

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**50-821**

**PHARMACOLOGY REVIEW(S)**

**Pharmacology/Toxicology Review  
Resubmission of NDA 50-821  
Cefepime for Injection USP and Dextrose Injection USP  
in the Duplex® Container, 1 g and 2 g**

**DATE:** 11/12/09

**TO:** J. Christopher Davi, M.S.  
Project Manager, DAIOP  
and  
File, NDA 50-821

**FROM:** Amy L. Ellis, Ph.D.  
Pharmacologist, DAIOP

**THROUGH:** Wendelyn Schmidt  
Supervisory Pharmacologist, DAIOP

**RE:** Pharmacology/Toxicology Labeling Comments for Cefepime for Injection USP  
and Dextrose Injection USP in the Duplex® container, 1g and 2g (NDA 50-821)

As stated in my previous memo, dated 5/5/09, NDA 50-821 does not require a pharmacology/toxicology review. The sponsor did not conduct any additional nonclinical toxicology studies to support the current NDA. The Division agreed that nonclinical studies would not be necessary as long as there are no impurities or degradation products in Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container that exceed ICH qualification threshold levels or the levels in comparable marketed products such as Maxipime®. The Chemistry Reviewer has not informed the pharmacologist that there are impurities or degradation products in the current product that require qualification via nonclinical testing.

The pharmacologist still has no objection to the approval of NDA 50-821 for Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container, provided that the Chemistry Reviewer agrees with the sponsor's assessment that the product contains no impurities or degradation products that need to be qualified via nonclinical testing. The label for this product should be consistent with the labels for Maxipime® (NDA 50-679), Cefepime Injection in GALAXY container (NDA 50-817), and other comparable cefepime products. The sponsor should be notified that the Maxipime® label was revised in March 2009 (see the Daily Med Website <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9923#nmlm34089-3>) and they should make the appropriate changes in the label for Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container to make it consistent with the innovator label. The dose multiples for the animal data described in the **Pregnancy and Carcinogenesis, Mutagenesis, Impairment of Fertility** sections of the label have changed, as has the description of the genotoxicity data. Thus, these sections should read as follows:

## **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 (1.6 times the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis) or to mice at doses up to 1200 mg/kg (approximately equal to the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis) or to rabbits at a dose level of 100 mg/kg (0.3 times the recommended maximum human dose calculated on a mg/m<sup>2</sup> 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.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No animal carcinogenicity studies have been conducted with cefepime. In chromosomal aberration studies, cefepime was positive for clastogenicity in primary human lymphocytes, but negative in Chinese hamster ovary cells. In other *in vitro* assays (bacterial and mammalian cell mutation, DNA repair in primary rat hepatocytes, and sister chromatid exchange in human lymphocytes), cefepime was negative for genotoxic effects. Moreover, *in vivo* assessments of cefepime in mice (2 chromosomal aberration and 2 micronucleus studies) were negative for clastogenicity. No untoward effects on fertility were observed in rats when cefepime was administered subcutaneously at doses up to 1000 mg/kg/day (1.6 times the recommended maximum human dose calculated on a mg/m<sup>2</sup> basis).

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

---

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

---

/s/

---

AMY L ELLIS  
11/17/2009

WENDELYN J SCHMIDT  
11/18/2009

**Pharmacology/Toxicology Review**  
**NDA 50-821**  
**Cefepime for Injection USP and Dextrose Injection USP**  
**in the Duplex® Container, 1 g and 2 g**

**DATE:** 5/5/09

**TO:** J. Christopher Davi, M.S.  
Project Manager, DAIOP  
and  
File, NDA 50-821

**FROM:** Amy L. Ellis, Ph.D.  
Pharmacologist, DAIOP

**THROUGH:** Wendelyn Schmidt  
Supervisory Pharmacologist, DAIOP

**RE:** Pharmacology/Toxicology Review for Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container, 1g and 2g (NDA 50-821)

This NDA is for a sterile dual chamber bag (Duplex® container) that contains Cefepime for Injection USP powder in one compartment and the diluent 5% Dextrose Injection USP in the other. Pressure is applied to the diluent chamber to break the seal between it and the chamber containing the powder, reconstituting the product for administration. For each gram of cefepime, approximately 725 mg of L-arginine is added to control the pH of the final mixed product at 4.0-6.0. The bags will contain about 50 ml of the 5% dextrose diluent. The sponsor, B. Braun Medical Inc. (Allentown, PA), is requesting approval of the current product for the same indications as the reference listed drug Maxipime® to which it is bioequivalent. As with Maxipime®, the current product will be marketed in 1g and 2 g dosage strengths. Additionally, the Duplex® container to be used for cefepime/5% dextrose is identical to the container used by the sponsor for their approved cefotetan product (NDA 65-430), among others.

NDA 50-821 does not require a pharmacology/toxicology review. The sponsor did not conduct any additional nonclinical toxicology studies to support the current NDA. The Division agreed that nonclinical studies would not be necessary as long as there are no impurities or degradation products in Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container that exceed ICH qualification threshold levels or the levels in comparable marketed products such as Maxipime®. Thus far, it appears that there are no impurities or degradation products in the current product that require qualification via nonclinical testing, according to the Chemistry Reviewer. The sponsor has requested that the Agency rely on its findings of safety and effectiveness for the approved product Maxipime® to support this NDA for the current product, Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container, as permitted under section 505(b)(2) of the FD&C Act.

