

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-817**

**PHARMACOLOGY REVIEW(S)**



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

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 50-817  
SERIAL NUMBER: 000  
DATE RECEIVED BY CENTER: 2/28/07  
PRODUCT: Cefepime Injection in GALAXY Container  
INTENDED CLINICAL POPULATION: Adult and Pediatric Patients ( $\geq$  1 year of age) with various bacterial infections  
SPONSOR: Baxter  
DOCUMENTS REVIEWED: -000  
REVIEW DIVISION: DAIOP  
PHARM/TOX REVIEWER: Amy L. Ellis  
ACTING PHARM/TOX TEAM LEADER: Wendelyn Schmidt  
ACTING DIVISION DIRECTOR: Wiley Chambers  
PROJECT MANAGER: Kyong Hyon

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## **EXECUTIVE SUMMARY**

### **I. Recommendations**

#### **A. Recommendation on approvability**

The pharmacologist has no objection to the approval of this NDA.

#### **B. Recommendation for nonclinical studies**

No additional nonclinical studies are recommended.

#### **C. Recommendations on labeling**

The label for cefepime injection should be consistent with that for Maxipime®, as applicable. Cefepime Injection in GALAXY Container contains the same active ingredient as Maxipime®, but it is a premixed solution in \_\_\_\_\_, and has a different profile of impurities and degradation products. When the febrile neutropenia indication was approved and the maximum recommended human daily dose for cefepime was increased, the label for Maxipime® was not updated to reflect new dose comparisons between the results of animal reproduction toxicity studies and the current recommended maximum clinical daily dose. The label should be updated so that the dose comparisons are accurate. Additionally, the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label should be edited to reflect the actual results of the mutagenicity assays and not just their overall conclusion and only the animal species used to conduct fertility testing should be mentioned in the discussion of this parameter. It may be necessary to request that the innovator company make these labeling changes before compelling Baxter to do so or the products may not be considered equivalent.

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### **II. Summary of nonclinical findings**

#### **A. Brief overview of nonclinical findings**

The profile of impurities and degradation products was investigated in a 14-day intravenous rat toxicity study, *in vitro* genotoxicity studies in mouse lymphoma cells and cultured human lymphocytes, and an *in vivo* mouse micronucleus test. The presence of different impurities and degradation products in Cefepime Injection in GALAXY Container did not alter its toxicity profile in comparison to Maxipime® under the conditions of these studies.

#### **B. Pharmacologic activity**

Cefepime exerts its antimicrobial activity by inhibiting bacterial cell wall synthesis.

#### **C. Nonclinical safety issues relevant to clinical use**

None. Cefepime Injection in GALAXY Container is expected to have a safety profile identical to that of Maxipime®.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-817

Review number: 1

Sequence number/date/type of submission: 000/28 FEB 2007/original NDA

Information to sponsor: Yes ( ) No (X)

Sponsor and/or agent: Baxter, McGaw Park, IL

Manufacturer for drug substance: \_\_\_\_\_

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Reviewer name: Amy L. Ellis

Division name: Anti-Infective and Ophthalmology Products

Review completion date: 11/6/07

#### Drug:

Trade name: Cefepime Injection in GALAXY Container

Generic name: cefepime

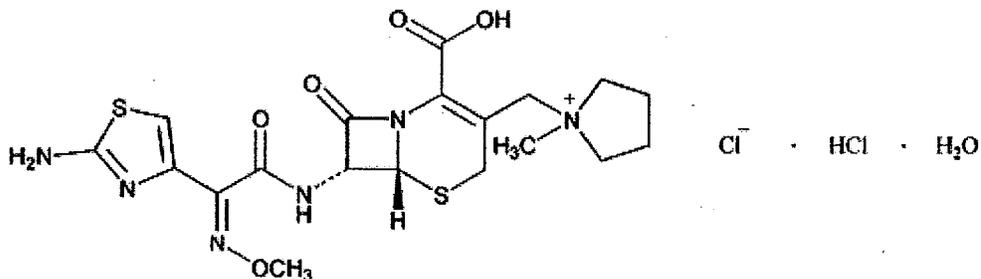
Code name: none

Chemical name: 1-[[[(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7*z*-(*Z*)-(Omethyloxime), monohydrochloride, monohydrate

CAS registry number: 123171-59-5

Molecular formula/molecular weight: 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/ 571.50

Structure:



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Relevant INDs/NDAs/DMFs: DMF \_\_\_\_\_, NDA 50-679 (but the sponsor has no right of reference to this NDA for Maxipime®)

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Drug class: Cephalosporin Antimicrobial

Intended clinical population: Adult and pediatric patients with bacterial infections

**Clinical formulation:**

From the NDA:

