1 Methods

The Applicant reviewed the literature articles which deal with predominantly *in vitro* issues such as isolation techniques or bacterial strain epidemiology, and have no relevance to or discussion of human safety issues.<sup>1-17</sup> The Applicant also reviewed other publications that discussed the efficacy and pharmacodynamics of cefepime.<sup>18-27</sup>

***MO Comment: Review of the articles (1 through 17 and 34) showed no information relevant to clinical safety of cefepime. The reviewer agrees with the applicant's safety review of the mentioned references. The reader is referred to the Appendices, subsection 9.1, Literature references) for the list of these articles. The subsequent literature articles that have clinical relevance to the safety of cefepime were reviewed.***

Review of literature articles that discuss clinical safety profile of cefepime:

- Dakin LE. Probable Trimethoprim/Sulfamethoxazole Induced Higher Level Gait Disorder and Nocturnal Delirium in an Elderly Man (January). Ann Pharmacother. 2008 Dec 23.

This article describes a case of probable trimethoprim/sulfamethoxazole (TMP/SMX) – induced higher-level gait disorder (HLGD) and nocturnal delirium in an 82-year-old man with a recent history of depression. The patient had no other significant past medical history and was not taking other medications. The report states that he was usually mobile without aid and was independent with his activities of daily living. He became comatose following an overdose of escitalopram and oxazepam. He was admitted, ventilated for 7 days in the ICU, and treated empirically with ampicillin sodium 1 g IV every 6 hours until day 4 for aspiration pneumonia. On day 5, antibiotic was changed to piperacillin/tazobactam 4g/0.5g IV every 8 hours for 48 hours. **On day 6, the antibiotic regimen was changed to cefepime 2 g IV every 12 hours following isolation of *Staphylococcus aureus* and *Serratia marcescens* from endotracheal aspirate and sputum.** Following discharge to a medical ward, *Stenotrophomonas maltophilia* was isolated from the sputum on day 12. This organism was sensitive to TMP/SMX and on day 15, TMP/SMX 800 mg/160 mg

1 tablet every 12 hours was initiated. On day 35, the dose was increased to 800 mg/160 mg, 2 tablets every 12 hours, because of partial clinical response with the initial regimen. By day 37, the patient was unsteady when attempting to stand. Laboratory results showed: urinalysis and urine culture (catheterized specimen) were negative; a complete blood cell count showed mild normocytic anemia with normal white blood cell count, differential and platelet count. Serum alkaline phosphatase was mildly elevated at 187 U/L (reference range 40–110) and g-glutamyl transferase was 189 U/L (<50). Serum albumin was decreased at 2.7 g/dL (3.5–5.0), but serum transaminase levels, bilirubin level, and prothrombin time were within normal limits. Serum urea, electrolyte, and creatinine levels were also within normal limits; however, the estimated glomerular filtration rate was reduced at 59 mL/min/L (>60). Results of thyroid function tests, serum vitamin B<sub>12</sub> level, and red blood cell folate levels were normal. A CT scan of the brain showed only mild atrophy consistent with the patient's age. From day 40, he was noted to have features of HLGD with gait impairment, poor balance, and frequent falls. There were no parkinsonian features. The patient also developed nocturnal delirium (i.e., perceptual disturbance with disorientation to place and time); but he was oriented during daytime. His other medications at this time were thiamine 100 mg daily, multivitamin 1 tablet daily, omeprazole 20 mg every 12 hours, and modified-release venlafaxine 150 mg daily. Investigation did not reveal any cause for his acute gait disturbance. On day 48, TMP/SMX was discontinued as it was suspected that the adverse reaction to the antibiotic might be the cause of the gait impairment. By day 51, the patient's condition improved dramatically and his gait had returned to normal and was able to mobilize with a wheeled mobility aid. No further nocturnal delirium was noted. According to the report, the patient was discharged home to independent living on day 70.

***MO Comment: The reviewer agrees with the author that this case of HLGD was probably associated with TMP/SMX. Given the age of the patient, the presence of risk factors (i.e., malnutrition, renal and hepatic dysfunction), and the administered high dose TMP/SMX probably contributed to the neurotoxic effects. Neuropsychiatric adverse reactions with TMP/SMX have been reported but infrequent. Although cefepime use is associated with neurotoxicity, the patient's gait impairment was probably not related to cefepime.***

- Thabet F, Al Maghrabi M, Al Barraq A, Tabarki B. Cefepime Induced Nonconvulsive Status Epilepticus: Case Report and Review. Neurocrit Care. 2008 Nov 25.

This article describes a case of cefepime induced non convulsive status epilepticus (NCSE) in a pediatric patient that resolved within 48 hours of discontinuing therapy. The authors summarized 25 published cases of NCSE through Medline review of the literature including the 15- year-old female patient in this case report.

Twenty-five cases of NCSE associated with cefepime that have been reported in the literature are reviewed. The average age was 60 years (15–86). Most of these cases were adults, and two cases were pediatric patients. The cefepime dosage was adjusted for renal function in 5 cases. All except 1 patient had impaired renal function (CRF: 17 cases, ARF: 7 cases). The symptoms started 1–15 days after starting cefepime (mean 6 days). The outcome was good after discontinuation of cefepime therapy and anticonvulsant treatment. A fatal outcome was reported in four cases. According to the articles, the causes of deaths were related to patient's underlying medical illness. One patient died of multi-organ failure with refractory status epilepticus (SE) and coma.

The case report describes a 15 year old girl on hemodialysis since the age of 4 years for end stage renal disease secondary to polycystic kidney. She was admitted to the hospital with a history of fever for 3 days. Blood culture showed *Pseudomonas aeruginosa* sensitive to cefepime. She was treated with IV cefepime 1 g every 12 h (100 mg/kg per day). On the 4th day of cefepime therapy the patient was noted to be lethargic and confused. By day 5, she developed myoclonic jerks in her arms which were relieved by diazepam. The consciousness level of the patient continued to deteriorate and she became mute. On neurological examination she was responsive only to painful stimulation (Glasgow coma scale of 8), there was no neck rigidity or any focal neurological deficit but she was having hyperreflexia in the lower limbs and bilateral ankle clonus. Temperature, vital signs and the rest of the physical examination were normal. CT scan of the brain and spinal fluid examination were unrevealing. Dextrostix and ammonia were within the normal range. Serum electrolytes and renal function, blood urea nitrogen, 27 mmol/l (normal: 1.8–6 mmol/l) and serum creatinine, 610 µmol/l (normal: 25–60 µmol/l)] showed no difference from the previous profile. EEG showed generalized spike and sharp wave activity compatible with NCSE. The patient was intubated, started on mechanical ventilation and on midazolam continuous infusion. Cefepime was discontinued after the first EEG, as no other etiology was determined. Forty eight hours later, the patient regained full consciousness (Glasgow coma scale of 15), and she was successfully extubated. Renal profile showed blood urea nitrogen of 18 mmol/l and creatinine of 490 µmol/l. Repeated EEG was normal.

