CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-369

Name: Cefepime for Injection USP
500 mg, 1 gram, and 2 grams

Sponsor: Orchid Healthcare

Approval Date: June 18, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANDA 65-369

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 65-369

Orgenus Pharma Inc.
Attention: Satish Srinivasan
U.S. Agent for: Orchid Healthcare
116 Village Boulevard, Suite 200
Princeton Forrestal Village
Princeton, NJ 08540-5799

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated November 2, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Cefepime for Injection USP, 500 mg/vial, 1 gram/vial, and 2 grams/vial. We note that this product is subject to the exception provisions of section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated September 16, and November 8, 2006; and February 9, March 20, April 13, May 14, May 21, and June 14, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Cefepime for Injection USP, 500 mg/vial, 1 gram/vial, and 2 grams/vial, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Maxipime® for Injection, 500 mg/vial, 1 gram (base)/vial, and 2 g (base)/vial, respectively, of Bristol Myers Squibb Company Pharmaceutical Research Institute.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
6/18/2007 02:33:40 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

LABELING

℞ Only

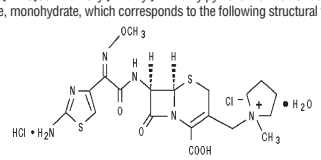
Cefepime for Injection, USP

For Intravenous or Intramuscular Use

DESCRIPTION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefepime for injection, USP and other antibacterial drugs, cefepime for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

Cefepime for injection, USP is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[[(6R,7R)-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, 7^2-(Z)-(O-methyloxime), monohydrochloride, monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride is a white to pale yellow powder. Cefepime hydrochloride contains the equivalent of not less than 825 mcg and not more than 911 mcg of cefepime ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on an anhydrous basis. It is highly soluble in water.

Cefepime for injection, USP is supplied for intramuscular or intravenous administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. (See **DOSAGE AND ADMINISTRATION**.) Cefepime for injection, USP is a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$). The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0 to 6.0. Freshly constituted solutions of cefepime for injection, USP will range in color from colorless to amber.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The average plasma concentrations of cefepime observed in healthy adult male volunteers (n 9) at various times following single 30 minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in **Table 1.** Elimination of cefepime is principally via renal excretion with an average (± SD) half-life of 2 (± 0.3) hours and total body clearance of 120 (± 8) mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers (n 7) receiving clinically relevant doses for a period of 9 days.

Absorption

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous administration are portrayed in **Table 1.**

Table 1: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (± SD), Intravenous Administration

	CEFEPIME		
Parameter	**500 mg IV**	**1 g IV**	**2 g IV**
0.5 h	38.2	78.7	163.1
1 h	21.6	44.5	85.8
2 h	11.6	24.3	44.8
4 h	5	10.5	19.2
8 h	1.4	2.4	3.9
12 h	0.2	0.6	1.1
C_{max}, mcg/mL	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, h•mcg/mL	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized in **Table 2.** The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g IM and do not vary with respect to treatment duration.

Table 2: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters (± SD), Intramuscular Administration

	CEFEPIME		
Parameter	**500 mg IM**	**1 g IM**	**2 g IM**
0.5 h	8.2	14.8	36.1
1 h	12.5	25.9	49.9
2 h	12	26.3	51.3
4 h	6.9	16	31.5
8 h	1.9	4.5	8.7
12 h	0.7	1.4	2.3
C_{max}, mcg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T_{max}, h	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, h•mcg/mL	60 (8)	137 (11)	262 (23)
Number of subjects (male)	6	6	12

Distribution

The average steady-state volume of distribution of cefepime is 18 (± 2) L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day. (See **PRECAUTIONS: Nursing Mothers.**)

Concentrations of cefepime achieved in specific tissues and body fluids are listed in **Table 3.**

Table 3: Average Concentrations of Cefepime in Specific Body Fluids (mcg/mL) or Tissues (mcg/g)

Tissue or Fluid	Dose/Route	# of Patients	Average Time of Sample Post-Dose (h)	Average Concentration
Blister Fluid	2 g IV	6	1.5	81.4 mcg/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 mcg/g
Sputum	2 g IV	5	4	7.4 mcg/mL
Urine	500 mg IV	8	0 - 4	292 mcg/mL
	1 g IV	12	0 - 4	926 mcg/mL
	2 g IV	12	0 - 4	3120 mcg/mL
Bile	2 g IV	26	9.4	17.8 mcg/mL
Peritoneal Fluid	2 g IV	19	4.4	18.3 mcg/mL
Appendix	2 g IV	31	5.7	5.2 mcg/g
Gallbladder	2 g IV	38	8.9	11.9 mcg/g
Prostate	2 g IV	5	1	31.5 mcg/g

Data suggest that cefepime does cross the inflamed blood-brain barrier. **The clinical relevance of these data are uncertain at this time.**

Metabolism and Excretion

Cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Less than 1% of the administered dose is recovered from urine as NMP, 6.8% as NMP-N-oxide, and 2.5% as an epimer of cefepime. Because renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See **DOSAGE AND ADMINISTRATION.**)

Special Populations

Pediatric patients

Cefepime pharmacokinetics have been evaluated in pediatric patients from 2 months to 11 years of age following single and multiple doses on q8h (n 29) and q12h (n 13) schedules. Following a single IV dose, total body clearance and the steady-state volume of distribution averaged 3.3 (± 1) mL/min/kg and 0.3 (± 0.1) L/kg, respectively. The urinary recovery of unchanged cefepime was 60.4 (± 30.4)% of the administered dose, and the average renal clearance was 2 (± 1.1) mL/min/kg. There were no significant effects of age or gender (25 male vs. 17 female) on total body clearance or volume of distribution, corrected for body weight. No accumulation was seen when cefepime was given at 50 mg/kg q12h (n 13), while C_{max}, AUC, and $t_{½}$ were increased about 15% at steady state after 50 mg/kg q8h. The exposure to cefepime following a 50 mg/kg IV dose in a pediatric patient is comparable to that in an adult treated with a 2 g IV dose. The absolute bioavailability of cefepime after an IM dose of 50 mg/kg was 82.3 (± 15)% in eight patients.

Geriatric patients

Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) men (n 12) and women (n 12) whose mean (SD) creatinine clearance was 74 (± 15) mL/min. There appeared to be a decrease in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less. (See **DOSAGE AND ADMINISTRATION**.)

Renal insufficiency

Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency (n 30). The average half-life in patients requiring hemodialysis was 13.5 (± 2.7) hours and in patients requiring continuous peritoneal dialysis was 19 (± 2) hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients. (See **DOSAGE AND ADMINISTRATION**.)

Hepatic insufficiency

The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose (n 11).

Microbiology

Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has a low affinity for chromosomally-encoded beta-lactamases. Cefepime is highly resistant to hydrolysis by most beta-lactamases and exhibits rapid penetration into gram-negative bacterial cells. Within bacterial cells, the molecular targets of cefepime are the penicillin binding proteins (PBP).

Cefepime has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-Negative Microorganisms:
Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus pyogenes (Lancefield's Group A streptococci)
Viridans group streptococci

The following *in vitro* data are available, **but their clinical significance is unknown**. Cefepime has been shown to have *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of cefepime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus agalactiae (Lancefield's Group B streptococci)

NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis*, and methicillin-resistant staphylococci are resistant to cefepime.

Aerobic Gram-Negative Microorganisms:
Acinetobacter calcoaceticus subsp. *Iwoffi*
Citrobacter diversus
Citrobacter freundii
Enterobacter agglomerans
Haemophilus influenzae (including beta-lactamase producing strains)
Hafnia alvei
Klebsiella oxytoca
Moraxella catarrhalis (including beta-lactamase producing strains)
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

NOTE: Cefepime is inactive against many strains of *Stenotrophomonas (*formerly *Xanthomonas maltophilia* and *Pseudomonas maltophilia).*

Anaerobic Microorganisms:

NOTE: Cefepime is inactive against most strains of *Clostridium difficile.*

Susceptibility Tests

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1](broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefepime powder. The MIC values should be interpreted according to the following criteria:

Table 4

	MIC (mcg/mL)		
Microorganism	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Microorganisms other than *Haemophilus* spp.* and *S. pneumoniae**	≤ 8	16	≥ 32
*Haemophilus spp.**	≤ 2	—*	—*
*Streptococcus pneumoniae**	≤ 0.5	1	≥ 2

*NOTE: Isolates from these species should be tested for susceptibility using specialized dilution testing methods.[1] Also, strains of *Haemophilus* spp. with MICs greater than 2 mcg/mL should be considered equivocal and should be further evaluated.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. Standard cefepime powder should provide the following MIC values (**Table 5**) when tested against the designated quality control strains:

Table 5

Microorganism	ATCC	MIC (mcg/mL)
Escherichia coli	25922	0.016 - 0.12
Staphylococcus aureus	29213	1 - 4
Pseudomonas aeruginosa	27853	1 - 4
Haemophilus influenzae	49247	0.5 - 2
Streptococcus pneumoniae	49619	0.06 - 0.25

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg of cefepime to test the susceptibility of microorganisms to cefepime. Interpretation is identical to that stated above for results using dilution techniques.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg cefepime disk should be interpreted according to the following criteria:

Table 6

	Zone Diameter (mm)		
Microorganism	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Microorganisms other than *Haemophilus* spp.* and *S. pneumoniae**	≥ 18	15 - 17	≤ 14
*Haemophilus spp.**	≥ 26	—*	—*

*NOTE: Isolates from these species should be tested for susceptibility using specialized diffusion testing methods[2]. Isolates of *Haemophilus* spp. with zones smaller than 26 mm should be considered equivocal and should be further evaluated. Isolates of *S.pneumoniae* should be tested against a 1 mcg oxacillin disk; isolates with oxacillin zone sizes larger than or equal to 20 mm may be considered susceptible to cefepime.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Laboratory control microorganisms are specific strains of microbiological assay organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains are not clinically significant in their current microbiological status. For the diffusion technique, the 30 mcg cefepime disk should provide the following zone diameters in these laboratory test quality control strains (**Table 7**):

Table 7

Microorganism	ATCC	Zone Size Range (mm)
Escherichia coli	25922	29 - 35
Staphylococcus aureus	25923	23 - 29
Pseudomonas aeruginosa	27853	24 - 30
Haemophilus influenzae	49247	25 - 31

INDICATIONS AND USAGE

Cefepime for injection is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms (see also **PRECAUTIONS: Pediatric Use** and **DOSAGE AND ADMINISTRATION**):

Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae,* including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa, Klebsiella pneumoniae,* or *Enterobacter* species.

Empiric Therapy for Febrile Neutropenic Patients. Cefepime as monotherapy is indicated for empiric treatment of febrile neutropenic patients. In patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia), antimicrobial monotherapy may not be appropriate. Insufficient data exist to support the efficacy of cefepime monotherapy in such patients. (See **CLINICAL STUDIES.**)

Uncomplicated and Complicated Urinary Tract Infections (including pyelonephritis) caused by *Escherichia coli* or *Klebsiella pneumoniae,* when the infection is severe, or caused by *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis*, when the infection is mild to moderate, including cases associated with concurrent bacteremia with these microorganisms.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (methicillin-susceptible strains only) or *Streptococcus pyogenes.*

Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* species, or *Bacteroides fragilis.* (See **CLINICAL STUDIES**.)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefepime for injection and other antibacterial drugs, cefepime for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CLINICAL STUDIES

Febrile Neutropenic Patients

The safety and efficacy of empiric cefepime monotherapy of febrile neutropenic patients have been assessed in two multicenter, randomized trials, comparing cefepime monotherapy (at a dose of 2 g IV q8h) to ceftazidime monotherapy (at a dose of 2 g IV q8h). These studies comprised 317 evaluable patients. **Table 8** describes the characteristics of the evaluable patient population.

Table 8: Demographics of Evaluable Patients (First Episodes Only)

	Cefepime	Ceftazidime
Total	**164**	**153**
Median age (yr)	56 (range, 18 - 82)	55 (range, 16 - 84)
Male	86 (52%)	85 (56%)
Female	78 (48%)	68 (44%)
Leukemia	65 (40%)	52 (34%)
Other hematologic malignancies	43 (26%)	36 (24%)
Solid tumor	54 (33%)	56 (37%)
Median ANC nadir (cells/microliter)	20 (range, 0 - 500)	20 (range, 0 - 500)
Median duration of neutropenia (days)	6 (range, 0 - 39)	6 (range, 0 - 32)
Indwelling venous catheter	97 (59%)	86 (56%)
Prophylactic antibiotics	62 (38%)	64 (42%)
Bone marrow graft	9 (5%)	7 (5%)
SBP < 90 mm Hg at entry	7 (4%)	2 (1%)

ANC absolute neutrophil count; SBP systolic blood pressure

Table 9 describes the clinical response rates observed. For all outcome measures, cefepime was therapeutically equivalent to ceftazidime.

Table 9: Pooled Response Rates for Empiric Therapy of Febrile Neutropenic Patients

	% Response	
Outcome Measures	**Cefepime (n=164)**	**Ceftazidime (n=153)**
Primary episode resolved with no treatment modification, no new febrile episodes or infection, and oral antibiotics allowed for completion of treatment	**51**	**55**
Primary episode resolved with no treatment modification, no new febrile episodes or infection and no post-treatment oral antibiotics	**34**	**39**
Survival, any treatment modification allowed	93	97
Primary episode resolved with no treatment modification and oral antibiotics allowed for completion of treatment	62	67
Primary episode resolved with no treatment modification and no post-treatment oral antibiotics	46	51

Insufficient data exist to support the efficacy of cefepime monotherapy in patients at high risk for severe infection (including patients with a history of recent bone marrow transplantation, with hypotension at presentation, with an underlying hematologic malignancy, or with severe or prolonged neutropenia). No data are available in patients with septic shock.

Complicated Intra-abdominal Infections

Patients hospitalized with complicated intra-abdominal infections participated in a randomized, double-blind, multicenter trial comparing the combination of cefepime (2 g q12h) plus intravenous metronidazole (500 mg q6h) versus imipenem/cilastatin (500 mg q6h) for a maximum duration of 14 days of therapy. The study was designed to demonstrate equivalence of the two therapies. The primary analyses were conducted on the protocol-valid population, which consisted of those with a surgically confirmed complicated infection, at least one pathogen isolated pretreatment, at least 5 days of treatment, and a 4 to 6 week follow-up assessment for cured patients. Subjects in the imipenem/cilastatin arm had higher APACHE II scores at baseline. The treatment groups were otherwise generally comparable with regard to their pretreatment characteristics. The overall clinical cure rate among the protocol-valid patients was 81% (51 cured/63 evaluable patients) in the cefepime plus metronidazole group and 66% (62/94) in the imipenem/cilastatin group. The observed differences in efficacy may have been due to a greater proportion of patients with high APACHE II scores in the imipenem/cilastatin group.