Component	Quality Standard	Function	Component Quantity		
			Per mL	Per 50 mL <sup>a</sup>	Per 100 mL <sup>b</sup>
Cefepime (added as Cefepime Hydrochloride)	USP	Active Ingredient	20 mg <sup>c</sup>	1 g <sup>c</sup>	2 g <sup>c</sup>
Dextrose Hydrus (added as _____)	USP	Osmolality Adjuster	20.6 mg (Approximate)	1.03 g (Approximate)	2.06 g (Approximate)
L-Arginine	USP	pH Adjuster	14.5 mg <sup>d</sup> (Approximate)	0.725 g <sup>d</sup> (Approximate)	1.45 g <sup>d</sup> (Approximate)
L-Arginine	USP	pH Adjuster	As needed	As needed	As needed
Hydrochloric Acid <sup>e</sup>	NF	pH Adjuster	As needed	As needed	As needed
Water for Injection	USP	Vehicle	Q.S.	Q.S.	Q.S.

a The 1g/50 mL presentation has a fill volume of 50 mL in a 50 mL container, with a fill volume range of \_\_\_\_\_

b The 2g/100 mL presentation has a fill volume of 100 mL in a 100 mL container, with a fill volume range of \_\_\_\_\_

c The drug product is formulated with \_\_\_\_\_ of Cefepime Hydrochloride, USP.

d L-Arginine is formulated at approximately 725 mg of L-Arginine per g of cefepime.

e Added as a \_\_\_\_\_ solution, as needed.

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**Concentrations of Impurities Requiring Qualification in the Test Articles of Baxter's Premixed Cefepime Injection: Comparison to Clinical Exposure and Proposed Product Limits**

Impurity	Concentration (%)		Amount relative to maximum clinical exposure <sup>1</sup>	Proposed Product Limit (%)
	Freshly Thawed	Thawed _____ at room temperature		
Peaks _____				
Peak _____				
Peak _____				
Peak _____				
Peak _____				
Total Related Compounds				

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<sup>1</sup> Example:  $8 = (2.78/2.4) * 7$  where 7 equals the safety margin employed in the 14-day toxicity study (i.e., 1,000 mg/kg/day divided by 150 mg/kg/day, which represents the maximum clinical exposure for the treatment of febrile neutropenic pediatric patients).

Cefepime Injection in GALAXY Container is a frozen premixed solution in contrast to Maxipime® which is a dry mixture that must be reconstituted before use. Thus, the levels of impurities/degradation products between the 2 products differs.

It should be noted that the sponsor's calculation of the amount of each impurity and \_\_\_\_\_ relative to the maximum clinical exposure is based on a straight mg/kg comparison between human pediatric patients and the rats used in the 14-day repeat dose toxicity study conducted to qualify these substances. For products that are administered systemically, it is more accurate to use body surface area comparisons ( $\text{mg}/\text{m}^2$ ) rather than nominal dose ( $\text{mg}/\text{kg}$ ) comparisons. Thus, rather than the safety margin of \_\_\_\_\_ assumed by the sponsor, there is a safety margin of 1.6 between rats and human pediatric patients. The 1000  $\text{mg}/\text{kg}$  dose in rats converts to 6000  $\text{mg}/\text{m}^2$  and the 150  $\text{mg}/\text{kg}$  dose in human pediatric patients converts to 3750  $\text{mg}/\text{m}^2$ . The impurities listed as peaks \_\_\_\_\_ and \_\_\_\_\_ have been defined as degradation products or compounds related to cefepime. Approximately \_\_\_\_\_% of a dose of cefepime is: \_\_\_\_\_ . Thus, the limits for these substances proposed by the sponsor are likely to be reasonably safe although the margin of safety between rats and humans is low to none. \_\_\_\_\_ It would have been difficult for the sponsor to have tested higher levels of most of these impurities in the rats.

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**Route of administration:** Intravenous

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Data reliance :** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 50-817 are owned by Baxter or are data for which Baxter has obtained a written right of reference. Any information or data necessary for approval of NDA 50-817 that Baxter does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Baxter does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 50-817.

**Studies reviewed within this submission:**

**Cefepime: 14-Day Intravenous Toxicity Study in Rats (Study No. 30877)**

**L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with Three Treatment Conditions (Study No. 6291-256)**

**Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes (Study No. 6291-258)**

***In Vivo* Mouse Bone Marrow Micronucleus Assay** (Study No. 6291-265, intravenous administration)

Studies not reviewed within this submission:

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## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

Cefepime exerts its antimicrobial activity by inhibiting bacterial cell wall synthesis.

### 2.6.2.2 Primary pharmacodynamics

Mechanism of action: Cefepime exerts its antimicrobial activity by inhibiting bacterial cell wall synthesis.

Drug activity related to proposed indication: Antimicrobial

### 2.6.2.3 Secondary pharmacodynamics

Nothing to report.

### 2.6.2.4 Safety pharmacology

Safety pharmacology studies were not necessary for this NDA.

### 2.6.2.5 Pharmacodynamic drug interactions

No nonclinical data to report.

## 2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not relevant for this product.

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

### 2.6.4.1 Brief summary

Cefepime is widely distributed to tissues, with a clinical volume of distribution at steady state of  $18.0 \pm 2.0$  L. Approximately 85% of a cefepime dose to humans is excreted in the urine as unchanged drug, but some is metabolized to N-methylpyrrolidine (NMP) which is, in turn, rapidly converted to NMP-N-oxide. The sponsor was not required to repeat animal or human biopharmaceutics studies for Cefepime Injection in GALAXY Container.