**Table 1: Summary of Literature Reported cases of Cefepime-induced NCSE**

PATIENT# AGE/ GENDER COUNTRY	INDICATION	CEFEPIME DOSE AND DURATION/ DOSE ADJUSTED TO RENAL FUNCTION	TYPE OF RENAL FUNCTION	LATENCY (DAYS)	CLINICAL FINDINGS	ANTI- EPILEPTIC DRUG/ TREATMENT	OUTCOME
1./54/M <sup>1</sup> Belgium	Neutropenic fever	1gm qd x 9 days/No	CRF	10	Confusion, myoclonic jerks	Phenytoin (PHT) valproic acid	Pt died (day 33) of invasive aspergillosis
2./60/F <sup>1</sup> Belgium	Febrile neutropenia	1 gm qd x 6 days/No	CRF	6	Convulsions	Valproic acid	Improved after d/c cefepime
3./79/F <sup>2</sup> USA	UTI	2 gm q12hx 2 days/Yes	Normal	2	Confusion, jerky movement	Lorazepam, valproic acid	Improved after d/c cefepime
4./76/F <sup>3</sup> Spain	Pyoderma <i>P.aeruginosa</i>	2 gm q 8hx 5 days/No	ARF	5	Agitation, confusion	Diazepam, phenytoin	Improved after d/c cefepime
5./38/F <sup>3</sup> Spain	<i>Serratia marcescens</i> bacteremia	2 gm q8h x 5 days/No	ARF	5	Agitation, disorientatio n	Diazepam, phenytoin	Improved after d/c cefepime + phenytoin
6./43/M <sup>3</sup> Spain	Abdominal sepsis	2 gm q12hx 2 days /No	ARF	2	Abnormal behavior; mutism	Diazepam, phenytoin	Improved after 20 hrs d/c cefepime+PHT
7./74/F <sup>4</sup> Italy	Bronchopneumonia	4 g/dx 7 days/No	RF	7	Stupor	Diazepam	Complete recovery after a week with d/c cefepime + hemodialysis
8./15/M <sup>5</sup> Turkey	Pneumonia	12.5 mg/kg/dx 6 days/Yes	CRF	6	Confusion, ataxia, asterixis	Diazepam	Improved after d/c cefepime
9./66/F <sup>6</sup>	Empiric antibiotic treatment	2 g q8 hx 7 days/No	ARF	12	Confusion, myoclonic jerk	Clonazepam, valproic acid	Improved after d/c cefepime + anti-epileptic tx
10./65/M <sup>7</sup> Spain	Persistent fever+ <i>S. aureus</i> bacteremia	2 g q8 h x 10 days /No	ARF	6	Coma, myoclonic jerks	Phenytoin	Improved after d/c cefepime; neuro normal after 1 month, discharge from hospital. Pt died after 7 months due to third relapse of Hodgkin's.
11./82/M <sup>8</sup> Italy	Pneumonia	1 g qd x 4 days /Yes	CRF	4	Confusion, seizures	Hemodialysis	Improved after d/c cefepime + hemodialysis. Complete recovery with 2 <sup>nd</sup> dialysis
12./65/M <sup>9</sup> France	Gram negative bacteremia +mediastinitis	2 g qd x12 days/No	ARF	12	Confusion, myoclonia	Clonazepam+ dialysis	Recovered

**Table 1: Summary of Literature Reported cases of Cefepime-induced NCSE (cont.)**

PATIENT# AGE/ GENDER COUNTRY	INDICATION	CEFEPIME DOSE AND PROBABLE DURATION/ DOSE ADJUSTED TO RENAL FUNCTION	TYPE OF RENAL FUNCTION	LATENCY (DAYS)	CLINICAL FINDINGS	ANTI- EPILEPTIC DRUG/ TREATMENT	OUTCOME
13./73/F <sup>9</sup> France	Infection of knee prosthesis	2 g qd/No	ARF	15	Coma	Clonazepam+ dialysis	Pt. died at unspecified date due to multi- organ failure + refractory SE and coma
14./69/F <sup>10</sup> Hongkong	CAP	2 g qd x 6 days/ No	CRF	6	Confusion	Diazepam, phenytoin	Improved after d/c cefepime
15./79yr/M <sup>11</sup> Spain	Pneumonia	1 g/24 hx 6 days /No	CRF	6	Confusion, myoclonus	Clonazepam, valproic acid	Improved after clonazepam
16./67yr/F <sup>11</sup> Spain	Pneumonia	2 g q6h x 5 days /No	CRF	5	Drowsiness, confusion	Clonazepam	Improved after clonazepam
17./64yr/F <sup>11</sup> Spain	Pneumonia	1 g/24 h/ x 5 days/No	CRF	5	Agitation, confusion, myoclonus	Clonazepam, phenytoin	Improved after clonazepam
18./54yr/M <sup>11</sup> Spain	Prophylaxis	2 g/24 h x 1 day/No	CRF	1	Agitation, confusion,	Clonazepam, diazepam	Recovered after clonazepam
19./86yr/M <sup>11</sup> Spain	Osteomyelitis	2 g q 12 h x 4 days/No	CRF	4	Agitation, confusion, myoclonus	Clonazepam, diazepam	Improved after 2 days
20./79yr/F <sup>11</sup> Spain	Pneumonia	2 g q 12 h x 10 days/No	CRF	10	Confusion, myoclonus	Clonazepam, Phenytoin, valproic acid	Improved but died 7 days later of heart failure
21./78yr/M <sup>12</sup> Spain	Pneumonia	1 g/q24hx 5 days/Yes	CRF	5	Confusion, hallucination	Clonazepam, valproic acid	Improved after clonazepam
22./64 yr/F <sup>12</sup> Spain	Pneumonia	1 g/q12 h/Yes	CRF	6	Disorientatio Confusion, myoclonus	Clonazepam,	Improved after clonazepam
23./44/M <sup>13</sup> USA	Recurrent pneumonia due to <i>P. aeruginosa</i>	2 g qd x 2 days/No	CRF	1	Confusion, tremor, hyperreflexia clonus	Lorazepam, valproic acid	Recovered after d/c cefepime
24./28/F <sup>13</sup> USA	UTI due to <i>P. aeruginosa</i>	2 g qd/ xNo	CRF	1	Confusion, tremor, twitching, hyperreflexia	Lorazepam, valproic acid	Improved after lorazepam and d/c cefepime
25./15/F* Saudi Arabia	<i>P. aeruginosa</i> bacteremia	1 g/12 h x 5 days/No	CRF	4	Confusion, myoclonic jerks, coma	Midazolam	Recovered and extubated 48 hours later.

<sup>1</sup>Spriet I, Meersseman W, De Troy E, Wilmer A, Casteels M, Willems L. Meropenem-valproic acid interaction in patients with cefepime-associated status epilepticus. Am J Health Syst Pharm. 2007;64(1):54–8.

<sup>2</sup>Maganti R, Jolin D, Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. Epilepsy Behav. 2006;8:312–4.

<sup>3</sup>Fernandez-Torre JL, Martinez-Martinez M, Gonzalez-Rato J, Maestro I, Alonso I, Rodrigo E, et al. Cephalosporin-induced nonconvulsive status epilepticus: clinical and electroencephalographic features. Epilepsia. 2005;46:1550–2.

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<sup>5</sup>Alpay H, Altun O, Biyikli NK. Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. 2004

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<sup>6</sup>Abanades S, et al. Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother.* 2004;38:606-8.

<sup>7</sup>Plensa E, et al. Nonconvulsive status epilepticus associated with cefepime in a patient undergoing autologous stem cell transplantation. *Bone Marrow Transplant.* 2004;33:119-20

<sup>8</sup>Ferrara N, et al. Neurotoxicity induced by cefepime in a very old hemodialysis patient. *Clin Nephrol.* 2003;59:388-90.

<sup>9</sup>Chatellier D, et al. Cefepime-induced neurotoxicity: an underestimated complication of ant biotherapy in patients with acute renal failure. *Intensive Care Med.* 2002;28:214-7.

<sup>10</sup>Chow KM, et al. Nonconvulsive status epilepticus in dialysis patients. *AM J Kidney Dis.* 2001; 38:400-5.

<sup>11</sup>Martinez-Rodriguez JE, et al. Non-convulsive status epilepticus associated with cephalosporin in patients with renal failure. *Am J Med.* 2001;111:115-9.

<sup>12</sup>Saurina A, et al. Non-convulsive status epilepticus secondary to adjusted cefepime doses in patients with chronic renal failure. *Nefrologia.* 2000;20:554-8.

<sup>13</sup>Dixit S, Kurle P, Buan-Dent L., Sheth RD. Status epilepticus associated with cefepime. *Neurology.* 2000;54:2153-5.