CONTRAINDICATIONS

Cefepime for injection is contraindicated in patients who have shown immediate hypersensitivity reactions to cefepime or the cephalosporin class of antibiotics, penicillins or other betalactam antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFEPIME FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS IMMEDIATE HYPERSENSITIVITY REACTIONS TO CEFEPIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFEPIME FOR INJECTION OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES INCLUDING OXYGEN, CORTICOSTEROIDS, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

In patients with impaired renal function (creatinine clearance ≤ 60 mL/min), the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination. Because high and prolonged serum antibiotic concentrations can occur from usual dosages in patients with renal insufficiency or other conditions that may compromise renal function, the maintenance dosage should be reduced when cefepime is administered to such patients. Continued dosage should be determined by degree of renal impairment, severity of infection, and susceptibility of the causative organisms. (See specific recommendations for dosing adjustment in **DOSAGE AND ADMINISTRATION**.) During postmarketing surveillance, serious adverse events have been reported including life-threatening or fatal occurrences of the following: encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, and seizures (see **ADVERSE REACTIONS: Postmarketing Experience**). Most cases occurred in patients with renal impairment who received doses of cefepime that exceeded the recommended dosage schedules. However, some cases of encephalopathy occurred in patients receiving a dosage adjustment for their renal function. In the majority of cases, symptoms of neurotoxicity were reversible and resolved after discontinuation of cefepime and/or after hemodialysis.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefepime and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General
Prescribing cefepime for injection in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antimicrobials, prolonged use of cefepime may result in overgrowth of nonsusceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

Many cephalosporins, including cefepime, have been associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy. Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.

Positive direct Coombs' tests have been reported during treatment with cefepime. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefepime for injection should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Arginine has been shown to alter glucose metabolism and elevate serum potassium transiently when administered at 33 times the amount provided by the maximum recommended human dose of cefepime. The effect of lower doses is not presently known.

Information for Patients
Patients should be counseled that antibacterial drugs including cefepime for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefepime for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefepime for injection or other antibacterial drugs in the future.

Drug Interactions
Renal function should be monitored carefully if high doses of aminoglycosides are to be administered with cefepime 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.

Drug/Laboratory Test Interactions
The administration of cefepime may result in a false-positive reaction for glucose in the urine when using Clinitest® tablets. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®) be used.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No long-term animal carcinogenicity studies have been conducted with cefepime. 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. No untoward effects on fertility or reproduction have been observed in rats, mice, and rabbits when cefepime is administered subcutaneously at 1 to 4 times the recommended maximum human dose calculated on a mg/m^2 basis.

Usage in Pregnancy-Teratogenic effects-Pregnancy Category B
Cefepime was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 1000 mg/kg/day (4 times the recommended maximum human dose calculated on a mg/m^2 basis) or to mice at doses up to 1200 mg/kg (2 times the recommended maximum human dose calculated on a mg/m^2 basis) or to rabbits at a dose level of 100 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m^2 basis).

There are, however, no adequate and well-controlled studies of cefepime use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Cefepime is excreted in human breast milk in very low concentrations (0.5 mcg/mL). Caution should be exercised when cefepime is administered to a nursing woman.

Labor and Delivery
Cefepime has not been studied for use during labor and delivery. Treatment should only be given if clearly indicated.

Pediatric Use
The safety and effectiveness of cefepime in the treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, pneumonia, and as empiric therapy for febrile neutropenic patients have been established in the age groups 2 months up to 16 years. Use of cefepime in these age groups is supported by evidence from adequate and well-controlled studies of cefepime in adults with additional pharmacokinetic and safety data from pediatric trials (see **CLINICAL PHARMACOLOGY**).

Safety and effectiveness in pediatric patients below the age of 2 months have not been established. There are insufficient clinical data to support the use of cefepime for injection in pediatric patients under 2 months of age or for the treatment of serious infections in the pediatric population where the suspected or proven pathogen is *Haemophilus influenzae* type b.

IN THOSE PATIENTS IN WHOM MENINGEAL SEEDING FROM A DISTANT INFECTION SITE OR IN WHOM MENINGITIS IS SUSPECTED OR DOCUMENTED, AN ALTERNATE AGENT WITH DEMONSTRATED CLINICAL EFFICACY IN THIS SETTING SHOULD BE USED.

Geriatric Use
Of the more than 6400 adults treated with cefepime for injection in clinical studies, 35% were 65 years or older while 16% were 75 years or older. When geriatric patients received the usual recommended adult dose, clinical efficacy and safety were comparable to clinical efficacy and safety in nongeriatric adult patients.

Serious adverse events have occurred in geriatric patients with renal insufficiency given unadjusted doses of cefepime, including life-threatening or fatal occurrences of the following: encephalopathy, myoclonus, and seizures. (See **WARNINGS** and **ADVERSE REACTIONS**.)

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. (See **CLINICAL PHARMACOLOGY: Special Populations, WARNINGS,** and **DOSAGE AND ADMINISTRATION.**)

ADVERSE REACTIONS

Clinical Trials
In clinical trials using multiple doses of cefepime, 4137 patients were treated with the recommended dosages of cefepime (500 mg to 2 g IV q12h). There were no deaths or permanent disabilities thought related to drug toxicity. Sixty-four (1.5%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or almost certainly related to drug toxicity. Thirty-three (51%) of these 64 patients who discontinued therapy did so because of rash. The percentage of cefepime-treated patients who discontinued study drug because of drug-related adverse events was very similar at daily doses of 500 mg, 1 g, and 2 g q12h (0.8%, 1.1%, and 2%, respectively). However, the incidence of discontinuation due to rash increased with the higher recommended doses.

The following adverse events were thought to be probably related to cefepime during evaluation of the drug in clinical trials conducted in North America (n 3125 cefepime-treated patients).

Table 10: Adverse Clinical Reactions
Cefepime Multiple-Dose Dosing Regimens
Clinical Trials-North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Local reactions (3%), including phlebitis (1.3%), pain and/or inflammation (0.6%)*; rash (1.1%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Colitis (including pseudomembranous colitis), diarrhea, fever,headache, nausea, oral moniliasis, pruritus, urticaria, vaginitis, vomiting

*local reactions, irrespective of relationship to cefepime in those patients who received intravenous infusion (n 3048).

At the higher dose of 2 g q8h, the incidence of probably-related adverse events was higher among the 795 patients who received this dose of cefepime. They consisted of rash (4%), diarrhea (3%), nausea (2%), vomiting (1%), pruritus (1%), fever (1%), and headache (1%).

The following adverse laboratory changes, irrespective of relationship to therapy with cefepime, were seen during clinical trials conducted in North America.

Table 11: Adverse Laboratory Changes
Cefepime Multiple-Dose Dosing Regimens
Clinical Trials-North America

INCIDENCE EQUAL TO OR GREATER THAN 1%	Positive Coombs' test (without hemolysis) (16.2%); decreased phosphorus (2.8%); increased ALT/SGPT (2.8%), AST/SGOT (2.4%), eosinophils (1.7%); abnormal PTT (1.6%), PT (1.4%)
INCIDENCE LESS THAN 1% BUT GREATER THAN 0.1%	Increased alkaline phosphatase, BUN, calcium, creatinine, phosphorus, potassium, total bilirubin; decreased calcium*, hematocrit, neutrophils, platelets, WBC

*Hypocalcemia was more common among elderly patients. Clinical consequences from changes in either calcium or phosphorus were not reported.

A similar safety profile was seen in clinical trials of pediatric patients (see **PRECAUTIONS: Pediatric Use**).

Postmarketing Experience
In addition to the events reported during North American clinical trials with cefepime, the following adverse experiences have been reported during worldwide postmarketing experience.

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 leukopenia, neutropenia, agranulocytosis and thrombocytopenia have been reported.

Cephalosporin-class Adverse Reactions
In addition to the adverse reactions listed above that have been observed in patients treated with cefepime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Stevens-Johnson syndrome, erythema mult forme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic dysfunction including cholestasis, and pancytopenia.

OVERDOSAGE

Patients who receive an overdose should be carefully observed and given supportive treatment. In the presence of renal insufficiency, hemodialysis, not peritoneal dialysis, is recommended to aid in the removal of cefepime from the body. Accidental overdosing has occurred when large doses were given to patients with impaired renal function. Symptoms of overdose include encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and neuromuscular excitability. (See **WARNINGS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**.)

DOSAGE AND ADMINISTRATION

The recommended adult and pediatric dosages and routes of administration are outlined in the following table. Cefepime for injection should be administered intravenously over approximately 30 minutes.

Table 12: Recommended Dosage Schedule for Cefepime for injection in Patients with CrCL > 60 mL/min

Site and Type of Infection	Dose	Frequency	Duration (days)
Adults			
Moderate to Severe Pneumonia due to *S. pneumoniae*, P. aeruginosa, K. pneumoniae,* or *Enterobacter species*	1 - 2 g IV	q12h	10
Empiric therapy for febrile neutropenic patients (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**.)	2 g IV	q8h	7**
Mild to Moderate Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli, K. pneumoniae,* or *P. mirabilis**	0.5 - 1 g IV/IM***	q12h	7 - 10
Severe Uncomplicated or Complicated Urinary Tract Infections, including pyelonephritis, due to *E. coli* or *K.pneumoniae**	2 g IV	q12h	10
Moderate to Severe Uncomplicated Skin and Skin Structure Infections due to *S. aureus* or *S. pyogenes*	2 g IV	q12h	10
Complicated Intra-abdominal Infections (used in combination with metronidazole) caused by *E. coli*, viridans group streptococci, *P. aeruginosa, K.pneumoniae, Enterobacter* species, or *B. fragilis*. (See **CLINICAL STUDIES**.)	2 g IV	q12h	7 - 10
Pediatric Patients (2 months up to 16 years) The maximum dose for pediatric patients should not exceed the recommended adult dose. The usual recommended dosage in pediatric patients up to 40 kg in weight for uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and pneumonia is 50 mg/kg/dose, administered q12h (50 mg/kg/dose, q8h for febrile neutropenic patients), for durations as given above.			

*including cases associated with concurrent bacteremia
**or until resolution of neutropenia. In patients whose fever resolves but who remain neutropenic for more than 7 days, the need for continued antimicrobial therapy should be re-evaluated frequently.
***IM route of administration is indicated only for mild to moderate, uncomplicated or complicated UTI's due to *E. coli* when the IM route is considered to be a more appropriate route of drug administration.

Impaired Hepatic Function
No adjustment is necessary for patients with impaired hepatic function.

Impaired Renal Function
In patients with impaired renal function (creatinine clearance ≤ 60 mL/min), the dose of cefepime should be adjusted to compensate for the slower rate of renal elimination. The recommended initial dose of cefepime should be the same as in patients with normal renal function except in patients undergoing hemodialysis. The recommended doses of cefepime in patients with renal insufficiency are presented in **Table 13.**

When only serum creatinine is available, the following formula (Cockcroft and Gault equation)[3] may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Males: Creatinine Clearance (mL/min) $= \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

Females: 0.85 x above value

Table 13: Recommended Dosing Schedule for Cefepime for injection in Adult Patients (Normal Renal Function, Renal Insufficiency, and Hemodialysis)

Creatinine Clearance (mL/min)	Recommended Maintenance Schedule			
> 60 Normal recommended dosing schedule	500 mg q12h	1 g q12h	2 g q12h	2 g q8h
30 - 60	500 mg q24h	1 g q24h	2 g q24h	2 g q12h
11 - 29	500 mg q24h	500 mg q24h	1 g q24h	2 g q24h
< 11	250 mg q24h	250 mg q24h	500 mg q24h	1 g q24h
CAPD	500 mg q48h	1 g q48h	2 g q48h	2 g q48h
Hemodialysis*	1 g on day 1, then 500 mg q24h thereafter			1 g q24h

*On hemodialys s days, cefepime should be administered following hemodialys s Whenever possible, cefepime should be administered at the same time each day

In patients undergoing continuous ambulatory peritoneal dialysis, cefepime for injection may be administered at normally recommended doses at a dosage interval of every 48 hours (see **Table 13**).

In patients undergoing hemodialysis, approximately 68% of the total amount of cefepime present in the body at the start of dialysis will be removed during a 3 hour dialysis period. The dosage of cefepime for injection for hemodialysis patients is 1 g on Day 1 followed by 500 mg q24h for the treatment of all infections except febrile neutropenia, which is 1 g q24h. Cefepime for injection should be administered at the same time each day and following the completion of hemodialysis on hemodialysis days (see **Table 13**).

Data in pediatric patients with impaired renal function are not available; however, since cefepime pharmacokinetics are similar in adults and pediatric patients (see **CLINICAL PHARMACOLOGY**), changes in the dosing regimen proportional to those in adults (see **Tables 12** and **13**) are recommended for pediatric patients.

Administration
For Intravenous Administration
Dilute with a suitable parenteral vehicle prior to intravenous infusion. Constitute the 500 mg, 1 g, or 2 g vial, and add an appropriate quantity of the resulting solution to an IV container with one of the compatible IV fluids in the **Compatibility and Stability** subsection. **THE RESULTING SOLUTION SHOULD BE ADMINISTERED OVER APPROXIMATELY 30 MINUTES.**

Intermittent IV infusion with a Y-type administration set can be accomplished with compatible solutions. However, during infusion of a solution containing cefepime, it is desirable to discontinue the other solution.

Intramuscular Administration
For IM administration, cefepime hydrochloride should be constituted with one of the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride, 5% Dextrose Injection, 0.5% or 1% Lidocaine Hydrochloride, or Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol (refer to **Table 14**).

Preparation of cefepime for injection solutions is summarized in **Table 14.**

Table 14: Preparation of Solutions of Cefepime for injection

Single-Dose Vials for Intravenous/Intramuscular Administration	Amount of Diluent to be added (mL)	Approximate Available Volume (mL)	Approximate Cefepime Concentration (mg/mL)
cefepime vial content			
500 mg (IV)	5	5.6	100
500 mg (IM)	1.3	1.8	280
1 g (IV)	10	11.3	100
1 g (IM)	2.4	3.6	280
2 g (IV)	10	12.5	160

Compatibility and Stability
Intravenous
Cefepime for injection is compatible at concentrations between 1 and 40 mg/mL with the following IV infusion fluids: 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, M/6 Sodium Lactate Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, Lactated Ringers and 5% Dextrose Injection, Normosol-R™, and Normosol-M™ in 5% Dextrose Injection. These solutions may be stored up to 24 hours at controlled room temperature 20° to 25° C (68° to 77° F) or 7 days in a refrigerator 2° to 8° C (36° to 46° F).

Cefepime for injection admixture compatibility information is summarized in **Table 15.**

Table 15: Cefepime Admixture Stability

Cefepime Concentration	Admixture and Concentration	IV Infusion Solutions	Stability Time for RT/L (20° to 25° C)	Stability Time for Refrigeration (2° to 8° C)
40 mg/mL	Amikacin 6 mg/mL	NS or D5W	24 hours	7 days
40 mg/mL	Ampicillin 1 mg/mL	D5W	8 hours	8 hours
40 mg/mL	Ampicillin 10 mg/mL	D5W	2 hours	8 hours
40 mg/mL	Ampicillin 1 mg/mL	NS	24 hours	48 hours
40 mg/mL	Ampicillin 10 mg/mL	NS	8 hours	48 hours
4 mg/mL	Ampicillin 40 mg/mL	NS	8 hours	8 hours
4 - 40 mg/mL	Clindamycin Phosphate 0.25 - 6 mg/mL	NS or D5W	24 hours	7 days
4 mg/mL	Heparin 10 - 50 units/mL	NS or D5W	24 hours	7 days
4 mg/mL	Potassium Chloride 10 - 40 mEq/L	NS or D5W	24 hours	7 days
4 mg/mL	Theophylline 0.8 mg/mL	D5W	24 hours	7 days
1 - 4 mg/mL	na	Aminosyn® II 4.25% with electrolytes and calcium	8 hours	3 days
0.125 - 0.25 mg/mL	na	Inpersol ™ with 4.25% dextrose	24 hours	7 days

NS 0.9% Sodium Chloride Injection
D5W 5% Dextrose Injection
na not applicable
RT/L Ambient room temperature and light

Solutions of cefepime for injection like those of most beta-lactam antibiotics, should not be added to solutions of ampicillin at a concentration greater than 40 mg/mL, and should not be added to metronidazole, vancomycin, gentamicin, tobramycin, netilmicin sulfate or aminophylline because of potential interaction. However, if concurrent therapy with cefepime is indicated, each of these antibiotics can be administered separately.