### 2.6.4.2 Methods of Analysis

Not applicable.

### 2.6.4.3 Absorption

The Maxipime® label states that cefepime is completely absorbed after intramuscular injection to humans.

### 2.6.4.4 Distribution

The Maxipime® label states that cefepime is distributed throughout the body with significant levels found in blister fluid, bronchial mucosa, urine, bile, and peritoneal fluid. The human volume of distribution at steady state is  $18.0 \pm 2.0$  L.

### 2.6.4.5 Metabolism

In humans, although most of a dose of cefepime is excreted unchanged, the compound is metabolized to N-methylpyrrolidine (NMP) which is, in turn, rapidly converted to NMP-N-oxide, according to the Maxipime® label.

### 2.6.4.6 Excretion

The Maxipime® label states that approximately 85% of a cefepime dose to humans is excreted in the urine as unchanged drug. Less than 1% is recovered in the urine as NMP, 6.8% is recovered as NMP-N-oxide, and 2.5% is recovered as an epimer of cefepime.

### 2.6.4.7 Pharmacokinetic drug interactions

According to the Maxipime® label, "Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with MAXIPIME because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide."

#### 2.6.4.8 Other Pharmacokinetic Studies

None

#### 2.6.4.9 Discussion and Conclusions

The differences in impurity and degradation products between Maxipime® and Cefepime Injection in GALAXY Container are unlikely to result in pharmacokinetic differences between the 2 products. The sponsor was not required to conduct any clinical trials with Cefepime Injection in GALAXY Container, including human biopharmaceutic studies.

#### 2.6.4.10 Tables and figures to include comparative TK summary

Not relevant for this product.

#### 2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided in the application and not relevant.

#### 2.6.6 TOXICOLOGY

##### 2.6.6.1 Overall toxicology summary

The toxicology studies compared Cefepime Injection in GALAXY Container that was freshly thawed or held for \_\_\_\_\_ at room temperature after thawing to Maxipime®. The sponsor chose the \_\_\_\_\_ time point to qualify levels of impurities and degradation products expected to be present when the frozen product is stored for \_\_\_\_\_ at -20°C plus 7 days in a refrigerator at 5°C or 24 hours at room temperature (~25°C). b(4)

Previous studies with cefepime have shown renal toxicity, leukopenia/neutropenia, thrombocytopenia, anemia, and seizure. These toxicities are known to occur with members of the cephalosporin class. Cefepime has little genotoxic potential. When both Cefepime Injection in GALAXY Container and Maxipime® were tested head to head in a battery of genotoxicity tests, neither drug product induced chromosome aberrations in cultured human lymphocytes and they were negative in the mouse micronucleus test. For both cefepime products, the mouse lymphoma assay was negative when a 4 hour incubation was used regardless of metabolic activation, but positive when a 24 hour incubation was used in the absence of metabolic activation.

No toxicity was observed in rats when \_\_\_\_\_ daily doses of Cefepime Injection in GALAXY Container (freshly thawed or held at room temperature for \_\_\_\_\_, or b(4) reconstituted Maxipime® stored for 24 hours at room temperature before use was administered IV once daily for 14 days.

In previously conducted studies, cefepime did not cause impairment of fertility or fetal harm in rats at doses up to 1000 mg/kg/day, mice at doses up to 1200 mg/kg/day, or rabbits at doses of up to 100 mg/kg/day. These doses are 0.3-1.6 times the maximum recommended adult human dose based on body surface area.

### 2.6.6.2 Single-dose toxicity

No single-dose toxicity studies were performed with Cefepime Injection in GALAXY Container.

### 2.6.6.3 Repeat-dose toxicity

#### Cefepime: 14-Day Intravenous Toxicity Study in Rats

**Key study findings:** Fourteen daily doses of 1000 mg/kg cefepime was not toxic to rats regardless of formulation. There did not appear to be any differences among the freshly thawed Cefepime Injection in GALAXY Container, the same formulation stored at room temperature for \_\_\_\_\_ after thawing, or reconstituted Maxipime® stored for 24 hours at room temperature before use. Although no MTD was observed in this study, it achieved its purpose of demonstrating that these cefepime formulations were equivalent under the conditions of the study.

**Study no.:** 30877

**Volume #, and page #:** Module 4, Volume 1

**Conducting laboratory and location:** Baxter, Round Lake, IL

**Date of study initiation:** 7/6/06

**GLP compliance:** U.S. GLP

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Cefepime Injection in GALAXY Container Batch 28088 42; Maxipime® for Injection in ADD-Vantage vial Lot 6B10047. The concentrations of select impurities in the freshly thawed Cefepime Injection in GALAXY Container vs. thawed and stored for \_\_\_\_\_, at room temperature can be found on page 3 under the heading Clinical Formulation. b(4)

**Formulation/vehicle:** Cefepime Injection in GALAXY Container was used as is (20 mg/ml) immediately after thawing and also following \_\_\_\_\_ of storage at room temperature after thawing. The study report stated that this test article was formulated at the lower end (~4.2) of the acceptable pH range 4.0-6.0 \_\_\_\_\_ b(4)

\_\_\_\_\_ Maxipime® was reconstituted with 5% dextrose (20 mg/ml) and stored for 24 hours at room temperature before use.