\* Current case report

***MO Comment: The reviewer modified the summary table in this article including addition of country of origin, cefepime indication, dose, probable duration, and patient outcome. Some of the missing data in the original table from the article were obtained and reviewed. Some of these cases were submitted to FDA's MedWatch (Medical Products Reporting Program).***

***Maganti and colleagues define NCSE as a heterogenous disorder with varied etiology, several subtypes, and apparent difference in clinical course in different age groups. A variety of terms have been used in the literature to denote NCSE including minor status epilepticus, spike-wave stupor, epileptic twilight state, petit mal, to name a few. There are no current universally accepted definitions of NCSE. Clinical symptoms may range from subtle encephalopathy, subtle clinical signs to a frank coma. Other authors believe that the boundaries between NCSE and encephalopathy may be imprecise. NCSE and metabolic encephalopathy are two different clinical conditions that can cause a confusional state. It is very important to be able to distinguish these entities because treatment varies based on the diagnosis.***

***According to Maganti et al, from the practical standpoint, NCSE can be defined as a condition with prolonged state of impaired consciousness or altered sensorium associated with continuous paroxysmal activity or EEG discharges. Etiology varies and includes metabolic/medical disorders; medications (e.g., penicillins, cephalosporins, fluoroquinolones, isoniazid, etc.); acute cerebral lesions; pre-existing epilepsy with or without encephalopathy; and in critically ill and comatose patients. \*Some forms of NCSE may require aggressive treatment and others may not. There is a considerable degree of controversy on whether to treat critically ill and elderly patients aggressively, as treatment paradigms may be associated with serious complications (i.e., multi-organ failure).***

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***\*Maganti, R, Gerber P, Drees, C, Chung S. Nonconvulsive status epilepticus. *Epilepsy & Behavior* 12 (2008) 572-586.***

- Bresson J, Paugam Burtz C, Josserand J, Bardin C, Mantz J, Pease S. Cefepime overdose with neurotoxicity recovered by high volume hemofiltration. J Antimicrob Chemother. 2008 Oct;62(4):849-50. Epub 2008 Jun 18.

This article describes an adult male who was admitted to an intensive care unit for surgical site infection following lumbar spinal stenosis surgery. Past medical history included hypertension, renal insufficiency, atrial fibrillation, respiratory insufficiency, and ischemic cerebrovascular accident. Medications included fludione, digoxin, acetylsalicylic acid, losartan and amlodipine. A decompressive laminectomy, followed by instrumental fusion of all lumbar vertebrae, was performed. Two weeks later, purulent material from the scar was noted. Surgical debridement was performed. High level AmpC  $\beta$  lactamase *Morganella morganii* was isolated from the sample. A combination of cefepime 6 g/day with amikacin 1.2 g/day once daily was started. Serum creatinine clearance was initially 50 mL/min, but later diminished. It was reported that 4 weeks after surgical debridement, the patient demonstrated intermittent altered consciousness and myoclonic jerks of the right arm, and was transferred to the ICU. Electroencephalogram showed status epilepticus requiring intravenous clonazepam and valproic acid. Mental status gradually returned to normal over the next hour. On the following day, the patient became lethargic and unresponsive. He had no fever and the remainder of his neurological examination was normal. CSF analysis was normal and culture was negative. A diagnosis of valproic acid encephalopathy was considered and the epileptic drug was switched to phenytoin. A second electroencephalogram was performed, showing slow symmetrical delta and theta activity, but no evidence of epileptic discharges. Cefepime induced encephalopathy was suspected, and cefepime was stopped. Serum and CSF levels were measured by HPLC: on day 30, 3 h after the last injection, the serum cefepime level was 284 mg/L (usual levels are between 2.5 and 5.1 mg/L) and the CSF cefepime level was 18 mg/L. The antibiotic regimen was then switched to ertapenem 1 g/day once daily. Renal replacement therapy with high-volume continuous veno-venous hemofiltration was started to enhance cefepime clearance. After 24 hours, serum cefepime level had dropped to 5.6 mg/L. Hemofiltration was continued for 12 hours, until the serum level reached 3.2 mg/L. The report states that the patient fully recovered from his neurological status.

**MO Comment: This article reports the consequence of overdosing cefepime in a patient with renal insufficiency. Clearly, this is a straightforward case of cefepime-induced encephalopathy with status epilepticus. Health-care professionals should be aware of this adverse**

***reaction in the hospital setting which could be managed when recognized early and appropriately.***

- Dehority W, Leake JA. Fever, hip pain, and headache in a 12 year old girl. Clin Pediatr (Phila). 2008 Nov;47(9):962-5. Epub 2008 Jun 6.

This case describes a previously healthy 12-year-old girl who presented to the emergency department with a 1-week history of headache and left hip pain. Three weeks prior to presentation, she developed high fever, diffuse abdominal pain, and non-bloody and non-bilious emesis. Three days later, she was diagnosed with left acute otitis media for which she completed a 10-day course of amoxicillin with improvement in her symptoms. One week prior to presentation, the patient developed diffuse headache, photophobia, left hip pain, and a limp, and 3 days prior to presentation, her fever returned. On admission, the patient received empiric vancomycin and cefepime. An MRI of the pelvis and lower extremities revealed abscesses of both gluteus maximi and left gluteus medius. The patient was taken to the operating room on hospital day 2, where a left tympanomastoidectomy and drainage of the gluteal abscesses were performed. Anaerobic cultures obtained intraoperatively from the left ear discharge and left mastoid and gluteal lesions demonstrated pure growth of *Fusobacterium necrophorum* (*F. necrophorum*). The patient was diagnosed with Lemierre's syndrome, with a presumed otic focus. The patient received anticoagulation and antibiotics were changed to meropenem. The patient improved and discharged after 3-weeks of hospitalization.

***MO Comment: In this case, there was no mention of any adverse event related to cefepime use. The dose of cefepime was not reported in this case.***

- Hettmer S, Heeney MM. Cefepime induced neutropenia in a teenager. Pediatr Blood Cancer. 2008 Nov;51(5):715-6.

This article describes a case of cefepime induced neutropenia in a 16 year old female. The patient had been well until 2 years prior, when she underwent spinal fusion for multiple spinal fractures sustained in a motor vehicle collision. Two months prior to presentation hardware was removed due to cord compression and she developed postoperative *Serratia marcescens* wound infection as evidenced by wound and tissue cultures. Blood cultures were negative. The patient was started with IV cefepime monotherapy (113 mg/kg/day divided in three doses) based on antibiotic sensitivities. Wound cultures cleared within nine days of starting cefepime. Repeat blood cultures remained negative. After 19 days of cefepime therapy, she experienced a sudden drop in ANC to 20/ $\mu$ l noted on a routine CBC without other change in clinical status. Baseline absolute

neutrophil count (ANC) ranged between 4,011/  $\mu$ l and 6,270/  $\mu$ l in the 2 months preceding cefepime therapy. Concurrent medications included docusate, acetaminophen and oxycodone. The patient was afebrile, and there were no signs or symptoms of sepsis or viral infection. Vital signs and physical examination were unremarkable, specifically no evidence for a neutrophil consumptive or sequestering process such as abscess. Pertinent laboratory findings included an acquired normocytic anemia related to repeated wound revisions and ongoing drainage of serosanguinous fluid from a vacuum dressing over her thoracic spine. Review of the peripheral blood smear confirmed neutropenia with normal leukocyte morphology. Cefepime was discontinued and replaced by vancomycin (42 mg/kg/day divided in three doses) and ciprofloxacin (23 mg/kg/day divided in two doses) based on bacterial sensitivities. Absolute neutrophil count (ANC) recovered to 1,450/  $\mu$ l within 5 days of cefepime cessation. A follow up CBC, four months later revealed a normal ANC at 3,670/ $\mu$ l.

***MO Comment: Neutropenia is mentioned in the cefepime (Maxipime) label as being reported in the clinical trials and during the postmarket experience of cefepime. The reviewer agrees that prolonged use of cefepime is associated with risk of developing severe neutropenia as reported in this case.***

- Towne TG, Lewis JS, Echevarria K. Efficacy and safety of cefepime. Lancet Infect Dis. 2009 Jan;9(1):4-6; author reply 6-7.

In this paper, the authors made a comment to the Yahav et al article on meta-analysis of cefepime. "Towne and colleagues believe that practitioners have the right and the responsibility to question and review data presented in a meta-analysis, especially if those data challenge our normal conceptions about medical practice. As evidenced by the recently released FDA memo concerning their safety review of cefepime, acquisition of the data used by Yahav and colleagues has been difficult and has yet to be completed. If a government body cannot obtain the necessary information to complete their analysis in a reasonable period of time, how is the everyday practitioner to make prescribing decisions based upon the meta-analysis? Taken without critical examination, the meta-analysis published by Yahav and colleagues seems to implicate cefepime as the cause of higher mortality compared with that among patients treated with other beta-lactam antibiotics. In an era with limited development of new antimicrobials for resistant Gram-negative organisms, agents like cefepime have a very important role. Losing cefepime as a major antimicrobial for the treatment and prophylaxis of complicated infections would have a profound impact on both pharmacy and medicine. Experience with cefepime is

extensive and there is a considerable literature to support the safety and efficacy of this drug for many serious infections. We must be careful not to place too much weight on a meta analysis without substantial biologic plausibility.”