The pharmacologist has no objection to the approval of NDA 50-821 for Cefepime for Injection USP and Dextrose Injection USP in the Duplex® container, provided that the Chemistry Reviewer agrees with the sponsor's assessment that the product contains no impurities or degradation products that need to be qualified via nonclinical testing. The label for this product should be consistent with the labels for Maxipime® (NDA 50-679), Cefepime Injection in GALAXY container (NDA 50-817), and other comparable cefepime products.

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

/s/

-----  
Amy Ellis

5/15/2009 10:04:40 AM

PHARMACOLOGIST

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

Wendy, you signed the paper copy of this review/memo  
on 5/14/09

Wendelyn Schmidt

5/18/2009 03:58:14 PM

PHARMACOLOGIST

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS**  
**MEMO TO FILE: PreNDA 50-821**

**DATE:** 7/3/08

**TO:** J. Christopher Davi, M.S.  
Project Manager, DAIOP  
and  
File, PreNDA 50-821 (cefepime/dextrose injection in Duplex® container)

**FROM:** Amy L. Ellis, Ph.D.  
Pharmacologist, DAIOP

**THROUGH:** Wendelyn Schmidt, Ph.D.  
Supervisory Pharmacologist, DAIOP

**RE:** PreNDA Questions from Sponsor (B. Braun Medical Inc.)

The sponsor, B. Braun Medical Inc. (Allentown, PA) is planning to apply to market Cefepime for Injection in the Duplex® Container. This container is a dual chamber bag that contains powder in one compartment and the diluent 5% Dextrose Injection in the other. Pressure is applied to the diluent chamber to break the seal between it and the chamber containing the powder, reconstituting the product for administration. The label would state that the reconstituted solution must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration. The sponsor would market 2 dosage strengths of Cefepime Injection in Duplex® Containers, one with 1 g of cefepime and the other with 2 g. Both would also contain 725 mg of L-arginine per 1 g of cefepime as a buffering agent to achieve a pH of 4.0-6.0 in the reconstituted product.

The proposed cefepime for injection product will be comparable to the approved product Maxipime® in ADD-Vantage® vials and the sponsor intends to use the Agency's findings of safety and effectiveness for this approved product to support an NDA for the current product, as permitted under section 505(b)(2) of the FD&C Act. The sponsor intends to request Division approval for the same indications and label (as applicable) that has been approved for Maxipime®.

Maxipime® is marketed by Bristol-Myers Squibb as a powder for reconstitution with 5% dextrose or 0.9% sodium chloride. Additionally, there are several approved antimicrobial products for injection in Duplex® Containers. These include cefazolin, cefuroxime, cefotaxime, ceftriaxone, cefoxitin, and cefotetan. Some of these products were approved as NDAs, others as ANDAs. Thus, there is ample precedent for the clinical use of antimicrobials available in the same type of container that would be used for the proposed cefepime for injection. Originally, the sponsor had intended to submit this product as an ANDA, but the FDA Office of Generic Drugs informed them that the filing status of their other Duplex® ANDAs was being changed to 505(b)(2) NDAs. Thus, the sponsor now plans to submit Cefepime for Injection in the Duplex® Container as a 505(b)(2) NDA.

The sponsor does not intend to conduct any additional studies with cefepime for injection other than stability studies. It appears that the sponsor assumes that the impurity/degradation profile of Cefepime for Injection in the Duplex® Container will not differ significantly from Maxipime® in the ADD-Vantage® vial or that any impurities or degradation products will not exceed the thresholds for qualification discussed in the applicable ICH guidance documents. Depending on the similarity between these cefepime products as determined by the Chemistry Review Team, the sponsor may need to demonstrate that this is the case. If the level of any impurities or degradation products in Cefepime for Injection in the Duplex® Container exceed those found in Maxipime® in the ADD-Vantage® vial and also exceed ICH qualification threshold levels (0.15% for a product administered at doses > 2g/day), the sponsor will need to qualify them. For a premixed cefepime solution stored frozen in Galaxy™ plastic containers, this was accomplished by conducting a 14-day repeat dose toxicity study in rats and a battery of genotoxicity tests (e.g., *in vitro* assays: mouse lymphoma, chromosome aberrations in cultured human lymphocytes; *in vivo* assay: mouse micronucleus).

The sponsor did not submit any nonclinical questions to the Division. The statement below could be sent to the sponsor if the Chemistry Reviewer believes it might be necessary to qualify this drug product:

*“You should demonstrate that the impurity/degradation profile of reconstituted Cefepime for Injection in the Duplex® Container stored as directed in your proposed label does not differ significantly from that of another marketed cefepime product (such as Maxipime®) OR show that any impurities or degradation products in your reconstituted/stored product do not exceed the thresholds for qualification discussed in the applicable ICH guidance documents. If there are no impurities or degradation products that exceed the levels in a marketed product or ICH qualification threshold levels, no nonclinical testing of Cefepime for Injection in the Duplex® Container will be needed. If there are impurities or degradation products that must be qualified, limited nonclinical testing would be needed. One possible qualification strategy would be to conduct a 14-day repeat dose toxicity study in rats and a standard battery of genotoxicity tests including *in vitro* tests covering both mutation and clastogenesis along with an *in vivo* rodent micronucleus test.”*

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

/s/

-----  
Amy Ellis

7/9/2008 03:04:19 PM

PHARMACOLOGIST

Comments for the sponsor have been placed on the  
shared drive "BUGS".

Wendy- You OK'd this memo on 7/7/08 via email.

Wendelyn Schmidt

7/18/2008 10:11:13 AM

PHARMACOLOGIST