Intramuscular
Cefepime for injection constituted as directed is stable for 24 hours at controlled room temperature 20° to 25° C (68° to 77° F) or for 7 days in a refrigerator 2° to 8° C (36° to 46° F) with the following diluents: Sterile Water for Injection, 0.9% Sodium Chloride Injection, 5% Dextrose Injection, Sterile Bacteriostatic Water for Injection with Parabens or Benzyl Alcohol, or 0.5% or 1% Lidocaine Hydrochloride.

NOTE: PARENTERAL DRUGS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER BEFORE ADMINISTRATION.

As with other cephalosporins, the color of cefepime powder, as well as its solutions, tend to darken depending on storage conditions; however, when stored as recommended, the product potency is not adversely affected.

HOW SUPPLIED

Each vial contains sterile cefepime hydrochloride equivalent to 500 mg, 1 g or 2 g of cefepime and L- arginine for pH adjustment.

Cefepime for injection, USP is supplied as a sterile powder in glass vials as follows:

Vials containing 500 mg equivalent of cefepime. Box of 1 (NDC 60505–0678–0) and box of 10 (NDC 60505–0678–4).
Vials containing 1 g equivalent of cefepime. Box of 1 (NDC 60505–0834–0) and box of 10 (NDC 60505–0834–4).
Vials containing 2 g equivalent of cefepime. Box of 1 (NDC 60505–0681–0) and box of 10 (NDC 60505–0681–4).

Storage
CEFEPIME FOR INJECTION IN THE DRY STATE SHOULD BE STORED BETWEEN 2°- 25° C (36°-77° F) AND PROTECTED FROM LIGHT.

REFERENCES

(1) National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically* -Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.

(2) National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

(3) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41.

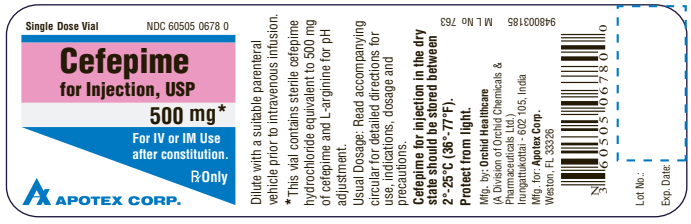
Mfg. by:
Orchid Healthcare
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.)
Irungattukottai - 602 105, India

Mfg. for:
Apotex Corp.
Weston, FL 33326

DATE OF ISSUANCE: February 2007

948025507

Container (Vial) Label for Cefepime for Injection USP, 500 mg (with NDC number for 1 vial carton box)

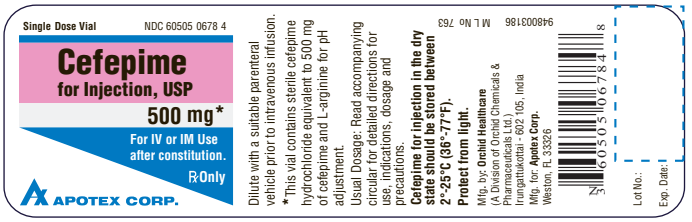


Actual Label size : 90 mm x 28 mm (Length x Height)

(b) (4)

Unvarnished Area

Container (Vial) Label for Cefepime for Injection USP, 500 mg (with NDC number for 10 vial carton box)



Actual Label size : 90 mm x 28 mm (Length x Height)

(b) (4)

Unvarnished Area

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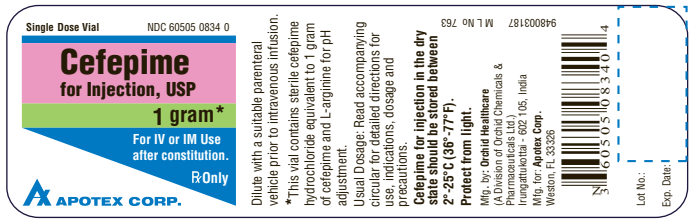

Actual Label size : 90 mm x 28 mm (Length x Height)

(b) (4)

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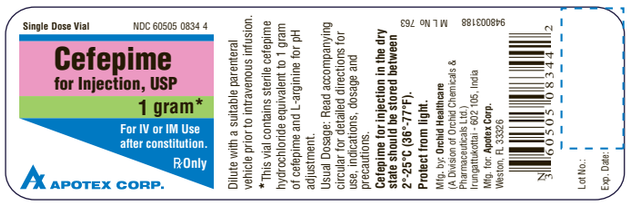

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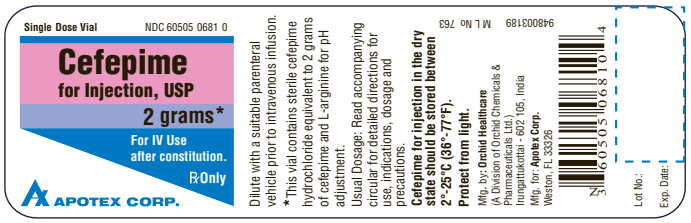
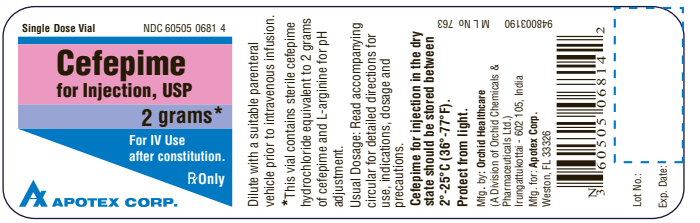


Actual Label size : 90 mm x 28 mm (Length x Height)

(b) (4)

Unvarnished Area

Container (Vial) Label for Cefepime for Injection USP, 2 g (with NDC number for 10 vial Carton box)



Actual Label size : 90 mm x 28 mm (Length x Height)

(b) (4)

Unvarnished Area

Carton for Cefepime for Injection USP, 500 mg
(1 vial Carton box)

Actual size: 41 mm x 41 mm x 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

Carton Box for Cefepime for Injection USP, 500 mg

(10 Vials pack)

Exp. Date:

Lot No.:

APOTEX CORP.

For IV or IM Use
after constitution.
℞Only

RETAIN IN CARTON UNTIL TIME OF USE

500 mg*

Cefepime
for Injection, USP

1 Box - 10 vials NDC 60505-0678-4

Dilute with a suitable parenteral vehicle prior to intravenous infusion.

* Each vial contains sterile cefepime hydrochloride equivalent to 500 mg of cefepime and L-arginine for pH adjustment.

Usual Dosage: Read accompanying circular for detailed directions for use, indications, dosage and precautions.

Cefepime for injection in the dry state should be stored between 2°-25°C (36°-77°F).

Protect from light.

Mfg. by: **Orchid Healthcare**
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.)
Irungattukottai - 602 105, India

Mfg. for: **Apotex Corp.**
Weston, FL 33326

M.L.No. 763

9491132

1 Box - 10 vials NDC 60505-0678-4

Cefepime
for Injection, USP

500 mg*

RETAIN IN CARTON UNTIL TIME OF USE

For IV or IM Use
after constitution.

℞Only

APOTEX CORP.

1 Box - 10 vials NDC 60505-0678-4

Cefepime
for Injection, USP

500 mg*

RETAIN IN CARTON UNTIL TIME OF USE

For IV or IM Use
after constitution.

SINGLE DOSE VIALS

℞Only

APOTEX CORP.

1 Box - 10 vials NDC 60505-0678-4

Cefepime
for Injection, USP

500 mg*

RETAIN IN CARTON UNTIL TIME OF USE

For IV or IM Use
after constitution.

℞Only

APOTEX CORP.

Actual size: 172 mm x 72 mmx 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

Carton for Cefepime for Injection USP, 1 g
(1 vial Carton box)

Actual size: 41 mm x 41 mm x 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

Carton Box for Cefepime for Injection USP, 1 g
(10 Vials pack)

Exp. Date:

Lot No.:

APOTEX CORP.

RETAIN IN CARTON UNTIL TIME OF USE
For IV or IM Use
after constitution.
℞Only

1 gram*

Cefepime
for Injection, USP

1 Box - 10 vials NDC 60505-0834-4

Dilute with a suitable parenteral vehicle prior to intravenous infusion.

* Each vial contains sterile cefepime hydrochloride equivalent to 1 gram of cefepime and L-arginine for pH adjustment.

Usual Dosage: Read accompanying circular for detailed directions for use, indications, dosage and precautions.

Cefepime for injection in the dry state should be stored between 2°-25°C (36°-77°F).

Protect from light.

949113267

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Pharmaceuticals Ltd.)
Irungattukottai - 602 105, India

Mfg. for: **Apotex Corp.**
Weston, FL 33326

N 3 60505 08344 2

M.L.No. 763

1 Box - 10 vials NDC 60505-0834-4

Cefepime
for Injection, USP

1 gram*

RETAIN IN CARTON UNTIL TIME OF USE
For IV or IM Use
after constitution.
℞Only

APOTEX CORP.

1 Box - 10 vials NDC 60505-0834-4

Cefepime
for Injection, USP

1 gram*

RETAIN IN CARTON UNTIL TIME OF USE
For IV or IM Use
after constitution.
℞Only

APOTEX CORP.

1 Box - 10 vials NDC 60505-0834-4

Cefepime
for Injection, USP

1 gram*

RETAIN IN CARTON UNTIL TIME OF USE
For IV or IM Use
after constitution.
℞Only

APOTEX CORP.

Actual size: 172 mm x 72 mmx 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

Carton for Cefepime for Injection USP, 2 g
(1 vial Carton box)

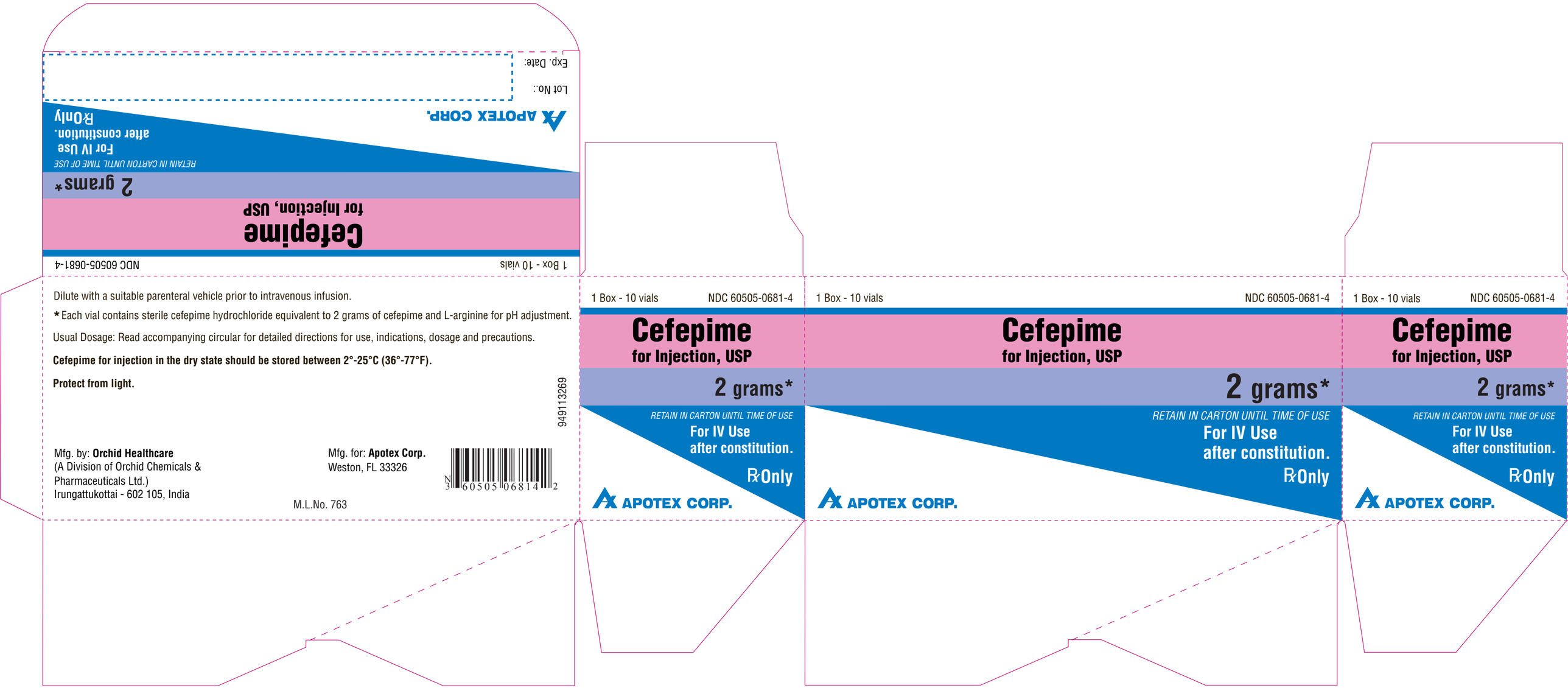
Actual size: 41 mm x 41 mm x 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

Carton Box for Cefepime for Injection USP, 2 g

(10 Vials pack)



Actual size: 172 mm x 72 mmx 78 mm (Length x Width x Height)

(b) (4)

Unvarnished Area

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-369

Date of Submission: November 2, 0005

Applicant's Name: Orchid Healthcare

Established Name: Cefepime for Injection USP, 500 mg, 1 gram and 2 grams vials

---

Labeling Deficiencies:

1. CONTAINER: 500 mg, 1 gram and 2 grams vials

    a. Front panel

        i. Add a comma prior to "USP".

        ii. Increase the size of the asterisk.

        ii. Print, "Single-Dose Vial" in bold print.

    b. Side panel

        i. To meet the USP labeling requirement add the statement, "Dilute with a suitable parenteral vehicle prior to intravenous infusion" as the first sentence on the side panel.

        ii. Increase the size of the asterisk.

        iii. If space permits add "Usual Dosage" prior to the statement, "Read ... precautions".

    c. Further differentiate the color of the strengths for the 500 mg and 2 grams labels.

2. CARTON: 500 mg, 1 gram and 2 grams – Individual and 10s

    a. See comments under CONTAINER.

b. To be consistent with the innovator, revise "___ x ___g vial" to read "1 Box - ___ vial(s)".

c. If space permits increase the size of the statement, "RETAIN IN CARTON UNTIL TIME OF USE" on the front and top panels. If space does not permit, print the statement using a different color and/or italic print.

d. 500 mg

Add "**SINGLE DOSE VIAL(S)**" in bold uppercase print on the front panel.

2. INSERT

a. GENERAL COMMENTS

You may omit the "USP" designation following the established name, except in the TITLE, DESCRIPTION and HOW SUPPLIED sections.

b. DESCRIPTION

Replace "Cefepime hydrochloride" with Cefepime for Injection" except in the third and the fourth paragraphs, [i.e, fourth paragraph "... cefepime hydrochloride and L-arginine of the DESCRIPTION section. It..."].

c. ADVERSE REACTIONS

i. Table 10

To be consistent with the innovator, print "Cefepime ...Regimens" in between "Adverse...Reactions" and "Clinical ...America". See below.