Yahav et al write in rebuttal of Towne et al, and conclude: “In summary, our review reported all cause mortality data extracted from 41 trials including 7388 patients. All cause mortality was significantly higher with cefepime (RR 1.26, 95% CI 1.08–1.49, p=0.005). Although we could not explain the increased mortality, considering the significance of the results and the wide variety of alternative antibiotic treatments, we believe that it is reasonable to reconsider the use of cefepime until the US FDA reaches a definite conclusion concerning the safety of cefepime.”

***MO comment: This article reiterates the author’s opinion about their meta-analyses of cefepime and the findings of Yahav et al meta-analyses.***

- Endimiani A, Perez F, Bonomo RA. Cefepime: a reappraisal in an era of increasing antimicrobial resistance. Expert Rev Anti Infect Ther. 2008 Dec;6(6):805–24.

This article provides a critical review of pharmacodynamics, pharmacokinetics, clinical efficacy, safety and tolerability of cefepime after more than a decade of clinical use. The authors state that cefepime is ineffective against ESBL-producing *Enterobacteriaceae*, *A. baumannii* and highly derepressed AmpC-producing *P. aeruginosa* isolates. The re-evaluation of existent CLSI Gram-negative susceptibility breakpoints for cefepime is necessary. The authors believe that based on the results of meta-analyses by Yahav et al, the use of cefepime as monotherapy should be tempered by a careful consideration of risks and benefit (at least in febrile neutropenia case).

***MO Comment: There is no mention of new safety information of cefepime in this article.***

The following references support the dextrose contraindication in the proposed Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container label:

1. Randolph TG, Rollins JP, Walter CK. Allergic reactions following the intravenous injection of corn sugar (Dextrose). Archives Surgery 1950; 554-564.

This paper describes five case reports of corn sugar (dextrose) sensitivity as follows:

Case #1: A 22-year-old woman who has a history of intermittent asthma since childhood, acute GI upsets at age 15, perennial allergic rhinitis and chronic fatigue at age 19. In the months of July and August for the preceding two years, she developed chronic colds accompanied by daily elevations of temperature and tender swollen cervical glands. Her reactions were not associated with high pollen or fungus counts or explained on the basis of infectious mononucleosis or other causes. However, the report states that her food diary revealed that she developed sneezing, pruritus and urticaria following meals containing corn on the cob. A food test with corn was followed by abdominal cramps, generalized itching, marked fatigue, and recurrence of tender, swollen anterior cervical glands. The report states that a complete elimination of corn products and continuation of dust therapy afforded complete relief of symptoms. A test was performed in which the patient ingested USP dextrose, and the patient developed acute reactive symptoms. Two years later, the patient received 25 cubic centimeters of 5% dextrose intravenously and 12 minutes later she developed severe headache with pain and tenderness of the mastoid area bilaterally, generalized aching of her extremities, and fatigue which persisted for two days. Four days later after being symptom free, she underwent another rechallenge test of intravenous injection of 20 cc. of 50% dextrose, which again led her to develop acute allergic myalgia with marked stiffness of her neck and back.

Case #2: A 30-year-old female dietician who has a history of constant headache, posterior cervical myalgia, generalized aching for three years, and a history of episodic nausea, vomiting, and diarrhea for eight years. Her history of hypersensitivity to administration of corn syrup was first noted when she was hospitalized for nausea of pregnancy and irritable colon. The patient received three intravenous injections of 5% dextrose in sodium chloride solution on successive days. Two hours after the third injection, she complained of chills with pain on the right side of her chest and midback; at three hours, an increase in nausea and diarrhea developed; and 3 ½ hours later, she developed severe chills and a fever of 100.4°F. Seven hours later, her temperature rose to 102°F and she developed severe abdominal cramps. She recovered after two days without receiving any further intravenous dextrose solution. These acute reactions were repeated during several hospitalizations and receiving dextrose solutions intravenously. A corn sugar test was performed and revealed similar acute reactive symptoms, while an isotonic sodium chloride solution test failed to develop such reactions.

Case #3: This is a 54-year-old housewife with a history of intermittent headaches for 15 years. Over the next decade, her headaches became constant and were

associated with dizziness. She also complained of weakness, alternating constipation and diarrhea, and chronic dermatitis in her hands. A food test showed that she was allergic to a wide variety of foods. Corn gave her the most reactions. Her sensitivity to corn persisted to such a degree that even ingestion of small amount of corn contained as excipients in pharmaceutical tablets and ingestion of dextrose encountered by accident in commercially prepared foods caused symptoms. She received intravenous injection of 5% dextrose as previously described for other cases. A few minutes later, she developed drowsiness, muscle pain over her neck and extremities, sniffing, coughing, lacrimation, headache and generalized fatigue. Her symptoms gradually tapered off during the following two days.

Case #4: A 37-year-old woman who has a chronic history of perennial nasal allergy with intermittent nasal obstruction and other acute exacerbation of symptoms such as sore throat and enlargement of anterior cervical glands. She underwent a food test and was found to be sensitive to wheat, corn, rye, milk, eggs and pork. Upon avoidance of all sources of corn, the patient reported an improvement for the first time in many months. After a second feeding test with corn meal gruel and corn sugar, she developed severe chills and headache. Two months later, she underwent the test of 25 cc. of 5% dextrose injection intravenously; seven hours later, she developed angioedema of the face but was otherwise stable and was reported as unusually tired and depressed. Ten days later, she was given another test of 500 cc. of 5% dextrose intravenously. Minutes later, she developed mild to severe frontal headache, neck and upper back pain, nasal congestion, belching, and excessive gas. Her severe fatigue, drowsiness, decreased mental acuity, and neck and back pain persisted until the following day. She apparently recovered after a day.

Case #5: A 41-year-old male engineer who has a two-year history of recurrent headaches and rhinitis. The patient's symptoms included a right frontal area pressure sensation, scotomas, inability to focus his eyes, neck pain, fatigue, nausea, and diarrhea. The report states that his physical examination showed no significant abnormalities. On allergy testing, he reacted to house dust on cutaneous testing. Individual food tests revealed corn sensitivity. With dust therapy and avoidance of corn, the patient reported a complete relief of his symptoms lasting for several weeks. He then underwent the intravenous 5% dextrose test and a few minutes later, he developed warm sensation and flushing of his face. After ten minutes, he developed chills and rigors and twenty minutes later, he developed headache, neck pain, and throat secretions.

2. Randolph TG, Rollins JP, Walter CK. Allergic reactions following the intravenous injection of corn sugar (Dextrose or Glucose). J. Lab & Clin Med 1949; 34:1741.

This abstract reiterates the four case reports of patients with corn sensitivity. In each case, the diagnosis of corn sensitivity was made as a result of the experimental feeding of corn meal gruel and corn sugar after four days of complete corn avoidance. Intravenous administration of 25 cc of 5% dextrose resulted in severe symptoms which were clinically similar to those observed following the ingestion of corn meal and corn sugar.

***MO Comment: It is not stated in this abstract whether these four cases are the same cases previously described by Randolph et al in article #1.***

3. Sandberg DH. Persistent vomiting due to sensitivity to corn sugar or dextrose present in intravenous fluids. *Pediatric Research* 1977; 11(4): 449(#466).

This is a case report of a 13-year-old white female admitted to the University of Miami Medical Center because of persistent vomiting with weight loss for two months. She also complained of chronic persistent abdominal pain. An exploratory surgery with appendectomy revealed no apparent abnormality. The patient developed nausea and vomiting after all oral intake postoperatively. A cineesophagogram and endoscopy revealed minimal esophagitis and pylorospasm. Her vomiting persisted while on intravenous fluids. The patient was given intragastric drip feedings of Sustacal R with temporary improvement of her symptoms. Intragastric milk was tolerated except for corn products. An intradermal provocative food testing with corn extract produced symptoms suggesting corn sensitivity. Intravenous administration of 25 ml 5% dextrose with water reproduced all her previous GI symptoms. A corn meal and corn syrup produced nausea and vomiting. Laboratory results including C3 was low with elevated serum IgE and IgM. The patient gained weight in 3 weeks after avoiding corn products and had no recurrence of her GI symptoms.