#### Methods

Doses: 0 (0.9% NaCl) or 1000 mg/kg

Species/strain: Sprague Dawley rats

Number/sex/group or time point: 10/sex/group

Route, volume: Test articles were given by intravenous administration at a dose

volume of 50 ml/kg and a rate of 1 ml/min.  
Satellite groups used for recovery: Not done  
Age: 6-13 weeks  
Weight: 200-235 g  
Sampling times for TK: Not done  
Unique study design or methodology: Rats received cefepime or saline for 14 consecutive days and were sacrificed and necropsied on Day 15.

## **Results:**

Mortality: Animals were observed for mortality and moribundity twice daily. There were no treatment-related deaths.

Clinical signs: Cageside observations were conducted once daily. Cefepime-treated rats displayed a dark discoloration of the tail. The investigators postulated that this finding was related to local vasoactive properties of the drug. There was no histopathological correlate to this finding. Swollen snout (possibly a mild anaphylactoid reaction) was observed in cefepime-treated female rats. The incidence was highest on Days 1 and 2 of treatment and it was not observed after Day 6. Loose stool observed in some cefepime-treated rats was likely due to changes in microbial flora. It is a common finding in rats treated with antimicrobials. There was no difference in the incidence or severity of clinical signs between cefepime groups.

Body weights: Measured before the initiation of dosing, weekly, and after fasting at the time of sacrifice. Treated-treated males gained slightly less body weight than saline controls ( $p < 0.05$ ) over the course of the study. None of the female rats, including controls, gained much weight over course of the study and most animals lost a small amount of weight during the first week of dosing. The pattern of body weight gain or loss did not differ between the cefepime groups.

Food consumption: Calculated weekly. Cefepime-treated rats had slightly lower food consumption during the first week of the study than controls ( $p < 0.05$ ). Food consumption rebounded during the second week of the study. Food consumption did not differ between cefepime groups.

Electrocardiogram: Not done.

Ophthalmoscopy: Indirect ophthalmoscopy was performed before the initiation of treatment and during the second week of dosing. No drug-related ophthalmic findings were observed.

Hematology/Clinical chemistry: Blood samples for hematology and clinical chemistry were drawn from fasted rats prior at the time of sacrifice. There were no changes in hematology or clinical chemistry parameters that appeared toxicologically significant. Slight, but consistent, elevations in ALT observed in cefepime-treated males were statistically significant ( $p < 0.05$ ), but the magnitude of the change was small ( $34 \pm 1$  for

controls to  $40-43 \pm 1-3$  in the cefepime-treated males) and there was no histopathologic correlate or changes in other relevant clinical chemistry parameters. Slight elevations in total white blood cells for the cefepime treated rats were not statistically significant for all drug-treated groups and were likely related to inflammation at the injection site and mature neutrophilia and/or leukocytosis seen in some of the animals. Serum fibrinogen concentrations were slightly higher in the drug-treated rats than controls, but only statistically significant ( $p < 0.01$ ) in females. This may also be secondary to inflammation. Slightly lower prothrombin times in the cefepime-treated females and activated partial thromboplastin times in the males were attributed to the slight fibrinogen elevations. It is important to note that none of these changes were of large magnitude, so their toxicological significance is doubtful. Other isolated occurrences of statistical significance in clinical chemistry and hematology parameters appeared to be related to biological variation and not to treatment.

Urinalysis: Rats were placed in metabolism cages for urine collection on the day prior to sacrifice. No drug-related changes in urinalysis parameters were observed with the exception of a higher urinary pH in the drug-treated groups.

Gross pathology: Gross necropsy did not reveal any findings that appeared drug-related.

Organ weights: Kidney weights were higher in the cefepime-treated rats than controls ( $p < 0.05$ ). Thymus weights were lower in the drug-treated rats than controls (not statistically significant for all cefepime groups), and liver weights were higher in the cefepime groups (statistically significant for females only,  $p < 0.05$ ). The magnitudes of these changes were small in each case and neither histopathologic nor clinical chemistry correlates were observed.

Histopathology: Adequate Battery: yes (x), no ( )  
Peer review: yes ( ), no (x)

A standard list of tissues was preserved, weighed, and underwent microscopic evaluation. There were no histopathologic changes that were attributable to cefepime treatment.

Toxicokinetics: Not done.

#### **2.6.6.4 Genetic toxicology**

The label for Maxipime® states “A battery of *in vivo* and *in vitro* genetic toxicity tests, including the Ames Salmonella reverse mutation assay, CHO/HGPRT mammalian cell forward gene mutation assay, chromosomal aberration and sister chromatid exchange assays in human lymphocytes, CHO fibroblast clastogenesis assay, and cytogenetic and micronucleus assays in mice were conducted. The overall conclusion of these tests indicated no definitive evidence of genotoxic potential.”