Adverse...Reactions
Cefepime ...Regimens
Clinical ...America

ii. Table 11

To be consistent with the innovator print "Cefepime ... Regimens" in between "Adverse...Changes" and "Clinical ...America". See below.

Adverse...Changes
Cefepime ...Regimens
Clinical ...America

d. DOSAGE AND ADMINISTRATION

i. Table 12

Add a blank line space between each "Site and Type of Infection".

ii. Administration

For Intravenous Administration

A) To meet the USP labeling requirement add the statement, "Dilute with a suitable parenteral vehicle prior to intravenous infusion" as the first sentence.

B) Revise the first sentence to read, "...IV fluids in the **Compatibility and Stability** subsection".

C) We note that omitted the second paragraph, "Intermittent ...other solution". This paragraph should be retained.

e. HOW SUPPLIED

a. To be consistent with the innovator, print the storage statement in uppercase bold print.

b. We note that your flip cap color is (b) (4) for both your 1 g and 2 g products. Please differentiate the color of the flip off caps.

Revise your labeling, as instructed above, and submit final printed labeling electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed copy of the reference listed drug's labeling with all differences annotated and explained.

NOTES/QUESTIONS TO THE CHEMIST

DOSAGE AND ADMINISTRATION section

1. Has the firm submitted stability data to support the text in Table 14, "Preparation of Solutions of Cefepime of Injection, USP"?

2. Has the firm submitted stability data to support the text under the Compatibility and Stability /Intravenous subsection?

3. Has the firm submitted stability data to support the text in Table 15, "Cefepime Admixture Stability"?

4. Has the firm submitted stability data to support the text under the Compatibility and Stability / Intramuscular subsection?

5. Has the firm submitted data to support the storage statement below.
   In the dry state should be stored between 2° – 25 °C
   (36° – 77 °F) and protected form light"?

You can view the text in the firm's insert labeling in the EDR. Or, if you prefer, I can mail it to you. Please let me know.

FOR THE RECORD:

1. MODEL LABELING

Maxipime by Bristol-Myers Squibb Company/NDA 50-679/S-023/apprvoved 6/4/04

The USP requires the labeling to indicate the following:
Labeling— Label it to indicate that it is to be diluted with a suitable parenteral vehicle prior to intravenous infusion.

2. Inactive ingredient

- The active ingredient list in the firm's DESCRIPTION section is consistent with the firm's components and composition statements.
[Vol. 1.1, p. 177]

3. The firm's physical description of the drug product is consistent with the description in the application.
[Vol. 1.3, p. 931]

4. Manufacturing Facility

Orchid Healthcare
Irungattukottai, India
[Vol. 1.1, p. 250]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD - 500 mg - 10s
1 g Piggyback bottle 100 mL – 10s
1 g ADD-Vantage vial – 10s
1 g 15 mL vial -10s
2 g Piggyback bottle 100 mL – 10s
2 g ADD-Vantage vial – 10s
2 g 20 mL vial -10s

ANDA - 500 mg, 1 g and 2 g– individual vial and 10s

7. Container/Closure:

Molded glass type I/gray rubber stopper/flip off cap

500 mg – blue cap
1 g and 2 g – (b) (4) cap
[Vol. 1.3, p. 722 to 725]

8. Storage and/or Dispensing:

USP - Packaging and storage— Preserve in tight, light-resistant *Containers for Sterile Solids* as described under *Injections* ⟨1⟩, and store in a refrigerator or at controlled room temperature. Store reconstituted powder in a refrigerator for no more than 7 days.

NDA - In the dry state should e stored between 2° – 25 °C (36° – 77 °F) and protected form light.

ANDA - Same

9. This is the first generic for this drug product.

Date of Review: 1/24/07

Date of Submission: 11/2/06

Primary Reviewer
Jacqueline Council, Pharm.D.

_____ Date: _____

Team Leader
Captain Lillie Golson

_____ Date _____

cc:

ANDA: 65-369
DUP/DIVISION FILE
V:\FIRMSNZ\OrchidHealthcare\LTRS&REV\65369na1.l.doc
Review

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

/s/

Jacqueline Council
2/8/2007 08:37:19 AM
MEDICAL OFFICER

Lillie Golson
2/8/2007 02:58:41 PM
MEDICAL OFFICER

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-369

Date of Submission: February 9, 2007 and March 20, 2007

Applicant's Name: Orchid Healthcare

Established Name: Cefepime for Injection USP, 500 mg, 1 gram and 2 grams vials

---

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? See EDR

- Container Labels: CONTAINER: 500 mg, 1 gram and 2 grams vials

Satisfactory as of the February 9, 2007 [See EDR]

- Carton: 500 mg, 1 gram and 2 grams – Individual and 10s
Satisfactory as of the February 9, 2007 [See EDR]

- Professional Package Insert Labeling:
Satisfactory as of the February 9, 2007 submission. [See EDR]
Insert code: 948025507/revised 2/2007

Revisions needed post-approval:

1. CONTAINER: 2 grams

   Use a lighter shade of violet as the background color for the strength. We refer you to your submission.

2. CARTON: 500 mg, 1 gram and 2 grams – Individual and 10s

   a. Relocate the text, "RETAIN IN CARTON UNTIL TIME OF USE" to appear beneath the routes of administration or in the blank white space prior to your company name.

   b. Print "RETAIN IN CARTON UNTIL TIME OF USE" on the top panels.

   c. 500 mg -10s

      As previously requested, add **"SINGLE DOSE VIALS"** in bold uppercase print on the front panel.

   d. 2 grams
      See comment under CONTAINER.

3. INSERT

   Improve the visibly of the asterisks, superscripts and subscripts by increasing the size and/or using bold print.

BASIS OF APPROVAL:

Patent/ Exclusivities: None
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Maxipime /NDA 50-679/S-023/approved 6/9/04

NDA Number: 50-679

NDA Drug Name: Cefepime for Injection

NDA Firm: Bristol-Myers Squibb Company
Date of Approval of NDA Insert and supplement #: S-023/approved 6/4/04
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

NOTES/QUESTIONS TO THE CHEMIST

In the firm's February 9, 2007 submission we were informed that the flip off cap colors were revised to green for the 1 g product and violet for the 2 g product.
Do you need any further documentation from the firm regarding the color changes?

From: Ruan, Xiumei
Sent: Monday, March 19, 2007 5:37 PM
To: Council, Jacqueline
Subject: FW: 65-369

Jackie:

It is not critical for the firm to change colors of the flip caps, so that we don't need further submission. But I don't mind to update colors of the caps in the approved CMC review. Please let me know the date of the amendment. Thanks.

Xiumei Ruan

DIV3/OGD/CDER/FDA
HFD-643, MPN II, #E124
Phone: (301) 594-1894

NOTES/QUESTIONS TO THE CHEMIST

DOSAGE AND ADMINISTRATION section

1. Has the firm submitted stability data to support the text in Table 14, "Preparation of Solutions of Cefepime of Injection, USP"?

2. Has the firm submitted stability data to support the text under the Compatibility and Stability /Intravenous subsection?

3. Has the firm submitted stability data to support the text in Table 15, "Cefepime Admixture Stability"?

4. Has the firm submitted stability data to support the text under the Compatibility and Stability / Intramuscular subsection?

5. Has the firm submitted data to support the storage statement below.
   In the dry state should be stored between 2° – 25 °C
   (36° – 77 °F) and protected form light"?

You can view the text in the firm's insert labeling in the EDR. Or, if you prefer, I can mail it to you. Please let me know.

From: Ruan, Xiumei
Sent: Wednesday, February 07, 2007 4:50 PM
To: Council, Jacqueline
Subject: FW: 65-369

Jackie:
The answer are in the blue ink

NOTES/QUESTIONS TO THE CHEMIST

DOSAGE AND ADMINISTRATION section

1. Has the firm submitted stability data to support the text in Table 14, "Preparation of Solutions of Cefepime of Injection, USP"?

A: Yes,

2. Has the firm submitted stability data to support the text under the Compatibility and Stability /Intravenous subsection?

A: Yes,

3. Has the firm submitted stability data to support the text in Table 15, "Cefepime Admixture Stability"?

A: Yes,

4. Has the firm submitted stability data to support the text under the Compatibility and Stability / Intramuscular subsection?

A: Yes,

5. Has the firm submitted data to support the storage statement below.
In the dry state should be stored between 2° – 25 °C (36° – 77 °F) and protected form light"?

A: Yes, data supports the claim. But there was a question for the labeling long time ago. Please see the comments posted in CMC review (below).

FOR THE RECORD:

1. MODEL LABELING

Maxipime by Bristol-Myers Squibb Company/NDA 50-679/S-023/approved 6/9/04

The USP requires the labeling to indicate the following:

Labeling— Label it to indicate that it is to be diluted with a suitable parenteral vehicle prior to intravenous infusion.

2. Inactive ingredient

- The active ingredient list in the firm's DESCRIPTION section is consistent with the firm's components and composition statements.
[Vol. 1.1, p. 177]

3. The firm's physical description of the drug product is consistent with the description in the application.
[Vol. 1.3, p. 931]

4. Manufacturing Facility

Orchid Healthcare
Irungattukottai, India
[Vol. 1.1, p. 250]

5. Patent and exclusivity –none pending

6. Package Sizes

RLD - 500 mg - 10s
1 g Piggyback bottle 100 mL – 10s
1 g ADD-Vantage vial – 10s
1 g 15 mL vial -10s
2 g Piggyback bottle 100 mL – 10s
2 g ADD-Vantage vial – 10s
2 g 20 mL vial -10s

ANDA - 500 mg, 1 g and 2 g– individual vial and 10s

7. Container/Closure:

Molded glass type I/gray rubber stopper/flip off cap

500 mg – blue cap
1 g and 2 g – (b) (4) cap See below.
[Vol. 1.3, p. 722 to 725]

February 9, 2007 submission
The firm revised the cap colors to green for the 1 g product and violet for the 2 g product.
[Vol. 3.1]

8. Storage and/or Dispensing:

USP - Packaging and storage— Preserve in tight, light-resistant *Containers for Sterile Solids* as described under ***Injections*** ⟨ 1 ⟩, and store in a refrigerator or at controlled room temperature. Store reconstituted powder in a refrigerator for no more than 7 days.

NDA - In the dry state should e stored between 2° – 25 °C (36° – 77 °F) and protected form light.

ANDA - Same

9. This is the first generic for this drug product.

10. The 3/20/07 submission provided the documents for the cap/closure color change.

Date of Review: 3/1/07

Date of Submission: 2/9/07

Primary Reviewer
Jacqueline Council, Pharm.D.

Date:

Team Leader
Captain Lillie Golson

Date

cc:

ANDA: 65-369
DUP/DIVISION FILE
V:\FIRMSNZ\OrchidHealthcare\LTRS&REV\65369na2.l.doc
Review

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

/s/

Jacqueline Council
3/21/2007 01:16:55 PM
MEDICAL OFFICER

Lillie Golson
3/23/2007 12:51:30 PM
MEDICAL OFFICER
Lillie Golson for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

CHEMISTRY REVIEWS

#1

ANDA 65-369

Cefepime for Injection USP
500 mg, 1 g and 2 g

Orchid Healthcare

Xiumei Ruan, Chemist
OGD, Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-369

2. REVIEW #1

3. REVIEW DATE: April 11, 2006

4. REVIEWER: X. Ruan

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	25-OCT-2005
Acceptable for Filing	4-NOV-2005
Telephone Amendment	10-JAN-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	**Orchid Healthcare**
Address:	Plot #B3-B6 & B11-B14 SIPCOT Industrial Park Irungattukottai Sriperumbudur Kancheepuram District – 602 105 INDIA
Representative:	Satish Srinivasan (in US)
Telephone:	Phone: (609)-951-2209 Fax: (609)-951-2213

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Cefepime for Injection USP, 500 mg, 1 g and 2 g

9. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product, MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679. The firm filed a patent certification and exclusivity statement to verify no unexpired patents and exclusivities noted (p. 10). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, and indications as the reference listed drug (p.17).

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 500 mg, 1 g and 2 g

13. ROUTE OF ADMINISTRATION: IV and IM

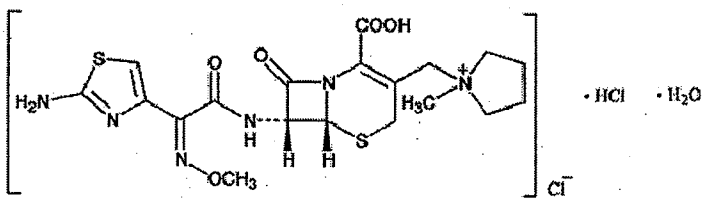
14. Rx/OTC DISPENSED: x Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, chloride, monohydrochloride, monohydrate, [6*R*-[6α,7β(*Z*)]]-. 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, 7^2-(*Z*)-(*O*-methyloxime), monohydrochloride, monohydrate [*123171-59-5*].

Molecular Formula: $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$
Molecular Weight: 571.50

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18923	II	Orchid	Cefepime + Arginine	1	Inadequate	4/11/06	X. Ruan
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	9/23/05	N/A
	III			3,4	Adequate	9/01/99	J. Vidra
	V			3,4	Adequate	5/05/03	A. Yu

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Waiver requested		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for 65-369

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Recommended for Approval (MINOR)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug

The Reference Listed Drug for this application is MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679.

Drug substance

The drug substance, Cefepime Hydrochloride USP is supplied as a mixture of Cefepime HC1 buffered with Arginine, manufactured by Orchid Chemical & Pharmaceuticals Ltd. of India. The DMF #18923 was reviewed and found inadequate on 4/11/06.

Drug product

The drug product Cefepime for Injection USP is indicated in the treatment of infections caused by susceptible strains of designated microorganisms. The product will be commercially available in 500 mg, 1 g and 2 g doses.

Cefepime for Injection, USP is a sterile, dry mixture of Cefepime HC1 and L-arginine. Each unit of the drug product contains Cefepime HC1 equivalent to 500 mg, 1 g or 2 g of Cefepime. The L-arginine is added at approx. 725 mg/g of Cefepime, to adjust pH of the constituted solution to 4-6. Freshly constituted solution appears as colorless to amber colored liquid.

The Cefepime for Injection, USP is marketed in a 20 mL clear type I glass vial, sealed with a 20 mm grey rubber stopper and blue (500 mg) or (b) (4) (1g & 2g) flip-off seal cap. When powder is constituted with sterile water for injection, it results in a clear very pale yellow to light amber solution.

The product in dry state should be stored at 2°-25°C (36°-77°F) and protected from light. After reconstituted with diluents, the product may be stored up to 24 hour at 20-25°C or 7 days at refrigerator condition of 2-4°C (p. 35).

B. Description of How the Drug Product is Intended to be Used

The product may be administrated intravenously or intramuscularly. The usual adult dose is recommended as 1-2 g every 12 hours.

For intravenous administration, the product should be constituted and an appropriate quantity of the resulting solution added to an IV container with one of the compatible IV fluids at concentration between 1- 40 mg/mL. The resulting solution should be administrated over approx. 30 minutes (p. 72). The constituted IV solution may be stored up to 24 hours at controlled RT temperature (20°-25°C or 68°-77°F) or 7 days in a refrigerator (2°-4°C or 36°-46°F) (p. 73-74).

For intramuscular use, the product should be constituted with one of compatible diluents the product powder with the appropriate diluent by injecting diluent into the vial, shaking vial thoroughly to form solution, then withdrawing entire contents of vial into syringe to equal total labeled dose.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to minor CMC deficiencies

III. Administrative

cc: ANDA 65-369
ANDA DUP
DIV FILE
Field Copy

TYPE OF LETTER: NOT APPROVABLE - MINOR

Following this page, 23 pages withheld in full (b)(4)- Chemistry review #1

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **65-369** APPLICANT: **Orchid Healthcare**

DRUG PRODUCT: **Cefepime for Injection USP, 500 mg, 1 g and 2 g**

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.