***MO Comment: The articles provided by the applicant support the dextrose contraindication in the proposed Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container label. This is acceptable.***

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

No studies were conducted in this submission. Literature articles were reviewed to provide the safety update for cefepime injection.

#### 7.1.2 Categorization of Adverse Events

Not applicable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

Not applicable.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Not applicable.

7.2.2 Explorations for Dose Response

Not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

7.3 Major Safety Results

Not applicable.

7.3.1 Deaths

Not applicable.

7.3.2 Nonfatal Serious Adverse Events

Not applicable.

7.3.3 Dropouts and/or Discontinuations

Not applicable.

7.3.4 Significant Adverse Events

Not applicable.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable.

7.4 Supportive Safety Results

Not applicable.

7.4.1 Common Adverse Events

Not applicable.

7.4.2 Laboratory Findings

Not applicable.

7.4.3 Vital Signs

Not applicable.

7.4.4 Electrocardiograms (ECGs)

Not applicable.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

## 7.5 Other Safety Explorations

Not applicable.

### 7.5.1 Dose Dependency for Adverse Events

Not applicable.

### 7.5.2 Time Dependency for Adverse Events

Not applicable.

### 7.5.3 Drug-Demographic Interactions

Not applicable.

### 7.5.4 Drug-Disease Interactions

Not applicable.

### 7.5.5 Drug-Drug Interactions

Not applicable.

## 7.6 Additional Safety Evaluations

Not applicable.

### 7.6.1 Human Carcinogenicity

Not applicable.

### 7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

## 7.7 Additional Submissions / Safety Issues

Not applicable.

## 8 Postmarket Experience

The AEs reported during the postmarket experience of cefepime are taken from the RLD, Maxipime® label as follows:

“As with some other drugs in this class, encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures have been reported. Although most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. (see also Warnings). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Precautions should be taken to adjust daily dosage in patients with renal insufficiency or other conditions that may compromise renal function to reduce antibiotic concentrations that can lead or contribute to these and other serious adverse events, including renal failure.

As with other cephalosporins, anaphylaxis including anaphylactic shock, transient leucopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported.”

## 9 Appendices

### 9.1 Literature review/references

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## 9.2 Labeling Recommendations

The Applicant made the following changes to the Cefepime for Injection and Dextrose Injection in Duplex<sup>®</sup> Container in PLR format: **(MO Note: The Applicant's proposed labeling revisions are highlighted in yellow.)**

- Replacement of RLD, Maxipime<sup>®</sup> by BMS specific information with B.Braun Medical Inc's product name, Cefepime for Injection and Dextrose Injection USP in Duplex<sup>®</sup> Container and IV route of administration.
- Deletion of all the text relating to intramuscular form.
- Addition of text under WARNINGS AND PRECAUTIONS section, regarding the possibility of patient's sensitivity to dextrose because the DUPLEX<sup>®</sup> container is only filled with Dextrose injection as the sole diluent for reconstitution.
- Addition of text under WARNINGS AND PRECAUTIONS section and Postmarketing Experience subsection, regarding Non-convulsive status epilepticus (NCSE) as a result of the information obtained from published literature for cefepime in the 120 day Safety update.
- Addition of text under the DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING sections, regarding description of the DUPLEX<sup>®</sup> container.

- In the Pediatric Use subsection and under DOSAGE AND ADMINISTRATION section, the pediatric information has been removed in order to ensure consistency among all Duplex products and conform with the Agency's original request for Cefazolin application, NDA 50-779.
- Minor editorial revisions (e.g., All "μ" for μg symbols in all tables have been replaced with "mc" to become "mcg"; addition of registered trademark symbol).
- Changed titles and subtitles as required for PLR format per Guidance for Industry, Labeling for Human Prescription Drug and Biological Products.

***MO Comment: Additional review of the labeling is deferred at this time, until all disciplines have completed their reviews. The clinical reviewer proposes to make changes to the Pediatric Use subsection and the addition of text under WARNINGS AND PRECAUTIONS section and Postmarketing Experience subsection regarding non-convulsive status epilepticus (NCSE).***

15 pages have been withheld in full immediately following this page as B4 (Draft Labeling)

### 9.3 Advisory Committee Meetings

Not applicable.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Alma Davidson  
6/1/2009 05:04:45 PM  
MEDICAL OFFICER

Janice Pohlman  
6/5/2009 02:42:05 PM  
MEDICAL OFFICER

## MEDICAL OFFICER'S REVIEW OF COMPLETE RESPONSE

**NDA: 50-821**

**Applicant:** B. Braun Medical Incorporated  
901 Marcon Boulevard  
Allentown, Pennsylvania 18109

**Resubmission date:** November 6, 2009

**Goal Due Date:** May 6, 2010

### Background

B. Braun Inc. has submitted NDA 50-821 for a new drug delivery system for cefepime injection (Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container) as a 505(b)(2) application. A 505(b)(2) application may include results of investigations necessary for approval which 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 for this NDA relies on prior FDA determination of safety and efficacy for the reference listed drug, MAXIPIME® (Cefepime hydrochloride) for Injection. MAXIPIME® manufactured by Bristol-Myers Squibb (BMS), approved for marketing on January 18, 1996.

NDA 50-821 was originally submitted on September 25, 2008 and received on September 26, 2008. This submission was not granted an approval due to deficiencies identified by FDA inspection of the drug substance manufacturing facility, (b) (4). Additionally, DMF (b) (4) was also found to be inadequate to support approval of NDA 50-821. In the complete response letter dated July 21, 2009, the Applicant was requested to submit responses to the deficiencies along with proposed labeling in structured product labeling (SPL) format and a safety update. **(MO Note: The reader is referred to the first submission, NDA 50-821, dated September 25, 2008 for details of that review.)**

On November 6, 2009, the Applicant submitted a complete response to the July 21, 2009 complete response letter issued by the Agency. The Applicant submitted a review of publications for the safety update, covering the 120 day period from February 10, 2009 to October 22, 2009.

## **Review of Safety Update**

The Applicant submitted this second safety update for NDA 50-821 in response to the Agency's complete response letter dated July 25, 2009. The Applicant has performed a literature search of the NLM database using PubMed to obtain recent safety information on cefepime. The search covered the period from February 10, 2009 to October 22, 2009. Their search yielded 86 publications, of which eight articles reported some safety and efficacy information for cefepime.

According to the Applicant, most publications deal with predominantly *in-vitro* issues such as isolation techniques, susceptibility testing, or bacterial strain epidemiology and have no relevance to human safety issues. Other publications discussed the antibacterial efficacy or pharmacodynamics/kinetics of cefepime and do not comment on drug safety issues. One article discussed another cephalosporin, ceftobiprole. Another publication discussed antibiotic prescribing errors. One article reported on phenytoin-induced hypersensitivity syndrome. The medical reviewer summarizes excerpts from the eight literature publications listed below:

1. Mebis J, Goossens H, Berneman ZN. Cefepime and mortality. *Lancet Infect Dis* 2009 Oct 2009; 10:585-6.

In this article, the authors discuss the 2007 Yahav et al<sup>1</sup> meta-analysis finding of a higher rate of all-cause mortality in patients treated with cefepime, especially in neutropenic patients, compared with patients treated with other  $\beta$ -lactams. The authors referred to an earlier response by Towne and colleagues<sup>2</sup> who had reviewed the 19 studies with neutropenia in this meta-analysis and found no difference between infectious causes of death in either treatment group. Additionally, no cases of non-convulsive status epilepticus were identified as a possible explanation for observed mortality. An article by Thao D Nguyen et al<sup>3</sup> was also noted, which reported on the five neutropenia studies in the Yahav et al<sup>1</sup> meta-analysis that showed a notable difference in the mortality rates. These studies showed that it was difficult to attribute mortality to an infectious episode because of the heterogeneous nature of the populations. The authors cited their recently published prospective survey with cefepime and amikacin as empiric treatment in high-risk patients with febrile neutropenia. For 220 consecutive episodes of febrile neutropenia in 136 patients, clinical cure was observed in 123 episodes (56%) after beginning the antibiotic protocol; another 22 became afebrile after modifying the initial antibiotic regimen 48 hr or more after beginning treatment. Eight of the 136 patients died (5.8% all-cause mortality); of these, five patients died because of an infection (3.6% mortality). According to the authors, results of this study are similar to other studies in this population of patients, not only with regard to efficacy but also mortality. The mortality rates seen in their high-risk population are lower than in some of the studies reviewed in the meta-analysis by Yahav and colleagues. One of the possible reasons hypothesized is the difference in regimen used in studies included in the Yahav et al analysis: either a lower dose of cefepime (2 g every 12 hr compared with 2 g every 8 hr in our study) as in the studies by Gomez and Biron or the use of cefepime as monotherapy as in the studies by Bow, Biron, and Chandrasekar