The sponsor conducted *in vitro* genotoxicity studies in mouse lymphoma cells and cultured human lymphocytes, and an *in vivo* mouse micronucleus test with Cefepime Injection in GALAXY Container to investigate whether the altered impurity/degradation product profile of this product (both freshly thawed and thawed at room temperature for \_\_\_\_\_) altered its genotoxic potential compared to freshly reconstituted Maxipime®. The results in all of these assays were consistent between Cefepime Injection in GALAXY Container (both freshly thawed and thawed for \_\_\_\_\_) and Maxipime®. These agents did not induce chromosome aberrations in cultured human lymphocytes and they were negative in the mouse micronucleus test. The mouse lymphoma assay was negative when a 4 hour incubation was used regardless of metabolic activation, but positive when a 24 hour incubation was used in the absence of metabolic activation.

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#### L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with Three Treatment Conditions

**Key findings:** Cefepime injection (both freshly thawed and thawed for \_\_\_\_\_) and Maxipime® were positive at concentrations of 80 and 100 µg/ml with a preferential increase for small colonies when a 24 hour incubation time was used for treatment in the absence of metabolic activation. Lower concentrations were negative. Cefepime for injection (both freshly thawed and thawed for \_\_\_\_\_) and Maxipime® did not induce mutation at the TK locus of L5178Y TK+/- mouse lymphoma cells during a 4 hour incubation in the presence of absence of S-9 at concentrations up to 2000 or 5000 µg/ml, respectively.

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**Study no.:** 6291-256

**Volume #, and page #:** Module 4, Volume 1

**Conducting laboratory and location:** \_\_\_\_\_

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**Date of study initiation:** 6/28/06

**GLP compliance:** U.S. GLP

**QA reports:** yes (X) no ( )

**Drug, lot #, and % purity:** Cefepime injection was Lot No. 28088 42 and Maxipime® was Lot 6B10047. Cefepime injection was tested immediately after thawing and following \_\_\_\_\_ at room temperature after thawing.

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#### Methods

**Cell line:** L5178Y TK+/- mouse lymphoma cells

**Doses used in definitive study:** Freshly thawed cefepime injection, 4 hour treatment, +/- S-9: 50, 100, 200, 400, 600, 800, 1000, 1200, 1600, and 2000 µg/ml (doses ≤ 100 µg/ml were not evaluated because the higher concentrations were adequate); 24 hour treatment: 10, 15, 20, 30, 40, 50, 60, 80, 100, 125, 150, 200, and 250 µg/ml (doses ≥ 125 µg/ml were not evaluated due to excessive cytotoxicity and 10 µg/ml was not evaluated because higher concentrations were adequate). Cefepime injection thawed for 48 hrs, 4 hour treatment, no S-9: 25, 50, 100, 200, 400, 500, 600, 700, 800, 1000, 1200, 1600, and 2000

µg/ml (doses ≤ 400 µg/ml were not evaluated because the higher concentrations were adequate); 4 hour treatment, with S-9: 50, 100, 200, 400, 600, 800, 1000, 1200, 1600, and 2000 µg/ml (doses ≤ 100 µg/ml were not evaluated because the higher concentrations were adequate); 24 hour treatment: 5, 10, 20, 30, 40, 50, 60, 80, 100, 125, 150, and 200 µg/ml (doses ≥ 125 µg/ml were not evaluated due to excessive cytotoxicity and 5 µg/ml was not evaluated because higher concentrations were adequate). Maxipime®, 4 hour treatment, +/- S-9: 62.5, 125, 250, 500, 1000, 2000, 2500, 3000, 3500, 4000 and 5000 µg/ml (doses ≤ 250 µg/ml were not evaluated because the higher concentrations were adequate); 24 hour treatment: 5, 10, 15, 20, 30, 40, 50, 60, 80, 100, 150, 200, 250, and 300 µg/ml (doses ≥ 150 µg/ml were not evaluated due to excessive cytotoxicity and doses ≤ 10 µg/ml were not evaluated because higher concentrations were adequate).

Basis of dose selection: A dose range finding study used concentrations from 3.93-2000 µg/ml for each test substance. The highest dose of cefepime injection that could be tested was 2000 µg/ml because it is a premixed solution of 20 mg/ml. Maxipime® is a powder and as it was not cytotoxic with a 4 hr incubation at 2000 µg/ml, it was tested at concentrations up to 5000 µg/ml in the definitive study.

Negative controls: 5% Dextrose was used as the vehicle control.

Positive controls: Methyl methanesulfonate (13 and 18 µg/ml for 4 hr incubation and 6.5 and 8 µg/ml for 24 hrs) was used in the absence of metabolic activation and methylcholanthrene (4 and 8 µg/ml) was used in the presence of S-9.