(b) (4)

7.

8.

9.

10.

11.

12.

13.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The DMF #18923 for Sterile blend of Cefepime HC1 and L-Arginine was reviewed and found inadequate. A letter has been forwarded to the DMF holder. Please be aware that this application cannot be approved until all deficiencies regarding to the DMF are satisfactorily resolved. It is recommended that you also contact the drug manufacturer for the specification update.

2. If available, please provide updated long-term stability data for the drug product in your amendment.

3. The application is currently being reviewed with respect to sterility assurance and labeling issues, any comments will be sent in separate communications.

Sincerely yours,

Vilayat A. Sayeed Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-369
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/XRuan/4/11/06/ 5/10/06

HFD-643/SZuk/5/5/06/ 5/10/06

HFD-617/RNguyen/5/9/06/ 5/10/06

V:\firmsnz\OrchirdHealthcare\ltrs&rev\65369R01.na.doc

F/T by: EW 5/10/06

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 65-369

Cefepime for Injection USP
500 mg, 1 g and 2 g

Orchid Healthcare

Xiumei Ruan, Chemist
OGD, Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-369

2. REVIEW #2

3. REVIEW DATE: August 17, 2006

4. REVIEWER: X. Ruan

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Telephone Amendment	10-JAN-2006
Acceptable for Filing	4-NOV-2005
Original Submission	25-OCT-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment #1 (CMC)	16-June-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Orchid Healthcare
Address:	Plot #B3-B6 & B11-B14 SIPCOT Industrial Park Irungattukottai Sriperumbudur Kancheepuram District – 602 105 INDIA
Representative:	Satish Srinivasan (in US)
Telephone:	Phone: (609)-951-2209 Fax: (609)-951-2213

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Cefepime for Injection USP, 500 mg, 1 g and 2 g

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION

Reference Listed drug product, MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679. The firm filed a patent certification and exclusivity statement to verify no unexpired patents and exclusivities noted (p. 10). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, and indications as the reference listed drug (p.17).

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 500 mg, 1 g and 2 g

13. ROUTE OF ADMINISTRATION: IV and IM

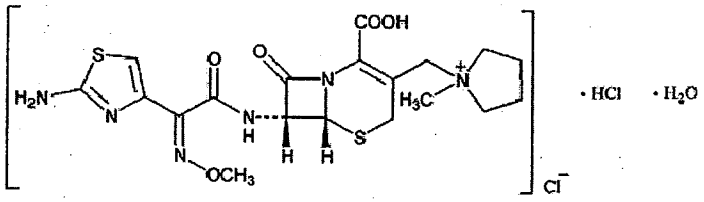
14. Rx/OTC DISPENSED: x Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name: Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, chloride, monohydrochloride, monohydrate, [6*R*-[6α,7β(*Z*)]]-.
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, 7^2-(*Z*)-(*O*-methyloxime), monohydrochloride, monohydrate [*123171-59-5*].

Molecular Formula: $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$
Molecular Weight: 571.50 (480.0 for only Cefixime base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18923	II	Orchid	Cefepime + Arginine	1	Inadequate	8/9/06	X. Ruan
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	9/23/05	N/A
	III			3,4	Adequate	9/01/99	J. Vidra
	V			3,4	Adequate	5/05/03	A. Yu

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Waiver requested		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
X Yes ____ No If no, explain reason(s) below:

The Chemistry Review for 65-369

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Recommended for Approval (Pending for DMF review)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug

The Reference Listed Drug for this application is MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679.

Drug substance

The drug substance, Cefepime Hydrochloride USP is supplied as a mixture of Cefepime HC1 buffered with Arginine, manufactured by Orchid Chemical & Pharmaceuticals Ltd. of India. The DMF #18923 was reviewed and found inadequate on 8/9/06.

Drug product

The drug product Cefepime for Injection USP is indicated in the treatment of infections caused by susceptible strains of designated microorganisms. The product will be commercially available in 500 mg, 1 g and 2 g doses.

Cefepime for Injection, USP is a sterile, dry mixture of Cefepime HC1 and L-arginine. Each unit of the drug product contains Cefepime HC1 equivalent to 500 mg, 1 g or 2 g of Cefepime. The L-arginine is added at approx. 725 mg/g of Cefepime, to adjust pH of the constituted solution to 4-6. Freshly constituted solution appears as colorless to amber colored liquid.

The Cefepime for Injection, USP is marketed in a 20 mL clear type I glass vial, sealed with a 20 mm grey rubber stopper and blue (500 mg) or (b) (4) (1g & 2g) flip-off seal cap. When powder is constituted with sterile water for injection, it results in a clear, very pale yellow to light amber solution.

The product in dry state should be stored at 2°-25°C (36°-77°F) and protected from light. After it is reconstituted with diluents, the product may be stored up to 24 hour at 20-25°C or 7 days at refrigerated condition of 2-4°C (p. 35).

B. Description of How the Drug Product is Intended to be Used

The product may be administrated intravenously or intramuscularly. The usual adult dose is recommended as 1-2 g every 12 hours.

For intravenous administration, the product should be constituted and an appropriate quantity of the resulting solution added to an IV container with one of the compatible IV fluids at concentration between 1- 40 mg/mL. The resulting solution should be administrated over approx. 30 minutes (p. 72). The constituted IV solution may be stored up to 24 hours at controlled RT temperature (20°-25°C or 68°-77°F) or 7 days in a refrigerator (2°-4°C or 36°-46°F) (p. 73-74).

For intramuscular use, the product should be constituted with one of compatible diluents the product powder with the appropriate diluent by injecting diluent into the vial, shaking vial thoroughly to form solution, then withdrawing entire contents of vial into syringe to equal total labeled dose.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable due to remaining deficiencies in the sterile bulk blend (DMF #18923) and the drug substance (DMF #18902).

III. Administrative

cc: ANDA 65-369
ANDA DUP
DIV FILE
Field Copy

TYPE OF LETTER: NOT APPROVABLE

Following this page, 22 pages withheld in full (b)(4)- Chemistry review #2

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **65-369** APPLICANT: **Orchid Healthcare**

DRUG PRODUCT: **Cefepime for Injection USP, 500 mg, 1 g and 2 g**

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

1. (b) (4)

2. The DMF #18923 for Sterile blend of Cefepime HC1 and L-Arginine remains inadequate. A letter has been forwarded to the DMF holder. Please be aware that this application cannot be approved until all deficiencies regarding to the DMF are satisfactorily resolved. It is recommended that you also contact the drug manufacturer for the DMF update.

Sincerely yours,

Vilayat A. Sayeed Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-369
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/XRuan/8/18/06/ XRuan 9/6/06

HFD-643/SZuk/8/29/06/ 9/6/06

HFD-617/RNguyen/ 9/8/06

V:\firmsnz\OrchidHealthcare\ltrs&rev\65369R02.na.doc

F/T by: RTN/08/31/06

TYPE OF LETTER: Not approvable

ANDA 65-369

Cefepime for Injection USP
500 mg, 1 g and 2 g

Orchid Healthcare

Xiumei Ruan, Chemist
OGD, Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-369

2. REVIEW: 3

3. REVIEW DATE: November 14, 2006 (AM #1 and Telephone AM #1)
May 23, 2007 (Telephone AM #2 and #3)
June 15, 2007 (Telephone AM #4)

4. REVIEWER: X. Ruan

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Micro Amendment	13-APR-2007
New Correspondence	28-MAR-2007
Labeling Amendment	20-MAR-2007
Labeling Amendment	09-FEB-2007
Telephone Amendment #1(CMC)	8-NOV-2006
Amendment #2 (CMC)	16-SEP-2006
Amendment #1 (CMC)	16-JUN-2006
Telephone Amendment	10-JAN-2006
New Correspondence	10-JAN-2006
Acceptable for Filing	04-NOV-2005
Original Submission	25-OCT-2005 (02-NOV-2005)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone amendment #4 (CMC)	14-JUN-2007
Telephone amendment #3 (CMC)	21-MAY-2007
Telephone amendment #2 (CMC)	14-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	**Orchid Healthcare**

Chemistry Review Data Sheet

Address:	Plot #B3-B6 & B11-B14 SIPCOT Industrial Park Irungattukottai Sriperumbudur Kancheepuram District – 602 105 INDIA
Representative:	Satish Srinivasan (in US)
Telephone:	Phone: (609)-951-2209 Fax: (609)-951-2213

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name: Cefepime for Injection USP, 500 mg, 1 g and 2 g

9. LEGAL BASIS FOR SUBMISSION

   Reference Listed drug product, MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679. The firm filed a patent certification and exclusivity statement to verify no unexpired patents and exclusivities noted (p. 10). The proposed drug product contains the same active ingredient and has the same strength, dosage form, route of administration, and indications as the reference listed drug (p.17).

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 500 mg, 1 g and 2 g

13. ROUTE OF ADMINISTRATION: IV and IM

14. Rx/OTC DISPENSED: x Rx ___OTC

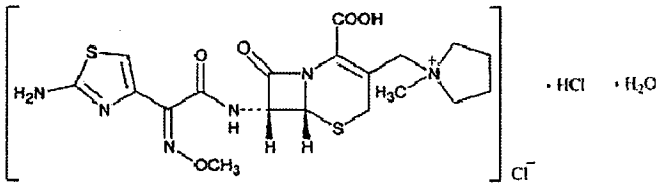
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    ___x___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet



Name: Pyrrolidinium, 1-[[7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-, chloride, monohydrochloride, monohydrate, [6*R*-[6α,7β(*Z*)]]-. 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, 7^2-(*Z*)-(*O*-methyloxime), monohydrochloride, monohydrate [*123171-59-5*].

Molecular Formula: $C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$
Molecular Weight: 571.50 (480.0 for only Cefixime base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18923	II	Orchid	Cefepime + Arginine	1	Adequate	5/23/07	5/21/07 AM was reviewed by X. Ruan
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	9/23/05	N/A
	III			3,4	Adequate	9/01/99	J. Vidra
	V			3,4	Adequate	5/05/03	A. Yu

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	05/03/07	R. Leblanc

Chemistry Review Data Sheet

EES	Acceptable	02/02/07	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	03/23/07	J. Council
Bioequivalence	Acceptable	12/05/06	S. Jones
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
x Yes ____ No If no, explain reason(s) below:

The Chemistry Review for 65-369

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommended for Approval

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Reference Listed Drug

The Reference Listed Drug for this application is MAXIPIME® (Cefepime Hydrochloride, USP) for Injection 500 mg, 1 g and 2 g, manufactured by Bristol Myers Squibb, approved in NDA #50-679.

Drug substance

The drug substance, Cefepime Hydrochloride USP is supplied as a mixture of Cefepime HCl buffered with Arginine, manufactured by Orchid Chemical & Pharmaceuticals Ltd. of India. DMF #18923 was reviewed and found adequate on 11/2/06.

Drug product

The drug product Cefepime for Injection USP is indicated in the treatment of infections caused by susceptible strains of designated microorganisms. The product will be commercially available in 500 mg, 1 g and 2 g doses.

Cefepime for Injection, USP is a sterile, dry mixture of Cefepime HCl and L-arginine. Each unit of the drug product contains Cefepime HCl equivalent to 500 mg, 1 g or 2 g of Cefepime. The L-arginine is added at approx. 725 mg/g of Cefepime, to adjust pH of the constituted solution to 4-6.

The Cefepime for Injection, USP is marketed in a 20 mL clear type I glass vial, sealed with a 20 mm grey rubber stopper and blue (500 mg) or (b) (4) (1g & 2g) flip-off seal cap. When powder is constituted with sterile water for injection, it results in a clear, very pale yellow to light amber solution.

The product in dry state should be stored at 2°-25°C (36°-77°F) and protected from light. After it is reconstituted with diluents, the product may be stored up to 24 hour at 20-25°C or 7 days at refrigerated condition of 2-4°C (p. 35).

B. Description of How the Drug Product is Intended to be Used

The product may be administrated intravenously or intramuscularly. The usual adult dose is recommended as 1-2 g every 12 hours.

For intravenous administration, the product should be constituted and an appropriate quantity of the resulting solution added to an IV container with one of the compatible IV fluids at concentration between 1- 40 mg/mL. The resulting solution should be administrated over approx. 30 minutes (p. 72). The constituted IV solution may be stored up to 24 hours at controlled RT temperature (20°-25°C or 68°-77°F) or 7 days in a refrigerator (2°-4°C or 36°-46°F) (p. 73-74).

For intramuscular use, the product should be constituted with one of the compatible diluents. The product powder is reconstituted with the appropriate diluent by injecting diluent into the vial, shaking vial thoroughly to form solution, then withdrawing entire contents of vial into syringe to equal total labeled dose.

C. Basis for Approvability or Not-Approval Recommendation

Recommended for approval

Following this page, 23 pages withheld in full (b)(4)- Chemistry review #3

33. ESTABLISHMENT INSPECTION – ***Satisfactory***

EES was found acceptable as of 02/02/07.

34. BIOEQUIVALENCE – ***Satisfactory***

Bio was found acceptable as of 12/05/06

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: - ***Satisfactory***

An environmental impact statement is included on page 1195 of the original submission.

cc: ANDA 65-369
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-643/XRuan/6/15/07/

HFD-643/SZuk/

HFD-617/RNguyen/

V:\Chemistry Division III\Team 6\Final Version for DFS Folder\65369.R03.ap.doc

F/T by:

TYPE OF LETTER: Approvable

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-65369	ORIG-1	ORCHID HEALTHCARE	CEFEPIME

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

/s/

CAROLYN F COHRAN
07/22/2010
Signed for Xiumei Ruan

SUSAN ZUK
07/22/2010

MARK A GONITZKE
07/22/2010

Review was not electronically archived in 2007. Archived in July 2010.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-369
Drug Product Name	Cefepime for Injection USP
Strength	500 mg base/vial, 1 g base/vial, and 2 g base/vial
Applicant Name	Orchid Healthcare
Address	US Agent: Orgenus Pharma, Inc. 116 Village Boulevard, Suite 200 Princeton, NJ 08540-5799
Contact Information	Satish Srinivasan, Director Business Development and Operations Phone: 609-951-2209 Fax: 609-951-2213
Submission Date(s)	November 2, 2005
Amendment Date(s)	N/A
Reviewer	Diem-Kieu H. Ngo, Pharm.D.
First Generic	**Yes**

Review of a Waiver Request

I. Executive Summary

This application consisted of waiver requests of *in vivo* bioequivalence study requirements for Cefepime for Injection USP, 500 mg base/vial, 1 g base/vial, and 2 g base/vial. The firm submitted the formulation of the test product for comparison with the RLD product, Bristol Myers Squibb's Maxipime® (Cefepime) Injection, 500 mg base/vial, 1 g base/vial, and 2 g base/vial (NDA 50-679). The route of administration, dosage form, and strength of the test products are the same as those of the RLD. After accounting for overfills and overages in the RLD formulation, the amounts of active and inactive ingredients between the test and reference products are within 4% difference. This small difference is not expected to affect the bioequivalence of the test products. The waivers of *in vivo* bioequivalence study requirements for Cefepime for Injection USP, 500 mg base/vial, 1 g base/vial, and 2 g base/vial, are granted per 21 CFR 320.22(b)(1).

