

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 50-792

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology & Biopharmaceutics Review

NDA 50-792	Cefotaxime for Injection in the Duplex [®] Container
PRODUCT	Cefotaxime
FORMULATION	IV (1.0 and 2.0 gram)
SUBMISSION DATE	September 29, 2003
SUBMISSION TYPE	505 (b) (2) NDA
SPONSOR	B. Braun Medical Inc. 2525 McGaw Avenue Irvine, CA 92623
REVIEWER	Paul W. Buehler, Pharm.D., Ph.D.
ACTING TEAM LEADER	Philip M. Colangelo, Pharm.D., Ph.D.

505 (b)(2) NDA Submission Review Cefotaxime (1.0/2.0 g / Dextrose) for Injection in the DUPLEX[®] Container

SUMMARY:

NDA 50-779 (Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX[®] Container) was approved on 07/2/00. NDA 50-780 (Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX[®] Container) was approved on 02/21/01. In the current submission the Sponsor is seeking approval of Cefotaxime in 1.0 and 2.0 g strengths in the DUPLEX[®] container. The DUPLEX[®] container is a patented drug delivery system consisting of a dual chamber, PVC-free, DEHP-free, and latex-free IV container. The diluent chamber contains 50 mL of the sterile diluent and the drug chamber contains either 1.0g or 2.0 g of the sterile API powder. The Sponsor is requesting right of reference in accordance with the provisions of the 505 (b) (2) provision to clinical and pre-clinical studies performed by Aventis Pharmaceuticals in support of their NDA submission (50-547) for Claforan[®] (Cefotaxime) approved 01/01/82. Thus the Sponsor is additionally requesting a waiver for submission of evidence demonstrating *in vivo* bioavailability/bioequivalence of Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container in accordance with 21 CFR § 320.22 (b) (1). The Sponsor is additionally requesting through right of reference the Clinical Pharmacology wording which exists in the Claforan[®] labeling (see Attachment 1).

COMMENTS:

1. The reviewer agrees with the Sponsors request for a biowaiver in accordance with 21 CFR § 320.22-(b) (1).
2. The reviewer agrees with the wording of the Clinical Pharmacology section to be inserted in the labeling for Cefotaxime DUPLEX.

RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation III (OCPB/DPE III) has reviewed 505 (b) (2) NDA submission 50-792. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view.

Paul W. Buehler, Pharm.D., Ph.D. _____
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip M. Colangelo, Pharm.D., Ph.D., _____
Acting Team Leader

cc:
Division File: NDA 50-792
HFD-520 (CSO/Peat)

HFD-520 (MO/Pohlman)
HFD-880 (Division File, Lazor, Selen, Colangelo, Buehler)
CDR (Clin. Pharm./Biopharm.)

Attachment 1

B.Braun Medical, Inc. 29 September 2003
NDA 50-792: Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX@ Container Original Submission

**NEW DRUG APPLICATION
ORIGINAL SUBMISSION
NDA 50-792**

DRUG PRODUCT

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX@ Container

SECTION 6

Human Pharmacokinetics and Bioavailability

APPLICANT

B. Braun Medical Inc. 2525 McGaw Avenue
Irvine, CA 92614

SUBMISSION DATE

29 September 2003

CONFIDENTIAL

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

I. Introduction

In accordance with 21 CFR § 320.22(b)(I), B. Braun Medical Inc. requests a waiver for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence of Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container.

Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container is a parenteral solution intended solely for administration by intravenous injection. Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container contains the same active and inactive ingredients as the reference listed drug, Aventis Pharmaceuticals' Claforan@ sterile cefotaxime for injection (NDA 50-547).

This section contains human pharmacology information for cefuroxime gleaned from the Clinical Pharmacology section of the package insert for the reference listed drug, Aventis Pharmaceuticals' Claforan@ sterile cefotaxime for injection (NDA 50-547).

II. Clinical Pharmacology

There was a dose-dependent increase in serum levels after the intravenous (IV) administration of 500 mg, 1 g, and 2 g of cefotaxime 38.9, 101.7, and 214.4 µg/mL, respectively) without alteration in the elimination half-life. There is no evidence of accumulation following repetitive IV infusion of 1 g doses every six hours for 14 days as there are no alterations of serum or renal clearance. About 60% of the administered dose was recovered from urine during the first six hours following the start of the infusion.

Approximately 20-36% of an intravenously administered dose of ¹⁴C-cefotaxime is excreted by the kidney as unchanged cefotaxime and 15- 25% as the desacetyl derivative, the major metabolite. The desacetyl metabolite has been shown to contribute to the bactericidal activity. Two other urinary metabolites (M2 and Ms) account for 20-25%. They lack bactericidal activity.

A single 50 mg/kg dose of cefotaxime was administered as an intravenous infusion over a 10- to 15-minute period to 29 newborn infants grouped according to birth weight and age. The mean half-life of cefotaxime in infants

CONFIDENTIAL

B.Braun Medical, Inc. 29 September 2003

NDA 50-792: Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container Original Submission

with lower birth weights (~1500 grams), regardless of age, was longer (4.6 hours) than the mean half-life (3.4 hours) in infants whose birth weight was greater than 1500 grams. Mean serum clearance was also smaller in the lower birth weight infants. Although the differences in mean half-life values are statistically significant for weight, they are not clinically important. Therefore, dosage should be based solely on age.

Additionally, no disulfiram-like reactions were reported in a study conducted in 22 health volunteers administered cefotaxime and ethanol.

CONFIDENTIAL

Appears This Way
On Original

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

/s/

Paul Buehler
10/16/03 02:12:20 PM
BIOPHARMACEUTICS

Phil Colangelo
10/17/03 05:35:57 PM
BIOPHARMACEUTICS

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

/s/

Paul Buehler
10/16/03 02:12:20 PM
BIOPHARMACEUTICS

Phil Colangelo
10/17/03 05:35:57 PM
BIOPHARMACEUTICS

nulldate
BIOPHARMACEUTICS