Incubation and sampling times: Incubation/growth medium was RPMI 1640 with 10% horse serum, Pluronic® F68, L-glutamine, sodium pyruvate, penicillin, and streptomycin. Cloning medium had the same components except it contained up to 20% horse serum, it did not contain Pluronic® F68, and 0.24% Noble agar was added. Selection medium was cloning medium with 3 µg/ml of TFT. The S-9 used for metabolic activation was obtained from the livers of male Sprague Dawley rats treated with Aroclor 1254. The incubation periods tested for each drug were 4 hours in the presence and absence of S-9 and 24 hours in the absence of S-9. After treatment, cells were washed and allowed to grow for 2 days to allow for expression of the mutant phenotype. Cultures with adequate growth were then subcultured in cloning medium and selection medium in triplicate. After 12-14 days, colonies were counted and sized using an LAI Automated Colony Counter.

## Results

Study validity: The study appeared valid for each test compound. The investigators had data for 8 concentrations per test compound for all of the assays. The compounds could be tested up to a maximum feasible dose (in the case of cefepime injection with 4 hours incubation), the limit dose (Maxipime® with 4 hours incubation), or to moderate cytotoxicity (all other incubation conditions). Average cloning efficiencies and mutation frequencies of the positive control substances were adequate. The positive controls

contained both large and small colonies, with a preferential increase of the latter at 24 hours.

Study outcome: Cefepime for injection (both freshly thawed and thawed for \_\_\_\_\_ and Maxipime® did not induce mutation at the TK locus of L5178Y TK+/- mouse lymphoma cells during a 4 hour incubation in the presence or absence of S-9 at concentrations up to 2000 or 5000 µg/ml, respectively. These test substances did induce mutations when the incubation period was extended to 24 hours in the absence of metabolic activation. Cefepime injection (both freshly thawed and thawed for \_\_\_\_\_ and Maxipime® were positive at concentrations of 80 and 100 µg/ml with a preferential increase for small colonies. Control mutant frequencies ranged from 37.5-81.1 X 10<sup>-6</sup> with relative growth 65.4-132.3%. MMS mutant frequencies ranged from 307.9-625.1 X 10<sup>-6</sup> with relative growth 102.8-177.1%. At 80 µg/ml, cefepime/ Maxipime® mutant frequencies ranged from 111.1-161.7 X 10<sup>-6</sup> with relative growth 24.7-38.4%. At 100 µg/ml, cefepime/ Maxipime® mutant frequencies ranged from 162.3-268.9 X 10<sup>-6</sup> with relative growth 10.6-18.3%. Lower cefepime/ Maxipime® concentrations were not mutagenic with the 24 hour incubation period.

b(4)

b(4)

### Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes

Key findings: Cefepime injection (both freshly thawed and thawed for \_\_\_\_\_, and Maxipime® did not induce chromosome aberrations, polyploidy, or endoreduplication at concentrations up to 2000 µg/ml in the presence or absence of metabolic activation with a 3 hour treatment period or at concentrations up to 1130 µg/ml when the drug treatment period was extended to 22 hours in the absence of metabolic activation.

b(4)

Study no.: 6291-258

Volume #, and page #: Module 4, Volume 2

Conducting laboratory and location: \_\_\_\_\_

b(4)

Date of study initiation: 6/23/06

GLP compliance: U.S. GLP

QA reports: yes (X) no ( )

Drug, lot #, and % purity: Cefepime injection was Lot No. 28088 42 and Maxipime® was Lot 6B10047 and Lot 5E07077. Cefepime injection was tested immediately after thawing and following \_\_\_\_\_ at room temperature after thawing.

b(4)

### Methods

Cell line: Human peripheral blood lymphocytes were taken from healthy adult donors (nonsmoking, no current viral infections, no history of radiotherapy, chemotherapy or drug use).

Doses used in definitive study: Duplicate cultures were incubated with cefepime injection (freshly thawed or thawed \_\_\_\_\_, or Maxipime® at concentrations of 281,

b(4)

563, 1130, 1500, and 2000 µg/ml, regardless of metabolic activation or treatment length. Slides from at least 3 concentration levels were analyzed for each cefepime test article.

Basis of dose selection: A dose range finding study used concentrations from 62.5-2000 µg/ml (the limit dose) for each test substance. This assay showed that doses of cefepime up to the limit dose of 2000 µg/ml could be tested, as excessive cytotoxicity was not produced at this concentration. There was no more than a 51% reduction in the mitotic index at 2000 µg/ml with either cefepime injection or Maxipime® in the range finding study.

Negative controls: 5% Dextrose was used as the vehicle control.

Positive controls: Mitomycin C was used in the absence of metabolic activation and cyclophosphamide was used in the presence of S-9. MMC was used at concentrations of 0.75, 1.0, and 1.5 µg/ml for the 3 hour incubation and at 0.20, 0.30, and 0.40 µg/ml for the ~22 hour incubation. CP was used at concentrations of 20, 25, and 40 µg/ml.