(compared with combination therapy administered in their study and in the study by Sanz, who also reported low mortality). The authors previously reported that the introduction of cefepime plus amikacin for the treatment of febrile neutropenia was successful in reversing the high antibiotic resistance rate in Enterobacteriaceae that arose after the use of ceftazidime. The authors have also studied the long-term antibacterial efficacy of cefepime. During a 10-year surveillance of bacterial epidemiology and susceptibility patterns during the empirical use of cefepime, a high susceptibility of all Gram-negative bacteria (especially inducible Enterobacteriaceae) remains for cefepime, despite its very intensive use.

***MO Comment: This Letter to the Editor reports on the continued efficacy of cefepime for treatment of fever in neutropenic patients, continued bacterial susceptibility to cefepime over time, and other author's conclusions regarding untreated infection as the cause for the higher mortality rates reported for cefepime.***

2. Gomez L, Quintana S, Garau J. Mortality associated with cefepime therapy among neutropenic patients. Clin Infect Dis 2009;49(6):987.

This correspondence to the editor of CID relates to the Yahav et al meta-analysis of the efficacy and safety of cefepime use, and comments on the literature article by Nguyen et al which raises questions about the finding of increased all-cause mortality associated with cefepime. Nguyen et al analyzed results of an interim analysis of this authors' prospective study comparing neutropenic febrile patients randomized to receive 2 g of cefepime every 12 h (plus 15 mg/kg of amikacin per day) with those randomized to receive 4 g of piperacillin-tazobactam every 8 h (plus 15 mg/kg of amikacin per day). Nguyen et al noted a discrepancy in the mortality rates reported in the Yahav et al<sup>1</sup> meta-analysis and the author's ICAAC abstract<sup>4</sup>. In this correspondence, the authors report on the final analyses of risk and causes of death in the group of patients treated with cefepime. One hundred ninety patients with 317 episodes of febrile neutropenia (152 episodes in the cefepime plus amikacin group and 165 episodes in the piperacillin-tazobactam plus amikacin group) were randomized. Six of 190 (3.1%) patients in the cefepime group died and six of 190 (3.1%) patients in the piperacillin-tazobactam group died. For the cefepime group, the all-cause mortality rate (at 28 days) was 7.8% (i.e., 15 of 190 patients died); for the piperacillin-tazobactam group, the all-cause mortality rate (at 28 days) was 8.9% (i.e., 17 of 190 patients died). The authors did not demonstrate any significant difference between the 2 arms of the study and concluded that combination therapy of low-dose beta-lactam with an aminoglycoside remains a useful option with increasing antimicrobial resistance among gram-negative bacteria. The authors agree with Nguyen et al that elimination of cefepime would be premature.

<sup>1</sup>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;7:338-48.

<sup>2</sup>Towne T, Lewis J, Echevarria K. Efficacy and safety of cefepime. Lancet Infect Dis 2009;9:4-5.

<sup>3</sup>Nguyen T, Williams B, Trang E. Cefepime therapy and all-cause mortality. Clin Infect Dis 2009;48:902-4.

<sup>4</sup>Gomez L, Estrada C, Gomez I, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin in the treatment of patients with fever and granulocytopenia [abstract L-771]. In: Proceedings of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). **2001**.

***MO Comment: This correspondence addresses the concerns raised by Nguyen et al in regard to discrepancy in mortality rates for the authors' study as reported in the Yahav et al meta-analysis and in an ICAAC abstract by the author. The authors noted that the findings of concern were based on an interim analysis and that patients may have been randomized more than once to explain the discrepancy in mortality rates. The authors provide results from the final analysis of their prospective study comparing neutropenic febrile patients randomized to receive 2 g of cefepime every 12 h (plus 15 mg/kg of amikacin per day) with those randomized to receive 4 g of piperacillin-tazobactam every 8 h (plus 15 mg/kg of amikacin per day). No difference in mortality rates were observed between the treatment groups.***

3. Shaheen T, Volles D, Calland F, et al. Cefepime-associated status epilepticus in an ICU patient with renal failure. *Chemother* 2009 Aug;21(4):452-4.

This article contains the case report of a 73-year-old female hospitalized for acute intraabdominal sepsis secondary to a large ischemic gastric perforation caused by stenosis of stents in the celiac and superior mesenteric artery. The patient had multiple medical comorbidities including chronic heart failure, myocardial infarction, COPD with pulmonary fibrosis, sigmoidectomy with descedostoma for colonic cancer and diabetes mellitus. Because of the patient's incipient multi-organ failure and history of multiple comorbidities, the family decided to focus on comfort measures. However, her medical condition stabilized and she was transferred to another hospital facility. She underwent laparotomy and the stents were reopened; subsequently the inferior mesenteric artery was stented. One week post-op, the patient developed ventilator-associated pneumonia and was treated empirically with cefepime, ciprofloxacin, and vancomycin. Sputum cultures grew *P. aeruginosa*. The patient improved, cefepime was discontinued, and the patient underwent percutaneous tracheostomy. She also required intermittent hemodialysis, however her renal function had significantly improved over the course of 8 weeks. The patient developed pleural effusions and pulmonary infiltrates and multidrug-resistant (MDR) *P. aeruginosa* was isolated from sputum and abdominal wound drainage cultures. Piperacillin/tazobactam at a dose of 3.375g 3x day was administered for 12 days without clinical or microbiological response. Cefepime and amikacin were restarted. At this time, her BUN and serum creatinine were 46 mg/dL and 1.6 mg/dL with an estimated creatinine clearance of 34 ml/min/m<sup>2</sup>. Due to increasing MIC values for cefepime (i.e., 4 to 8 g/mL), a 2g bolus was given followed by continuous infusion of 4g per 24 hours. Four days later, the patient developed decreased level of consciousness, agitation, global aphasia, non-rhythmic movements in her left forearm, and odd repetitive movements involving her lips and cheeks. Lorazepam 3 mg dose was given with no clinical response. A head CT showed disproportionately enlarged ventricles and mild diffuse cerebral volume loss and white matter disease with no focal lesions. An EEG showed continuous runs of rhythmic, generalized, anteriorly dominant, high-amplitude triphasic waves at roughly two cycles per second. The EEG was reported to be diagnostic for nonconvulsive status epilepticus (NCSE). Cefepime was suspected as the most likely etiology and was stopped immediately, however the patient received a total of 22 g of cefepime over 5 days. Piperacillin/tazobactam was

restarted and amikacin was continued. A midazolam drip was started at 1 mg/h and titrated up to 2.5 mg/h until the EEG seizure activity ceased. The next day, the 24-h continuous EEG showed diffusely slow activities consistent with a moderate encephalopathy and resolution of NCSE. Over the next few weeks, the patient's mental status returned to baseline, her pneumonia improved, she was weaned off from the ventilator and had the tracheostomy removed. The patient was eventually discharged to a nursing home in stable condition and without hemodialysis.

***MO Comment: This paper illustrates a case of nonconvulsive status epilepticus most likely induced by high dose cefepime in an elderly patient with renal impairment and multiple comorbidities. The EEG activity was consistent with a diagnosis of NCSE. Health care professionals should be aware of this potential neurotoxicity of cefepime particularly when using this antibiotic in elderly patients.***

4. Paul M, Yahav D, Fraser A, Leibovici L. Cefepime and all-cause mortality. Clin Infect Dis 2009 Aug 15;49(4):640-1; author reply 641-2.