II. Submission Summary

A. Drug Product Information

Test Product	Cefepime for Injection, USP, 500 mg base/vial, 1 g base/vial, and 2 g base/vial
Reference Product	Maxipime® Injection (Cefepime HCl [Arginine Formulation], USP), 500 mg base/vial, 1 g base/vial, and 2 g base/vial
RLD Manufacturer	Bristol Myers Squibb
NDA No.	50-679
RLD Approval Date	Jan 18, 1996
Indication	Treatment of pneumonia, febrile neutropenia, uncomplicated and complicated urinary tract infections, uncomplicated skin and skin structure infections, and complicated intra-abdominal infections.

B. Formulation

(b) (4)

Comments on Formulation:

- The test product formulation provided in the original ANDA submission was incomplete. The firm submitted a complete components and composition statement in its CMC amendment dated 6/16/2006, which was used for the above formulation table.
- Cefepime for Injection, USP is a sterile, dry mixture of Cefepime HCl and L-arginine. Each unit of the drug product contains the Cefepime HC1 equivalent to 500 mg, 1 g or 2 g of Cefepime base. For both the test product and RLD, the API is a sterile blend of Cefepime HCl and L-arginine. This blend is the sole product ingredient. For the test product's API, the L-arginine is added at approximately (b) (4) of Cefepime base, to adjust the pH of the reconstituted solution to 4.0 – 6.0. For the RLD's API, the L-arginine is added at approximately 725 mg/g of Cefepime base.
- (b) (4), the amounts of active and inactive ingredients between the test and reference products are (b) (4). This small difference is not expected to affect the bioequivalence of the test products.

[1] OND Review of NDA 50-679, submission dated June 30, 1992

C. Waiver Requests

Strengths for which waivers are requested	500 mg base/vial, 1 g base/vial, and 2 g base/vial
Regulation cited	21 CFR 320.22(b)(1)
Proportional to strength tested in vivo?	N/A
Waivers granted?	Yes
If not then why?	N/A

The firm's test product is a parenteral drug product intended for administration by injection. The route of administration, dosage form, and strength of the test products are the same as those of the RLD. (b) (4), the amounts of active and inactive ingredients between the test and reference products are (b) (4). Therefore, the waiver requests are granted.

D. Deficiency Comments

None.

E. Recommendations

The Division of Bioequivalence (DBE) agree that the information submitted by Orchid Healthcare demonstrate that its test products, Cefepime for Injection USP, 500 mg base/vial, 1 g base/vial, and 2 g base/vial, fall under the criteria set forth in 21 CFR 320.22(b)(1). From the bioequivalence point of view, the DBE deems the test products bioequivalent to Bristol Myers Squibb's Maxipime® (Cefepime HCl [Arginine Formulation] USP) Injection, 500 mg base/vial, 1 g base/vial, and 2 g base/vial, (NDA 50-679). The waivers of *in vivo* bioequivalence study requirements for the test product are granted.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-369 APPLICANT: Orchid Healthcare

DRUG PRODUCT: Cefepime for Injection, USP, 500 mg base/vial, 1 g base/vial, and 2 g base/vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #65-369
BIOEQUIVALENCE – ACCEPTABLE

Submission Date: November 2, 2005

1. **WAIVER** (WAI)

Strength: 500 mg base/vial
Outcome: AC

2. **WAIVER** (WAI)

Strength: 1 g base/vial
Outcome: AC

3. **WAIVER** (WAI)

Strength: 2 g base/vial
Outcome: AC

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

/s/

S Christopher Jones
12/5/2006 01:27:59 PM
BIOPHARMACEUTICS
signing for Diem K. Ngo

Devvrat Patel
12/5/2006 02:25:16 PM
BIOPHARMACEUTICS
Signing for Kuldeep Dhariwal

Barbara Davit
12/5/2006 04:38:39 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review
Review for HFD-630

March 8, 2007

ANDA: 65-369

Drug Product Name
Proprietary: N/A
Non-proprietary: Cefepime for Injection USP (500mg, 1g, and 2g)
Drug Product Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
Nov. 2, 2005	Nov. 4, 2005	N/A	Jan. 8, 2007

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Orchid Healthcare
Address: Orgenus Pharma, Inc. (US agent)
116 Village Blvd, Suite 200
Princeton, NJ 08540-5799
Representative: Satish Srinivasan
Telephone: 609-951-2209

Name of Reviewer: Rona LeBlanc, Ph.D.
Conclusion: This submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original ANDA

2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product.

3. **MANUFACTURING SITE:**
Orchid Healthcare
Plot Nos. B3-B6 & B11-B14, Sipcot Industrial Park,
Irungattukottai, Sriperumbudur, Kancheepuram District 602 105, India

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile powder, I.V. or I.M injection, 500mg, 1g, and 2g in 20 ml vial.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Pneumonia, febrile neutropenic patients, urinary tract infections, skin infections, intra-abdominal infections.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF-18923: for Cefepime Arginine (sterile); DMF Holder is Orchid.
DMF- (b) (4)
DMF-
DMF-
DMF-18843: Arginine, sterile bulk; DMF holder is Orchid.
DMF-18902: Cefepime, sterile bulk; DMF holder is Orchid.

REMARKS: I reviewed the blue copy of this application.

DMF- (b) (4) was reviewed Jan. 31, 2006 and found adequate for sterility assurance (V:\microrev\DMFreviews (b) (4) nic4a1.doc).

filename: 65-369.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4) .

B. Brief Description of Microbiology Deficiencies – Incomplete information regarding requalification of the (b) (4) ; lack of letter of authorization for DMF-18923.

C. Assessment of Risk Due to Microbiology Deficiencies -

The safety risk associated with the microbiology deficiencies is considered high.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Rona LeBlanc, Ph.D.
Microbiology Team Leader / Neal Sweeney, Ph.D.

C. CC Block

cc:
Field copy

Following this page, 12 pages withheld in full (b)(4)- Microbiology review #2

H. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS

ANDA: 65-369 APPLICANT: Orchid Healthcare

DRUG PRODUCT: Cefepime for Injection (500mg, 1g, 2g)

A. Microbiology Deficiencies:

1. (b) (4)
2.
3.
4.
5.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please consider the inclusion of a compromised positive control vial in future container/closure integrity validation studies to demonstrate that the test can detect a breach in container/closure integrity.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

Neal Sweeney, Ph.D.
Microbiology Team Leader
Office of Generic Drugs

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

/s/

Rona A. Leblanc
4/18/2007 07:50:49 AM
MICROBIOLOGIST

Bonnie McNeal
4/18/2007 11:29:16 AM
MICROBIOLOGIST
Checked for submission link only.

Neal Sweeney
4/20/2007 02:58:06 PM
MICROBIOLOGIST

Product Quality Microbiology Review
Review for HFD-630

April 30, 2007

ANDA: 65-369

Drug Product Name
Proprietary: N/A
Non-proprietary: Cefepime for Injection USP (500mg, 1g, and 2g)
Drug Product Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
Apr. 13, 2007	Apr. 17, 2007	N/A	Apr. 30, 2007

Submission History (for amendments only) –

Submission Date(s)	Microbiology Review #	Review Date(s)
Nov. 2, 2005	1	March 8, 2007

Applicant/Sponsor
Name: Orchid Healthcare
Address: Orgenus Pharma, Inc. (US agent)
116 Village Blvd, Suite 200
Princeton, NJ 08540-5799
Representative: Satish Srinivasan
Telephone: 609-951-2209

Name of Reviewer: Rona LeBlanc, Ph.D.
Conclusion: This submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Amendment

2. **SUBMISSION PROVIDES FOR:** Response to deficiency letter.

3. **MANUFACTURING SITE:**
Orchid Healthcare
Plot Nos. B3-B6 & B11-B14, Sipcot Industrial Park,
Irungattukottai, Sriperumbudur, Kancheepuram District 602 105, India

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile powder, I.V. or I.M injection, 500mg, 1g, and 2g in 20 ml vial.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Pneumonia, febrile neutropenic patients, urinary tract infections, skin infections, intra-abdominal infections.

B. **SUPPORTING/RELATED DOCUMENTS:**
DMF-18923: for Cefepime Arginine (sterile); DMF Holder is Orchid.
DMF- (b) (4)
DMF-
DMF-
DMF-18843: Arginine, sterile bulk; DMF holder is Orchid.
DMF-18902: Cefepime, sterile bulk; DMF holder is Orchid.

REMARKS: I reviewed the blue copy of this application.

filename: 65-369a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies – None identified.

C. Assessment of Risk Due to Microbiology Deficiencies -
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Rona LeBlanc, Ph.D.
Microbiology Team Leader/Neal Sweeney, Ph.D.

C. CC Block
cc:
Field copy

Following this page, 2 pages withheld in full (b)(4)- Microbiology review #1

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please consider the inclusion of a compromised positive control vial in future container/closure integrity validation studies to demonstrate that the test can detect a breach in container/closure integrity.

Applicant response: The Agency's comment has been acknowledged.

Acceptable

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

/s/

Rona A. Leblanc
5/2/2007 03:48:16 PM
MICROBIOLOGIST

Bonnie McNeal
5/2/2007 03:56:12 PM
MICROBIOLOGIST
Checked for submission link only.

Neal Sweeney
5/3/2007 11:11:07 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-369

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date : October 25, 2005

65-369
N-000

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: **Cefepime for Injection USP, 500 mg, 1 g and 2 g**
Abbreviated New Drug Application

Dear Sir/ Madam:

Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Limited) herewith submits an Abbreviated New Drug Application (ANDA) for Cefepime for Injection USP, 500 mg, 1 g and 2 g pursuant to Section 505 (j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, Maxipime® (Cefepime for Injection USP), 500 mg, 1 g and 2 g which is manufactured by Bristol Myers Squibb, USA the holder of the approved application and which is listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).

Cefepime for Injection USP, 500 mg, 1 g and 2 g have been developed and will be manufactured, tested and packaged by Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.), Irungattukottai - 602 105, INDIA manufacturing facility, in accordance with 21 CFR § 210 and 211.

The manufacturer of the drug substance used to produce the ANDA of this product is Orchid Chemicals & Pharmaceuticals Limited, Plot No.: 138-149, SIDCO Industrial Estate, Allathur Tq., Kancheepuram District – 603 110, Tamilnadu, INDIA.

The test data of Orchid's Cefepime for Injection USP 500 mg, 1 g and 2 g are comparable to that of Maxipime® (Cefepime for Injection, USP)

Tel : (91) - 4111 - 256793, 256794, 256815 Fax : (91) 4111 - 256816 E-mail : corporate@orchidpharma.com
Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,
Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Food and Drug Administration
Cefepime for Injection USP, 500 mg, 1 g and 2 g
Abbreviated New Drug Application

A request for waiver of Bioavailability / Bioequivalence study requirements for Cefepime for Injection USP, 500 mg, 1 g and 2 g is submitted, as it is intended for administration as parenteral solution after reconstitution. It contains the same active ingredient in the same concentration as that for the innovator product Maxipime® (Cefepime for Injection, USP), and there are no excipients contained in the formulation.

Cefepime for Injection USP, 500 mg, 1 g and 2 g are stable and a two-year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C ± 2°C/ 75% ± 5% Relative Humidity) in the fill size of the container / closure system package proposed for marketing. The stability studies were conducted under a stability protocol that is in conformance with the current FDA Stability guidelines.

The archival, review and field copies of this ANDA are submitted in different volumes as indicated below.

ANDA Volumes	**Archival Copy**	**Review Copy – CMC**	**Review Copy – Bioequivalence**	**Field Copy**
	ANDA Sections (As per table of contents)			
Vol - I	Sec I – X	Sec I – X (excluding Sec-VI)	Sec I – VI	Sec I – X (excluding Sec-VI)
Vol - II	Sec – XI - XII	Sec – XI - XII	-	Sec – XI - XII
Vol - III	Sec – XIII - XXI	Sec – XIII - XXI	-	Sec – XIII - XXI
Vol - IV	Sec – XXII (Contd.,)	Sec – XXII (Contd.,)	-	Sec – XXII (Contd.,)
Vol - V	Sec – XXII	Sec – XXII	-	Sec – XXII

Tel : (91) - 4111 - 256793, 256794, 256815 Fax : (91) 4111 - 256816 E-mail : corporate@orchidpharma.com
Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Food and Drug Administration
Cefepime for Injection USP, 500 mg, 1 g and 2 g
Abbreviated New Drug Application

The dosage form, route of administration, active ingredient, potency and labeling (except DESCRIPTION & HOW SUPPLIED) for Cefepime for Injection USP, 500 mg, 1 g and 2 g are same as those for Maxipime® (Cefepime for Injection USP), 500 mg, 1 g and 2 g.

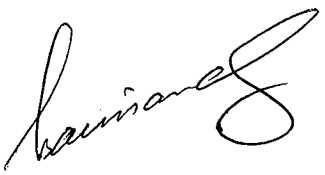
The product will be marketed by Apotex Corp. Weston, FL 33326.

The labeling information in Section IV and Section V of this ANDA is also submitted as an electronic copy (CD) as required by the agency.

Pursuant to 21 CFR 314.440 (a) (4), a third copy of this application is also enclosed. This is the required field copy and we certify that it is a true copy of the technical section as described in 21 CFR 314.50 (d) (1).

Please contact our U.S. agent Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609) -951-2213, if you have any questions concerning this submission.