Incubation and sampling times: Cultures were incubated in RPMI 1640 with 20% fetal bovine serum, 25 mM HEPES buffer, 2 mM L-glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin, and 2% PHA-M. Lymphocytes were allowed to proliferate for 2 days prior to drug exposure. The S-9 used for metabolic activation was obtained from the livers of rats treated with Aroclor 1254. Duplicate cultures were treated for each concentration of drug. The drug exposure periods tested for each drug were 3 hours in the presence and absence of S-9 and 22 hours in the absence of S-9. After the 3 hour treatment, cells were washed and put in fresh medium for the remainder of the 22 hour incubation with 0.1 µg/ml Colcemid® added for the last 2 hours before harvest. For the continuous 22 hour treatment, 0.1 µg/ml Colcemid® was added to the medium that contained drug for the last 2 hours. At the end of the drug exposure period, cells were harvested by centrifugation, swollen with 75 mM KCl and fixed with methanol:glacial acetic acid (3:1, v/v). Fixed cells were dropped onto glass slides, air dried, and stained with 5% Giemsa before permanent mounting. Slides were coded for blind evaluation. If possible, 100 cells from each duplicate culture were analyzed for chromosome aberrations. For cultures with >25% cells with at least one aberration, at least 25 cells were analyzed. The mitotic index was calculated by counting the number of mitotic cells in at least 1000 cells per culture and comparing the test articles to vehicle controls. The percentage of cells with polyploidy and endoreduplication were analyzed by evaluating 100 metaphases per culture.

## Results

Study validity: The study appeared valid for each test compound. The vehicle control contained fewer than 5% cells with aberrations. The investigators had data for at least 3 concentrations per test compound for all of the assays. The compounds could be tested up to a maximum feasible dose (in the case of cefepime injection with 4 hours incubation), the limit dose (Maxipime® with 4 hours incubation), or to moderate

cytotoxicity (all other incubation conditions). The positive control cultures contained a significant percentage of cells with chromosome aberrations.

Study outcome: Cefepime for injection (both freshly thawed and thawed for \_\_\_\_\_ and Maxipime® did not induce chromosome aberrations in isolated human peripheral blood lymphocytes during a 3 hour incubation in the presence of absence of S-9 at concentrations up to 2000 µg/ml (mitotic indices reduced 2-40% compared to controls at the high concentration). Additionally, these test substances did not induce aberrations at concentrations up to 1130 µg/ml when the drug treatment period was extended to 22 hours in the absence of metabolic activation (mitotic indices reduced 51-57% compared to controls at the high concentration). Neither polyploidy nor endoreduplication were observed in cefepime-treated cultures. The percentage of chromosome aberrations in vehicle control cells ranged from 0-1% (including or excluding gaps). MMC aberration percentages ranged from 34-41% excluding gaps and 36-47% with gaps. CP aberration percentage was 31% excluding gaps and 40% with gaps. b(4)

#### ***In Vivo* Mouse Bone Marrow Micronucleus Assay**

Key findings: Cefepime injection (both freshly thawed and thawed for \_\_\_\_\_ and Maxipime® did not induce the formation of micronucleated polychromatic erythrocytes in the bone marrow of male mice given intravenous doses of up to 1000 mg/kg. b(4)

Study no.: 6291-265

Volume #, and page #: Module 4, Volume 2

Conducting laboratory and location: \_\_\_\_\_ b(4)

Date of study initiation: 11/20/06

GLP compliance: U.S. GLP

QA reports: yes (X) no ( )

Drug, lot #, and % purity: Cefepime injection was Lot No. 28088 42 and Maxipime® was Lot 6J19557. Cefepime injection was tested immediately after thawing and following \_\_\_\_\_ at room temperature after thawing. b(4)

#### **Methods**

Strains/species: Male CD-1®(ICR)BR mice (~9 weeks old, 31.1-37.7 g), 5 animals per dose and sampling time, were used for the definitive assay.

Doses used in definitive study: 250, 500, and 1000 mg/kg of cefepime test articles were administered intravenously at a dose volume of 50 ml/kg.

Basis of dose selection: In a range finding study, 1000 mg/ml (the limit dose) of each cefepime test substance was administered to 3 male and 3 female mice (same strain as used for the definitive study) by slow IV bolus. Mice were observed for 48 hours for signs of toxicity. All of the animals survived. As there were no differences in toxicity between the sexes, only male mice were used in the definitive assay.

Negative control: 5% dextrose administered at the same dose volume as the cefepime test articles (50 ml/kg) was used as the vehicle control.

Positive control: Cyclophosphamide was administered orally at 80 mg/kg (10 ml/kg dose volume).