This letter by Paul and colleagues to the editor of CID provides comment relating to the publication by Nguyen et al. Paul et al notes that the primary outcome in their (Yahav) meta-analysis of cefepime was all-cause mortality and did not use infection-related mortality. When all-cause mortality data were not provided in a published trial, they contacted the authors of that trial and asked for 30-day all-cause mortality data by intention to treat. They added that infection-related mortality may not be reliable and can be biased. According to the authors, they wanted to capture all deaths, including those related to adverse events, superinfections, and *Clostridium difficile* infection. Nguyen et al raised the issue of confounders, both during a trial and between trials. Bow et al used adequate randomization methods, resulting in equal distribution of the risk factors related to mortality between the study groups. However, in the authors' meta-analysis, in which they combined effects (not individuals), the main confounder considered was the comparator antibiotic. There was no heterogeneity between trials in the analysis for mortality (risk ratio, 1.26; 95% confidence interval, 1.08–1.49;  $I^2=0\%$ ). The authors stated that three explanations for the difference in all-cause mortality might be examined. First, there may have been a publication bias against cefepime therapy. Data on mortality were not available for 16 trials (i.e., 2180 patients). However, for the pooled relative risk for mortality to reach 1, the mortality rates in the comparator arms in these studies should have been 5 times higher than the rates in the cefepime arms (an unlikely occurrence). Second, inadequate randomization concealment methods could have led to (biased) allocation of cefepime to sicker patients. In their assessment, baseline patient characteristics did not reveal such differences. Finally, the difference could have been due to a true biological effect, whether related to efficacy or adverse events. Recent studies have shown that in critically ill patients, only continuous doses of cefepime 6 g/day achieved adequate concentrations that were greater than the minimum inhibitory concentration, especially for patients with *Pseudomonas aeruginosa* infection. In 43 randomized controlled trials, patients who were given cefepime died more often than patients who were given another beta-lactam antibiotic (number needed to harm,

50; 95% confidence interval, 33– 100). The authors stated that unless convincing data are produced showing that this excess mortality is not related to cefepime, they would advise clinicians to avoid using the drug. Such data can be compiled from all trials looking at baseline patient characteristics and all cause mortality, preferably on an individual patient level. According to the authors, these data were not divulged, although our analysis was first presented in 2006 and published in full in 2007.

***MO Comment: This correspondence provides support for the original conclusion of increased mortality with cefepime treatment from the Yhav et al meta-analysis.***

5. Pereira CA, Petrilli AS, Carlesse FA, et al. Cefepime monotherapy is as effective as ceftriaxone plus amikacin in pediatric patients with cancer and high-risk febrile neutropenia in a randomized comparison. *J Microbiol Immunol Infect* 2009;42(2):141-7.

This article reports on a prospective randomized open study conducted at the Pediatric Oncology Institute, San Paulo, Brazil. Children and adolescents with lymphoma or leukemia who had fever and neutropenia during chemotherapy were randomized to receive cefepime (CFP) monotherapy or ceftriaxone (CFT) plus amikacin (AK). Fifty-seven patients with 125 episodes of fever and neutropenia were evaluated (CFP, 62 episodes; CFT+AK, 63 episodes). The mean neutrophil count at admission to hospital was 118.6 cells/mm<sup>3</sup> for patients in the CFP group and 107 cells/mm<sup>3</sup> for patients in the CFT+AK group. Analysis of only the first episodes for each patient showed that CFP treatment was successful for 65.5% of episodes and CFT+AK successful for 64.3% of episodes. The overall rates of success with modification were 90% for the CFP group and 89% for the CFT+AK group. The main causes of failure were persistent fever without clinical deterioration and microbiological evidence for both treatment groups.

Adverse events (AEs) were reported in 21 episodes (16%); 10 in the CFP group and 11 in the CFT+AK group. The main AEs were diarrhea (1 episode in each group), increased liver enzymes (3 episodes in the CFT+AK group), headache (2 episodes in the CFP group and 3 episodes in the CFT+AK group), and increased creatinine (1 episode in the CFP group and 2 episodes in the CFT+AK group). The article states that all changes returned to normal after the end of treatment. One death occurred in each treatment group (one was caused by therapeutic failure in a patient with multi-resistant *P. aeruginosa* and the other was due to pneumonia).

***MO Comment: In this study, the AEs reported were mainly related to the gastrointestinal tract. Combination therapies with beta-lactams and aminoglycosides have been associated with a significantly higher rate of AEs, primarily nephrotoxicity, than other therapies. In this study, one episode of increased creatinine occurred in the cefepime group and two episodes in the CFT+AK group. Mortality was low (one patient in each treatment group) in this study.***

6. Uygun V, Karasu GT, Ogunc D, et al. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. *Pediatr Blood Cancer* 2009;53(4):610-4.

This article describes a prospective, randomized, and open-label clinical trial that examines the efficacy and safety of piperacillin/tazobactam (PIP/TAZO) monotherapy in comparison to cefepime (CEF), for the empirical treatment of pediatric cancer patients with neutropenia and fever. One hundred thirty-one consecutive febrile episodes in 70 neutropenic pediatric cancer patients were randomized to treatment either with PIP/TAZO (80 mg/kg piperacillin/10 mg/kg tazobactam) every 6 hr or CEF (50 mg/kg) every 8 hr. Clinical response was determined at completion of therapy. Duration of fever, neutropenia, hospitalization, the need for modification of the therapy, and mortality rates were compared between the two groups. One hundred twenty-seven episodes in 69 patients (35 females, 34 males) with a median age of 4.2 years were assessed for efficacy (65 PIP/TAZO, 62 CEF). The frequency of success without modification of treatment was nearly identical for both PIP/TAZO (60.0%) and CEF (61.3%). The overall response rate, with or without modification of assigned treatment, was 96.9% for PIP/TAZO and 98.4% for CEP. Infection related mortality at the end of the febrile episode was 2.4%. Duration of fever and hospitalization were not different between the treatment groups. This study reports that the most frequent side effect was rash (7.7% in PIP/TAZO, 6.4% in CEF) followed by diarrhea (6.1% in PIP/TAZO, 6.4% in CEF). There was no major toxicity observed in either treatment group. No deaths were reported in this paper. According to the authors, although their study was very small, they did not observe that cefepime was associated with increased all-cause mortality. The authors concluded that PIP/TAZO treatment was as effective and safe as CEF monotherapy as an initial empirical regimen in pediatric cancer patients with fever and neutropenia.

***MO Comment: The most common AEs experienced by patients in this study included rash and diarrhea which are included in the cefepime label.***

7. Weathers AL, Lewis SL. Rare and unusual ... or are they? Less commonly diagnosed encephalopathies associated with systemic disease. *Semin Neurol* 2009;29:136-53.

This paper reviews a variety of encephalopathies including medication-induced encephalopathy. The authors discussed cefepime as a medication-induced associated, stating that cefepime is often used as empiric therapy in critically ill, septic patients. Other etiologies of encephalopathy such as electrolyte alterations, metabolic disorders, hypoxia, and sedating medications are common in this population, and there is likely a considerable amount of overlap. A search for other reversible causes of encephalopathy should be rigorously undertaken, and, if found, aggressively corrected. Septic encephalopathy is also in the differential diagnosis of cefepime encephalopathy. Regardless of whether cefepime neurotoxicity is manifested by the development of an encephalopathy or by NCSE, the first step in management is cessation of the drug. In both situations this may be sufficient, with clinical improvement often occurring within

hours. Rapid clinical improvement has been reported following hemodialysis in patients with acute and chronic renal failure. Prognosis is usually excellent, with full recovery of cefepime neurotoxicity generally occurring within a week, with corresponding improvement seen on EEG. Although rare, refractory status epilepticus and death have been reported. In patients with cefepime-induced nonconvulsive status epilepticus, anticonvulsant therapy does not need to be continued following recovery.