Sincerely,



Sumant Baukhandi, Ph.D.,
President – Regulatory Affairs & Quality Affairs,
Orchid Healthcare
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.,)
Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) – 602 105
Kancheepuram District, Tamil Nadu, India.
Phone: 91-44-27156292 Fax: 91-44-27156816
e-mail: sumant@orchidpharma.com

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 65-369 **FIRM NAME:** ORCHID HEALTHCARE

RELATED APPLICATION(S): NA

First Generic Product Received? YES

DRUG NAME: CEFEPIME

DOSAGE FORM: FOR INJECTION USP, 500 MG, 1 GRAM, 2 GRAM

Bio Assignments:		
☒ BPH	☐ BCE	☒ Micro Review
☐ BST	☐ BDI	

Random Queue: 6

Chem Team Leader: Susan Zuk PM: Ryan Nguyen Labeling Reviewer: Jacqueline Council

Letter Date: OCTOBER 25, 2005	**Received Date:** NOVEMBER 04, 2005
Comments: EC- 3 YES **On Cards:** YES **Therapeutic Code:** 4010300 CEPHALOSPORINS SYSTEMIC	
Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES	
Methods Validation Package (3 copies PAPER archive) **NO** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Zadecky, Leo **Date 01-04-06**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 10 Jan 2006
ADDITIONAL COMMENTS REGARDING THE ANDA: **See T-con 1)USP designation on 356h missing, 2) dmf auth for api Missing 3) Dmf for container closure seal missing** See 1-10-06 correspondence	
Top 200 Drug Product:	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES yes, note usp not in established field	☒
Sec. II	**Basis for Submission** **NDA# : 50-679** Ref Listed Drug: MAXIPIME Firm: BRSTOL MYERS SQUIBB ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: I 2. Expiration of Patent: NA A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use y 2. Active ingredients y 3. Route of administration y 4. Dosage Form y 5. Strength y	☒
Sec. V	**Labeling** (E-Submission in EDR) 1. 4 copies of draft (each strength and container) or 12 copies of FPL y 2. 1 RLD label and 1 RLD container label y 3. 1 side by side labeling comparison with all differences annotated and explained y 4. Was a proprietary name request submitted? no (	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): YES** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) YES q1 / q2 **4. Lot Numbers of Products used in BE Study(ies):** n/a **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: NO	☐

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☒
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation YES 2. Inactive ingredients as appropriate None	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers YES b. Type II DMF authorization letters or synthesis Orchid dmf 18923, no auth letter provided c. COA(s) specifications and test results from drug substance mfgr(s) y d. Applicant certificate of analysis y e. Testing specifications and data from drug product manufacturer(s) y f. Spectra and chromatograms for reference standards and test samples y g. CFN numbers 2. **Inactive Ingredients NONE** a. Source of inactive ingredients identified n/a b. Testing specifications (including identification and characterization) n/a c. Suppliers' COA (specifications and test results) n/a d. Applicant certificate of analysis n/a	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories NONE** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES (b) (4) 3.If sterile product: (b) (4) yes 4.Filter validation (if aseptic fill) n/a powder for INJ 5. Reprocessing Statement Yes	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation yes (b) (4) 2. In-process Controls - Specifications and data y	☒

Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) y 2. Components Specification and Test Data (Type III DMF References) Yes 3. Packaging Configuration and Sizes y 4. Container/Closure Testing y 5. Source of supply and suppliers address y	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data y 2. Certificate of Analysis for Finished Dosage Form y	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted y 2. Post Approval Commitments y 3. Expiration Dating Period 24 months requested 4. Stability Data Submitted yes a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch Yes	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Yes 2. Finished Dosage Form YES 3. Same lot numbers Yes	☒
Sec. XVII	**Environmental Impact Analysis Statement** Yes waiver claimed under 21 cfr 25.31 a	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) YES	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe

ANDA 65-369 Final Check List for Branch Chief

- ✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.
- ✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.
- ✓ 3) Check for gross errors in letter.
- ✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- ✓ 5) Check address and contact person on letter vs. 356h.
- ✓ 6) Check for any t-cons and verify date and correspondence date.
- ✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- ✓ 8) Check for any comments or problems raised by reviewer on Check List.
- ✓ 9) If first generic, copy BE review and file.
- ✓ 10) Sign Check List.
- ✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. MAXAPTMA
- N/A 12) Check for MOU patents
- ✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- ✓ 14) Review Basis for Submission.
- ✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.
- ✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- ✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.
- ✓ 18) Pull USP information. (USP ✓ yes ____ no)
- ✓ 19) Final Grammar review on letter.
- ✓ 20) Verify information in OGD Patent Tracking System.
- ✓ 21) EES slip.
- ✓ 22) Document in record book.

Signature [signature] date 10 Jan 2006

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: January 10, 2006

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AC

Reference : **TELEPHONE AMENDMENT**

- **Cefepime for Injection USP 500 mg, 1 g and 2 g**
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated, January 06, 2006

Kind attention: Dr. Leo Zadecky, CDER (FDA)

In response to the agency's telephonic communication dated January 06, 2006 for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Limited), hereby submits a TELEPHONE AMENDMENT to include the following information:

A. Telephone Deficiencies:

Agency Comment:

1. Provide provide the DMF # for the API [Cefepime + Arginine (Sterile Bulk)]

Orchid Response:

The DMF # for the API [Cefepime + Arginine (Sterile Bulk)] is 18923. The letter of access from the drug substance (API) manufacturer pertaining to the same is provided in ***Exhibit – 1.***

RECEIVED
JAN 11 2006
OGD/CDER

Tel : (91) - 4111 - 256793, 256794, 256815 Fax : (91) 4111 - 256816 E-mail : corporate@orchidpharma.com
Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Agency Comment:

2. **Please provide DMF Authorization for the flip-off seal from** (b) (4) (b) (4).

Orchid Response:

The flip-off seal is the secondary packaging component and does not come into direct contact with the drug product. The flip-off seals are supplied by (b) (4) (b) (4). The detailed specifications with dimensional drawings of the flip-off seals are part of the original submission (Kindly refer Section XIII, page 816-818, 825-827). (b) (4) does not have the DMF for the seals.

Agency Comment:

3. **Please provide corrected 356h. The established name needs to be entered showing "USP".**

Orchid Response:

As recommended by the agency, the corrected 356h form with appropriate reference to the established name showing "USP" is provided as a part of response to this telephone deficiency.

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at 609-951-2209 or by fax at 609-951-2213

Sincerely,

10/01/06

Imtiyaz Basade
Vice President – Regulatory Affairs
Orchid Healthcare,
(A Division of Orchid Chemicals & Pharmaceuticals Limited)
Plot Nos. B3-B6 & B11-B14,
SIPCOT Industrial Park, Irungattukottai,
Kancheepuram District – 602 105
Tamil Nadu, INDIA.
Phone: 91-44-27156292 Fax: 91-44-27156816
e-mail: imtiyazb@orchidpharma.com

ANDA 65-369

JAN 11 2006

Orgenus Pharma, Inc.
U.S.Agent For: Orchid Healthcare
Attention: Mr. Satish Srinivasan
116 Village Boulevard, Suite 200
Princeton, NJ 08540-5799

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated January 6, 2006 and your correspondence dated January 10, 2006.

NAME OF DRUG: Cefepime for Injection USP, 500 mg, 1 g and 2 g per vial

DATE OF APPLICATION: October 25, 2005

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 4, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ryan Nguyen
Project Manager
301-827-5739

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 65-369

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/
HFD-143/OIM/DRM

Endorsement:
HFD-615/M.Shimer, Chief, RSB_____date
HFD-615/L.Zadecky, CSO_____date

Word File
\\CDSNAS\OGDS11\FIRMSNZ/Orchidhealthcare/LTRS&REV/65369.ACK

F/T

ANDA Acknowledgment Letter!

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: 16 June, 2006

MINOR AMENDMENT

ORIG AMENDMENT
a/AM

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
JUN 21 2006
OGD / CDER

Reference: **MINOR AMENDMENT (CMC)**

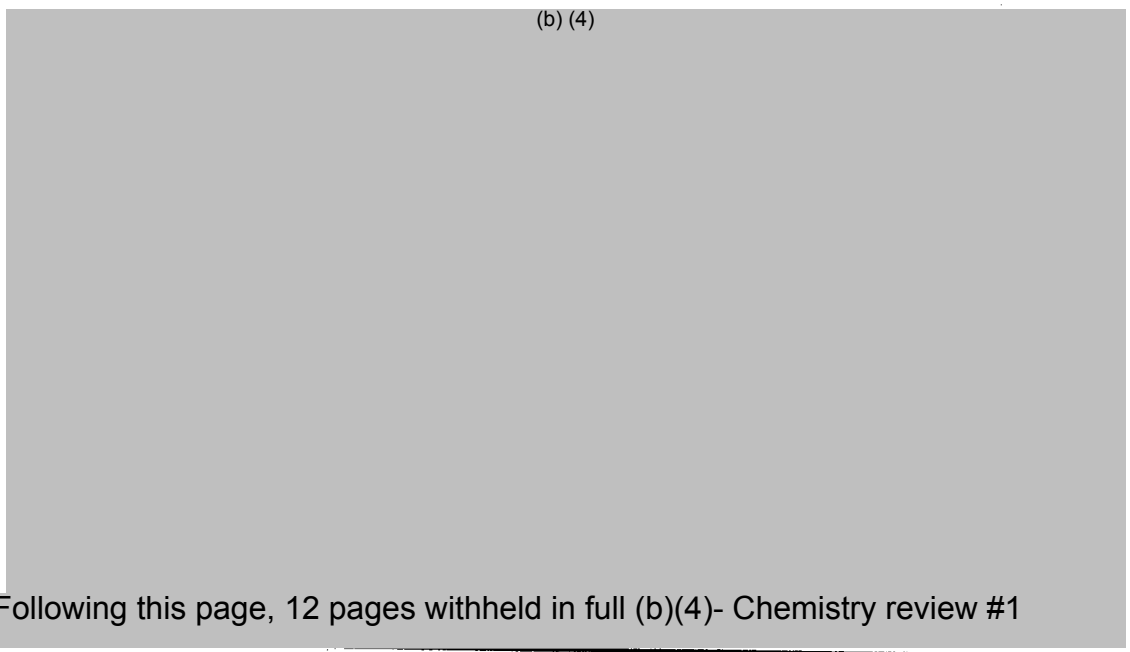
- **Cefepime for Injection USP 500 mg, 1 g and 2 g**
  Abbreviated New Drug Application, **ANDA # 65-369**
- FDA Deficiency letter dated, May 10, 2006

Kind attention: Dr. Ryan Nguyen, Project manager, OGD, CDER, FDA

In response to the Agency's deficiencies letter dated May 10, 2006 for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.), hereby submits a MINOR AMENDMENT to include the following information:

A. Chemistry Deficiencies:

(b) (4)



Following this page, 12 pages withheld in full (b)(4)- Chemistry review #1

Tel : (91)-44-27156793, 27156794 Fax : (91)-44-27156816 E-mail : corporate@orchidpharma.com
Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

recommended that you also contact the drug manufacturer for the specification update.

Orchid's Response:

We acknowledge Agency's comment. The DMF holder has informed us that the response to DMF deficiencies has been submitted to the Agency. A copy of the letter is enclosed in **Exhibit-12.**

Agency's Comment:

2. If available, please provide update long-term stability data for the drug product in your amendment.

Orchid's Response:

The updated Long term stability data has been provided in **Exhibit-13.**

Agency's Comment:

3. The application is currently being reviewed with respect to sterility assurance and labeling issues, any comments be sent in separate communications.

Orchid's Response:

We acknowledge Agency's comments.

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

June 16, 2006

Imtiyaz Basade
Vice President – Regulatory Affairs
Orchid Healthcare
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.)

MINOR AMENDMENT

ANDA 65-369

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

SEP 08 2006

APPLICANT: Orchid Healthcare TEL: 609-951-2209

ATTN: Satish Srinivasan FAX: 609-951-2213

FROM: Ryan Nguyen, Pharm.D. PROJECT MANAGER: (301) 827-5737

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 2, 2005, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cefepime for Injection USP, 500 mg, 1 g, and 2 g.

Reference is also made to your amendment dated June 16, 2006.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachment (__1__ page). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **65-369** APPLICANT: **Orchid Healthcare**

DRUG PRODUCT: **Cefepime for Injection USP, 500 mg, 1 g and 2 g**

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies: SEP 08 2006

1. The product label indicates that, when reconstituted, the color of solution may range from colorless to amber. We request that you add a specification for color of solution to release and stability testing protocols. A quantitative color test should be utilized rather than a visual test.

2. The DMF #18923 for Sterile blend of Cefepime HC1 and L-Arginine remains inadequate. A letter has been forwarded to the DMF holder. Please be aware that this application cannot be approved until all deficiencies regarding to the DMF are satisfactorily resolved. It is recommended that you also contact the drug manufacturer for the DMF update.

Sincerely yours,

Vilayat A. Sayeed Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: September 16, 2006

MINOR AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

N/AM

Reference: **MINOR AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Minor deficiencies (Chemistry) letter dated September 08, 2006.

Kind attention: Dr. Ryan Nguyen, Project Manager, OGD, CDER, FDA

Dear Sir:

In response to the Agency's minor deficiencies letter dated September 08, 2006 for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.), hereby submits a MINOR AMENDMENT to include the following information:

A. Minor Deficiencies (Chemistry):

Agency's Comment:

1. **The product label indicates that, when reconstituted, the color of solution may range from colorless to amber. We request that you add a specification for color of solution to release and stability testing protocols. A quantitative color test should be utilized rather than a visual test.**

Orchid's Response:

As per Agency's recommendation the test for color of solution is included in release and stability testing specifications. A copy of revised release specifications and stability testing specifications along with the revised test procedures to include the same are provided in ***Exhibit – 1*** and ***Exhibit – 2*** respectively.

The test results for the color of solution for Cefepime for Injection USP 500 mg, 1 g and 2 g performed on the on-going stability samples are provided in ***Exhibit – 3.***

Tel : (91)-44-27156793, 27156794 Fax : (91)-44-27156816 E-mail : corporate@orchidpharma.com
Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

2. **The DMF # 18923 for Sterile blend of Cefepime HCl and L-Arginine remains inadequate. A letter has been forwarded to the DMF holder. Please be aware that this application cannot be approved until all deficiencies regarding to the DMF are satisfactorily resolved. It is recommended that you also contact the drug manufacturer for the DMF update.**

Orchid's Response:

The drug substance manufacturer (Orchid Chemicals & Pharmaceuticals Ltd.) for sterile blend of Cefepime HCl and L-Arginine has informed us that the response to the DMF deficiencies was submitted to the Agency on September 7, 2006.

A copy of the cover letter submitted to the FDA by the drug substance manufacturer for the response to the DMF deficiencies is provided in ***Exhibit – 4.***

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

September 16, 2006

Imtiyaz Basade
Vice President – Regulatory Affairs
Orchid Healthcare,
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.)

Orchid HEALTHCARE

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: November 8, 2006

TELEPHONE AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Reference: **TELEPHONE AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated November 07, 2006.

Kind attention: Dr. Susan Zuk, Team Leader, OGD, CDER, FDA

Dear Madam:
In response to the Agency's Telephone Deficiency communication (received telephonically by Ms. Diana Wilk from Dr. Susan Zuk) for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this TELEPHONE AMENDMENT to include the following information:

Telephone Deficiency (Chemistry):

(b) (4)

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

RECEIVED
DEC 2 8 2006
OGD / CDER

November 08, 2006

Imtiyaz Basade
Vice President – Regulatory Affairs

Orchid HEALTHCARE

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: February 09, 2007

LABELING AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Reference: **LABELING AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Labeling deficiency letter dated February 08, 2007 enclosed.

Kind Attention: Dr. William Peter Rickman, Director, Division of Labeling and Program Support

Dear Sir,

In response to the Agency's labeling deficiency letter for the above referred ANDA of Cefepime for injection USP, 500 mg, 1g and 2 g, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.) hereby submits a LABELING AMENDMENT to include the following information:

Labeling Deficiencies:

1. CONTAINER- 500 mg, 1 gram and 2 gram vials

Agency's Comment:

a. Front panel

i. Add a comma prior to "USP".

Orchid's Response:

As recommended by the Agency, a comma has been included prior to "USP" on the front panel of all the container labels. Please refer ***Exhibit-1***.

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Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

ii. Increase the size of the asterisk.

Orchid's Response:

As recommended by the Agency, the size of the asterisk has been increased on the front panel of all the container labels. Please refer ***Exhibit-1***.

Agency's Comment:

iii. Print, "Single-Dose Vial" in bold print.

Orchid's Response:

As recommended by the Agency, the term "**Single-Dose Vial**" is printed in bold print on the front panel of all the container labels. Please refer ***Exhibit-1***.

Agency's Comment:

b. Side panel

i. To meet the USP labeling requirement add the statement, "Dilute with a suitable parenteral vehicle prior to intravenous infusion" as the first sentence on the side panel.

Orchid's Response:

The statement, "Dilute with a suitable parenteral vehicle prior to intravenous infusion" has been included as the first sentence on the side panel of all the container labels. Please refer *Exhibit-1*.

Agency's Comment:

ii. Increase the size of the asterisk.

Orchid's Response:

As recommended by the Agency, the size of the asterisk has been increased on the side panel of all the container labels. Please refer ***Exhibit-1***.

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

iii. If space permits add "Usual Dosage" prior to the statement. "Read ... precautions".

Orchid's Response:

The term "Usual Dosage" has been included prior to the statement, "Read ... precautions". Please refer ***Exhibit-1***.