Sampling times: Test articles were administered to mice and the animals were sacrificed 24 hours later. An additional 5 mice/group received vehicle, cefepime injection (freshly thawed or thawed \_\_\_\_\_ or Maxipime® at the high (1000 mg/kg) dose and were sacrificed 48 hours after administration. Bone marrow cells were harvested from the hind limb tibias of 5 surviving animals in each treatment group (flushed with 3-5 ml of fetal bovine serum). Samples of the cell pellet were spread on slides, air dried, fixed with methanol, and stained with May-Grünwald solution and Giemsa. Slides were coded for blind evaluation. Micronucleus frequency was determined by determining the number of micronucleated polychromatic erythrocytes (PCEs) from at least 2000 PCEs per animal. The ratio of PCEs to normochromatic erythrocytes (NCEs) was determined by observing at least 500 erythrocytes per animal.

b(4)

## Results

Study validity: The study appeared valid. The mid and high doses were associated with clinical signs of toxicity (irregular respiration and recumbency) in a few animals. Several animals in the cefepime injection groups died during the dosing procedure, but all of these were replaced. It appeared that these deaths were related to the dosing procedure itself and not to drug. The bone marrow harvested from the vehicle control group had approximately 0.07% micronucleated PCEs, within the historical control range. The positive control, cyclophosphamide, induced micronucleated PCEs in the mouse bone marrow ( $1.89 \pm 0.13\%$ ) compared to the control.

Study outcome: Cefepime for injection (both freshly thawed and thawed for \_\_\_\_\_ and Maxipime® did not induce micronucleated PCEs in bone marrow when administered intravenously to male mice at doses up to 1000 mg/kg. Overall, cefepime did not appear toxic to the bone marrow, as indicated by the PCE:NCE ratio. At 250 mg/kg, freshly thawed cefepime injection and Maxipime® were associated with statistically significant modest decreased in the PCE:NCE ratio, but there were no statistically significant reductions at the 500 or 1000 mg/kg doses. Bone marrow from the cefepime injection and Maxipime® groups contained  $0.06 \pm 0.02\%$  or fewer micronucleated PCEs, regardless of dose or harvest time (24 or 48 hours), below the concurrent control as well as the historical control range.

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### 2.6.6.5 Carcinogenicity

The label for Maxipime® states that carcinogenicity studies have not been performed with cefepime. In general, carcinogenicity studies are not needed for drug products that will be labeled for only short term use.



not enhance its toxicity compared to previously approved and marketed cefepime products.

Cefepime Injection in GALAXY Container appears reasonably safe to use as directed in the proposed product label.

#### 2.6.6.10 Tables and Figures

All tables and figures relevant to this NDA have been included in other sections of this review.

#### 2.6.7 TOXICOLOGY TABULATED SUMMARY

Not provided in the NDA.

### OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Cefepime Injection in GALAXY Container appears reasonably safe to use as directed in the proposed product label. This product appears interchangeable with cefepime products that were previously approved by the Agency and are currently marketed.

Unresolved toxicology issues: None.

Recommendations: The pharmacologist has no objection to the approval of this NDA.

Suggested labeling: The sponsor has proposed a label for Cefepime Injection in GALAXY Container that is consistent with the Maxipime® label. This is appropriate and consistent with how the Division has previously handled this type of 505(b)(2) application. Of note, the dose multiple calculations for these labels were apparently based on a \_\_\_\_\_ than is the current standard (6 g/day). The dose multiples should be recalculated based on the current maximum recommended human dose and the labels modified accordingly, although the innovator may have to do this before the subsequent cefepime products can be compelled to comply. Ideally, the innovator company should also be requested to edit the discussion of mutagenicity data in the Carcinogenesis, Mutagenesis, Impairment of Fertility Section of their label to reflect the actual results of the assays and not just the overall conclusion, to reflect current labeling practice. Additionally, the animal species used to study fertility should be the only one(s) mentioned in this section. b(4)

The dose multiple comparisons in the cefepime labels (in both the Pregnancy and Carcinogenesis, Mutagenesis, Impairment of Fertility Sections) should be as follows:

The highest recommended clinical dose is 2 g every 8 hours, for a total of 6 g per day. In a 60 kg person, this is a 100 mg/kg dose. Using a conversion factor of 37, this dose can

be converted to 3700 mg/m<sup>2</sup>. It is appropriate to base dose comparisons for systemically distributed intravenous drug products using body surface area when there are not sufficient animal pharmacokinetic data available for comparison to human. The reproduction toxicity studies in rats, mice, and rabbits used doses up to \_\_\_\_\_, \_\_\_\_\_, respectively. Using conversion factors for each species of 6 (rat), 3 (mouse), and 12 (rabbit), these doses convert to 6000 mg/m<sup>2</sup>, 3600 mg/m<sup>2</sup>, and 1200 mg/m<sup>2</sup>. In turn, the comparison of these doses to the maximum recommended human dose are: rat, 1.6X; mouse, approximately equal, and rabbit, 0.3X.

b(4)

Signatures:

Reviewer Signature \_\_\_\_\_

Acting Team Leader Signature \_\_\_\_\_ Concurrence Yes \_\_\_ No \_\_\_

**APPENDIX/ATTACHMENTS**

None.

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/s/  
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Amy Ellis  
11/19/2007 04:24:25 PM  
PHARMACOLOGIST

Wendy- You signed the paper copy of this review on 11/19/07.

Wendelyn Schmidt  
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