***MO Comment: It is noteworthy that this paper focused on review of different causes of encephalopathy. The section on medication-induced encephalopathy includes discussion of cefepime potential for neurotoxicity. This serious adverse reaction requires that health care professionals be vigilant, especially in the treatment of patients with renal failure.***

8. Nguyen TD, Williams B, Trang E. Cefepime Therapy and All-Cause Mortality. Clin Infect Dis 2009;48:902-904.

This article describes the authors' perspective and review on the data contained and methods used for the Yahav et al meta-analysis (e.g., the method of data collection) on efficacy and safety of cefepime and question about the conclusion. The authors call for additional review of the clinical data before any effort is made to limit or eliminate cefepime from the current practice guidelines. The authors made a number of recommendations on the appropriate use of cefepime therapy while awaiting further FDA advice. They conclude by recommending:

1. Clinicians should be cautious of using only the meta-analysis by Yahav et al to change current clinical practice or to call into question current IDSA guidelines. Cefepime usage should be consistent with current practice guidelines, institutional antibiograms, and indicated conditions.
2. Nursing, medical, and pharmacy staff should become more aware of the signs and symptoms of encephalopathy and nonconvulsive status epilepticus in patients who are being treated with cefepime. It should be noted that patients treated with cefepime did have higher rates of encephalopathy and nonconvulsive status epilepticus than did patients treated with other beta-lactams. The signs and symptoms of encephalopathy include delirium, acute confusion, impaired attention or memory, decreased alertness, and disorientation. The signs and symptoms of nonconvulsive status epilepticus include altered mental status with confusion, psychosis, lethargy, or coma.
3. The dosage of cefepime should be adjusted according to the patient's renal function. One of the important risk factors for encephalopathy and nonconvulsive status epilepticus is a dosage of cefepime that is not adjusted for renal insufficiency.

***MO Comment: This article provides the Nguyen et al views on the conclusions made by Yahav et al on the basis of their meta-analysis on safety and efficacy of cefepime and has been cited by other critics of the meta-analysis.***

**MO Conclusion and Recommendation:**

Based on the review of the safety update for cefepime injection and the recently completed extensive FDA review of the Yahav et al meta-analysis and febrile neutropenia trials in which cefepime treatment was utilized, the reviewer finds no major safety concerns with cefepime at this time.

The Agency's review of Yahav's meta-analysis and additional studies not included in the meta-analysis did not find an association between an increase in all-cause mortality and cefepime. The Agency, in conjunction with the Premier Healthcare Informatics database is currently performing a postmarketing analysis of mortality associated with administration of cefepime versus comparable antimicrobial agents.

The two safety updates (the first submitted with the original supplement and the second with the complete response) for cefepime provide recent literature publications that included safety information regarding non convulsive status epilepticus (NCSE) associated with cefepime use. The publications of Thabet et al and Shaheen et al provided case reports of cefepime-induced non convulsive status epilepticus (NCSE). (Note: Refer to review of the first submission of NDA 50-821.) NCSE is not mentioned in the Maxipime<sup>®</sup> (reference-listed drug) label; however, there is mention of encephalopathy, a serious related neurological disorder to NCSE. Based on the review of these cases, it is appropriate to add NCSE to the RLD label and other cefepime products. Manufacturers of cefepime drug products should be issued a supplement request for inclusion of NCSE in their product labels.

From a clinical standpoint, this application is recommended for approval. However, the overall approval of this application is contingent upon the conclusions of the chemistry, manufacturing, and controls (CMC) review, particularly in regarding to resolution of problems at the drug manufacturing site.

### Labeling Recommendations:

The Applicant made the following changes to the Cefepime for Injection and Dextrose Injection in the Duplex® Container label in PLR format:

- Replacement of Maxipime® specific information (RLD) with the B. Braun Medical Inc's product name, Cefepime for Injection and Dextrose Injection USP in Duplex® Container.
- Cefepime for Injection and Dextrose Injection in the DUPLEX® is for IV administration only; therefore all text relating to intramuscular administration was deleted.
- Addition of text under WARNINGS AND PRECAUTIONS section, regarding the possibility of patient's sensitivity to dextrose because the DUPLEX® container is filled with Dextrose Injection as the sole diluent for reconstitution.
- Addition of text under WARNINGS AND PRECAUTIONS section and Postmarketing Experience subsection, regarding non-convulsive status epilepticus (NCSE) as a result of the information obtained from published literature for cefepime in the Safety Update.
- Addition of text under the DESCRIPTION and HOW SUPPLIED/STORAGE AND HANDLING sections, regarding description of the DUPLEX® container.
- In the Pediatric Use subsection and DOSAGE AND ADMINISTRATION section, a statement indicating that Cefepime for Injection and Dextrose Injection in the DUPLEX® container is to be administered only to those pediatric patients who require a 1 or 2 g dose.
- Minor editorial revisions (e.g., All “μ” for μg symbols in tables have been replaced with “mc” to become “mcg”; addition of registered trademark symbol).
- Changed titles and subtitles as required for PLR format per Guidance for Industry, Labeling for Human Prescription Drug and Biological Products.

***MO Comment: The reviewers from different disciplines made several changes to the Cefepime for Injection and Dextrose Injection in the Duplex® Container label in PLR format as indicated by the yellow highlighted text in the following label. It should be noted that some labeling changes applied to this product are consistent with some of the changes made to both the RLD and another cefepime injection product label. Final product labeling is pending and will be based on continued discussion with the Applicant. A labeling change regarding the addition of NCSE to the Postmarketing Experience and Warnings and Precautions sections will be sent to both manufacturers.***

16 pages have been withheld in full immediately following this page  
as B4 (Draft Labeling)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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/s/

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ALMA C DAVIDSON  
04/29/2010

JANICE K POHLMAN  
05/03/2010

# **45-DAY FILING CHECKLIST**

## **CLINICAL**

### **NDA 50-821**

**Established Name:** Cefepime for Injection USP and Dextrose Injection USP in the Duplex<sup>®</sup> Container  
**Non-Proprietary Name of Drug Product:** Cefepime for Injection, USP

**Applicant:** B. Braun Medical Inc.

**Date of submission:** September 25, 2008

**Date of 45-day NDA filing meeting:** November 3, 2008

**PDUFA Goal Date:** July 25, 2009

	<b>Yes</b>	<b>No</b>
<b>(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?</b>		<b>N/A*</b>
<b>(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?</b>		<b>N/A</b>
<b>(3) On its face, is the clinical section of the NDA legible so that substantive review can begin?</b>		<b>N/A</b>
<b>(4) If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?</b>		<b>N/A</b>
<b>(5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?</b>		<b>N/A</b>
<b>(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?</b>		<b>N/A</b>
<b>(7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?</b>		<b>N/A</b>

- (8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? N/A
- (9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data ? Has the applicant submitted line listings in the format agreed to previously by the Division? N/A
- (10) Has the applicant submitted all additional required case report forms (beyond deaths and drop-outs) previously requested by the Division? N/A
- (11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? N/A
- (12) Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? No
- (13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development packages? No
- (14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? N/A
- (15) From a clinical perspective, is this NDA fileable? If “no”, please state below why it is not. Yes

**If certain claims are not fileable, please state which claims they are and why they are not fileable.**

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\*N/A= None applicable.

*MO Comment: This new drug application can be filed in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act as regulated under 21 CFR 314.54. Section 505(b)(2) allows an applicant to rely on information from studies not conducted by the applicant and for which the applicant has not obtained a right of reference. As described in 21 CFR 314.54, the regulation allows the applicant to rely on the Agency’s finding of safety and effectiveness for an approved, reference listed drug to the extent that such reliance would be permitted under the generic drug approval provisions in Section 505(j) of the Act. This application is submitted to support the use of a new delivery system for cefepime injection. The Applicant provided literature references in support of the addition of the dextrose contraindication as well as the diabetes statement in the Precaution section of the label. However, there is no safety update for cefepime injection provided.*

*Conclusion: There are no clinical filing issues at this time. This NDA could be filed. The draft labeling should be submitted in PLR format. The applicant should provide a summary of updated clinical safety information from recently published literature (i.e. since last product label update) which could have an impact on the safety labeling for this product.*

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Alma Davidson, M.D.  
Medical Officer  
DAIOP

**Concurrence only:**

Janice Pohlman, M.D., M.P.H.  
Medical Officer Team Leader  
DAIOP

cc: DAIOP files

DAIOP: Acting DivDirector/WChambers  
DAIOP: Division Deputy Director/KLaessig  
DAIOP: Division Safety Deputy Director/SNambiar  
DAIOP: Supervisory PM/FLeSane  
DAIOP: PM/CDavi

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/s/

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Alma Davidson  
11/3/2008 05:01:28 PM  
MEDICAL OFFICER

Janice Pohlman  
11/6/2008 05:22:48 PM  
MEDICAL OFFICER