Agency's Comment:

c. Further differentiate the color of the strengths for the 500 mg and 2 grams labels.

Orchid's Response:

The color of the strengths for the 500 mg and 2 grams labels has been differentiated. Please refer ***Exhibit-1***.

2. CARTON: 500 mg, 1 gram and 2 grams - Individual and 10s

Agency's Comment:

a. See comments under CONTAINER.

Orchid's Response:

We hereby notify the Agency that the comments related to container has been complied in Carton. Please refer ***Exhibit-2.***

Agency's Comment:

b. To be consistent with the innovator, revise "_____ x_____ g vial" to read "1 Box - _____ vial(s)".

Orchid's Response:

The statement "_____ x_____ g vial" has been revised to read as, "1 Box -_____ vial(s)". Please refer ***Exhibit-2.***

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

c. If space permits increase the size of the statement, "RETAIN IN CARTON UNTIL TIME OF USE" on the front and top panels. If space does not permit, print the statement using a different color and / or italic print.

Orchid's Response:

The statement, "RETAIN IN CARTON UNTIL TIME OF USE" on the front and top panels has been printed in italic print. Please refer ***Exhibit-2.***

Agency's Comment:

d. 500 mg

Add "SINGLE DOSE VIAL (S)" in bold uppercase print on the front panel.

Orchid's Response:

The statement "SINGLE DOSE VIAL (S)" has been included in bold uppercase print on the front panel. Please refer ***Exhibit-2.***

2. INSERT

Agency's Comment:

a. GENERAL COMMENTS

You may omit the "USP" designation following the established name, except in the TITLE, DESCRIPTION and HOW SUPPLIED sections.

Orchid's Response:

The "USP" designation following the established name, has been deleted except in the TITLE, DESCRIPTION and HOW SUPPLIED sections. Please refer ***Exhibit-3.***

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

b. DESCRIPTION

Replace "Cefepime hydrochloride" with "Cefepime for Injection" except In the third and the fourth paragraphs, [i.e, fourth paragraph "... cefepime hydrochloride and L-arginine of the DESCRIPTION section. It..."].

Orchid's Response:

As recommended by the Agency, "Cefepime hydrochloride" has been replaced with 'Cefepime for Injection" except in the third and the fourth paragraphs. Please refer *Exhibit-3.*

Agency's Comment:

c. ADVERSE REACTIONS

i. Table 10

To be consistent with the innovator, print "Cefepime ... Regimens" in between "Adverse ... Reactions" and "Clinical ... America". See below.

Adverse ... Reactions
Cefepime ... Regimens
Clinical ... America

ii. Table 11

To be consistent with the innovator print "Cefepime ... Regimens" in between "Adverse ... Changes" and "Clinical ... America". See below

Adverse ... Changes
Cefepime ... Regimens
Clinical ... America

Orchid's Response:

The comments provided by the Agency under "Adverse Reactions" section for Table 10 and Table 11 have been complied. Please refer ***Exhibit-3***.

Plot No. B3-B6 & B11-B14
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Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

d. DOSAGE AND ADMINISTRATION

i. Table 12

Add a blank line space between each "Site and Type of Infection".

Orchid's Response:

A blank line space between each "Site and Type of Infection" has been provided in Table 12. Please refer ***Exhibit-3.***

Agency's Comment:

ii. Administration

For Intravenous Administration

A) **To meet the USP labeling requirement add the statement, "Dilute with a suitable parenteral vehicle prior to intravenous infusion" as the first sentence.**

Orchid's Response:

The statement "Dilute with a suitable parenteral vehicle prior to intravenous infusion" has been included as the first statement under "Administration" section. Please refer ***Exhibit-3.***

Agency's Comment:

B) **Revise the first sentence to read, "...IV fluids in the Compatibility and Stability subsection".**

Orchid's Response:

The first sentence under "Administration" section has been revised to read as "...IV fluids in the **Compatibility and Stability** subsection". Please refer ***Exhibit-3***.

Plot No. B3-B6 & B11-B14
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Kancheepuram District, Tamil Nadu, INDIA.

Agency's Comment:

C) We note that omitted the second paragraph, "Intermittent ... other solution". This paragraph should be retained.

Orchid's Response:

The second paragraph "Intermittent ... other solution" has been retained. Please refer ***Exhibit-3.***

Agency's Comment:

e. HOW SUPPLIED

a. To be consistent with the innovator, print the storage statement in uppercase bold print.

Orchid's Response:

The storage statement has been printed in uppercase bold print. Please refer ***Exhibit-3.***

Agency's Comment:

b. We note that your flip cap color, is (b) (4) for both your 1 g and 2 g products. Please differentiate the color of the flip off caps.

Orchid's Response:

We hereby notify the Agency that the flip cap color for 1 g and 2 g has been changed to green and violet respectively.

As recommended by the Agency and in accordance with the 21 CFR 314.94(a)(8)(iv), a side-by-side comparison of the proposed package insert labeling with the reference listed drug's package insert with all differences annotated and explained, is provided in ***Exhibit – 4***. This side-by-side comparison is also included in electronic format in the labeling CD.

The revised final printed container label, carton and package insert labeling in the electronic format as required by the Agency have been included in the enclosed Compact Disk (CD) as PDF and MS-Word files.

Orchid HEALTHCARE

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

IAsade. February 09, 2007.

Imtiyaz Basade
Vice President – Regulatory Affairs
Orchid Healthcare,
(A Division of Orchid Chemicals & Pharmaceuticals Ltd.)

Orchid HEALTHCARE

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Date: March 20, 2007

TELEPHONE LABELING AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Reference: **TELEPHONE LABELING AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated March 19, 2007

Kind attention: Dr. Jackie Counsel, labeling division, OGD, CDER, FDA

Dear Madam:

In response to the Agency's Telephone Deficiency communication (received telephonically by Mr. Satish Srinivasan from Dr. Jackie Counsel) for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this TELEPHONE LABELING AMENDMENT to include the following information:

Telephone Deficiency (Labeling):

Agency's Conversation Note:

MAR 2 2 2007
OGD / CDER

With reference to the response (labeling amendment) dated February 09, 2007 to the previous labeling deficiency, the Agency had requested for change in color of the flip off caps for 1 g and 2 g strengths and keeping them distinct. This was complied by the applicant by changing the color to green for 1 g and violet for 2 g strength.

Kindly submit paper documentation to clearly confirm this change.

Orchid's Response:

As per Agency's recommendation, the paper copies (drug product release specifications) to confirm the change of color of the flip off caps to green for 1 g strength and violet for 2 g strength are provided in ***Exhibit – 1***.

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

R. Sanakara Rama
March 20, 2007

for **Imtiyaz Basade**
Vice President – Regulatory Affairs

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Orchid HEALTHCARE

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Date: April 13, 2007

RESPONSE TO MICROBIOLOGY DEFICIENCIES

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AS

Reference: **RESPONSE TO MICROBIOLOGY DEFICIENCIES**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**

- Microbiology Deficiencies letter dated April 12, 2007

Kind attention: Dr. Bonnie McNeal, Microbiology Project Manager, OGD, CDER, FDA

Dear Madam:

In response to the Agency's Microbiology Deficiencies letter dated April 12, 2007 for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this RESPONSE TO MICROBIOLOGY DEFICIENCIES to include the following information:

A. Microbiology Deficiencies:

(b) (4)

[redacted]

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OGD / CDER

Following this page, 5 pages withheld in full (b)(4)- Microbiology review #1

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Website : www.orchidpharma.com Health Portal : www.healthorchid.com

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please consider the inclusion of a compromised positive control vial in future container/closure integrity validation studies to demonstrate that the test can detect a breach in container/closure integrity.

Orchid's Response:

We acknowledge the Agency's comment regarding the inclusion of a compromised positive control vial in the future container/closure integrity validation studies to demonstrate that the test can detect a breach in container/closure integrity.

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

I Basade April 13, 2007

Imtiyaz Basade
Vice President – Regulatory Affairs

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: May 14, 2007

TELEPHONE AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Reference: **TELEPHONE AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated May 10, 2007

Kind attention: Ms. Susan Zuk, Ph.D., Team Leader, OGD, CDER, FDA

Dear Madam:

In response to the Agency's Telephone Deficiency communication (received telephonically from Ms. Susan Zuk) for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this TELEPHONE AMENDMENT to include the following information:

Telephone Deficiency (CMC):

Agency's Conversation Note:

Kindly provide the justification how (b) (4) ;

(b) (4)

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Orchid's Response:

(b) (4)

Following this page, 1 page withheld in full (b)(4)

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,
Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

(b) (4)

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

May 14, 2007

Imtiyaz Basade
Vice President – Regulatory Affairs

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Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. 83-86 & 811-814
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: May 21, 2007

TELEPHONE AMENDMENT

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Reference: **TELEPHONE AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated May 17, 2007

Kind attention: Ms. Susan Zuk, Ph.D., Team Leader, OGD, CDER, FDA

Dear Madam:

In response to the Agency's Telephone Deficiency communication (received telephonically from Ms. Susan Zuk) for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this TELEPHONE AMENDMENT to include the following information:

Telephone Deficiency (CMC):

Agency's Conversation Note:

(b) (4)

Orchid's Response:

(b) (4)

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Orchid HEALTHCARE

Plot No. B3-B6 & B11-B14
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

(b) (4)

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

21/5/2007

Imtiyaz Basade
Vice President – Regulatory Affairs

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Website : www.orchidpharma.com Health Portal : www.healthorchid.com

Orchid HEALTHCARE
A Division of Orchid Chemicals & Pharmaceuticals Ltd.,

Plot No. 83-86 & 811-814
Sipcot Industrial Park, Irungattukottai,
Sriperumbudur (TK) - 602 105.
Kancheepuram District, Tamil Nadu, INDIA.

Date: June 14, 2007

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: **TELEPHONE AMENDMENT**

- Cefepime for Injection USP, 500 mg, 1 g and 2 g
  Abbreviated New Drug Application, **ANDA # 65-369**
- Telephone deficiency communication dated June 14, 2007

Kind attention: Ms. Susan Zuk, Ph.D., Team Leader, OGD, CDER, FDA

Dear Madam:

In response to the Agency's Telephone Deficiency communication (received telephonically from Ms. Susan Zuk) for the above referred ANDA, Orchid Healthcare (A Division of Orchid Chemicals & Pharmaceuticals Ltd.,) hereby submits this TELEPHONE AMENDMENT to include the following information:

Telephone Deficiency (CMC):

Agency's Conversation Note:

Please provide the updated long term stability data especially to observe the results for N-methylpyrrolidine (NMP) content.

Orchid's Response:

As per Agency's recommendation, the updated long term stability data for Cefepime for Injection USP, 500 mg, 1 g and 2g is provided in Exhibit-1, Exhibit-2 and Exhibit-3 respectively.

As can be seen from the stability data the level of N-methylpyrrolidine is well below the USP limit of NMT 1.0%.

Should you have any questions on this submission or need any clarifications, please contact our US agent, Mr. Satish Srinivasan at (609)-951-2209 or by fax at (609)-951-2213.

Sincerely,

14/6/2007

Imtiyaz Basade
Vice President – Regulatory Affairs

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-369 Applicant Orchid Healthcare
Drug Cefepime for Injection USP Strength(s) 500 mg/vial, 1 g/vial, and 2 g/vial

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: | **DRAFT Package** | **FINAL Package**

1. **Martin Shimer**
   Chief, Reg. Support Branch
   Date 4 May 2007 | Date 6/18/07
   Initials MHS | Initials rlw/for
   Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
   Determ. of Involvement? Yes ☐ No ☒
   Pediatric Exclusivity System
   RLD = _____ NDA# 50-679
   Patent/Exclusivity Certification: Yes ☒ No ☐
   Date Checked N/A
   If Para. IV Certification- did applicant
   Nothing Submitted ☐
   Notify patent holder/NDA holder Yes ☐ No ☐
   Written request issued ☐
   Was applicant sued w/in 45 days: Yes ☐ No ☐
   Study Submitted ☐
   Has case been settled: Yes ☐ No ☐
   Date settled:
   Is applicant eligible for 180 day
   Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
   Date of latest Labeling Review/Approval Summary _____
   Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
   Type of Letter: Full Approval
   Comments: No patents or exclusivities protecting the RLD. Therefore, the ANDA is eligible for Full Approval.

2. Project Manager, Ryan Nguyen Team6
   Review Support Branch
   Date _____ | Date _____
   Initials _____ | Initials _____

   Original Rec'd date 10/25/05
   Date Acceptable for Filing 11/04/05
   Patent Certification (type) 1
   Date Patent/Exclus.expires
   Citizens' Petition/Legal Case Yes ☐ No ☒
   (If YES, attach email from PM to CP coord)
   First Generic Yes ☒ No ☐
   Priority Approval Yes ☒ No ☐
   (If yes, prepare Draft Press Release, Email it to Cecelia Parise)
   Acceptable Bio review tabbed Yes ☐ No ☒
   Bio Review Filed in DFS: Yes ☒ No ☐
   Suitability Petition/Pediatric Waiver
   Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
   Previously reviewed and tentatively approved ☐ Date _____
   Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
   Comments:

   EER Status Pending ☐ Acceptable ☒ OAI ☐
   Date of EER Status 02/02/07
   Date of Office Bio Review 12/05/06
   Date of Labeling Approv. Sum 03/23/07
   Date of Sterility Assur. App. 05/03/07
   Methods Val. Samples Pending Yes ☐ No ☒
   MV Commitment Rcd. from Firm Yes ☐ No ☒
   Modified-release dosage form: Yes ☐ No ☒
   Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement
   Reviewer:
   Date 5/8/07
   Name/Initials RTN for JC

   Labeling Team Leader:
   Date 5/8/07
   Name/Initials RTN for LG

   Comments:

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐
   OGD Regulatory Counsel, Post-MMA Language Included ☐
   Comments: N/A. No patents listed in the "Orange Book."
   Date 6/18/07
   Initials rlw/for

5. Div. Dir./Deputy Dir.
   Chemistry Div. I II OR III
   Comments: cmc acceptable
   Date 5/30/07
   Initials VAS

6. Frank Holcombe **First Generics Only** Date 6/15/07
Assoc. Dir. For Chemistry Initials RR
Comments: (First generic drug review)
CMC acceptable - For Frank, Radhika

7. Vacant Date _____
Deputy Dir., DLPS Initials _____
RLD = Maxipime for Injection 500 mg (base), 1 gram (base), and 2 grams (base)/vial
Bristol Myers Squibb Co. Pharm. Research Institute
NDA 50-679 (001, 002, 003)

8. Peter Rickman Date 6/18/07
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence waiver granted under 21 CFR 320.22(b)(1). Drug product is "Q&Q" to the RLD. Bio endorsed in DFS 12/5/06.

Sterility/Microbiology found acceptable for approval 5/3/07 (Micro Review #2) - in DFS.

FPL found acceptable for approval 3/23/07, as endorsed 5/8/07, above.

CMC found acceptable for approval (Chemistry Review #3) - in DFS. First-generic CMC audit completed.

OR

8. Robert L. West Date 6/18/07
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 2/2/07 (Verified 6/18/07). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

This drug product does not meet the criteria for a press releass.

This ANDA is recommended for approval.

9. Gary Buehler Date 6/18/07
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Roberta Szydlo Date 6/18/07
Review Support Branch Initials RTS

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:20 Time notified of approval by phone
3:20 Time approval letter faxed

FDA Notification:

06/18/07Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
06/18/07Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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

/s/

Roberta Szydlo
6/18/2007 03:36:06 PM