

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 50-792

Pharmacology Review(s)

EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: The active ingredient in this product (cefotaxime) was approved in 1982 as CLAFORAN®, NDA 50-547 by Aventis Pharmaceuticals. This current application is 505(b) (2) for a novel packaging system- the DUPLEX® container. The DUPLEX® container is a two compartmented, non-PVC plastic container/closure system with a sterile diluent (50 mL) and sterile active pharmaceutical ingredient powder (cefotaxime free acid) in separate chambers. As the active ingredient remains the same, there are no remaining pharmacology/toxicology issues as the only new study provided was literature reports of genetic toxicology studies to bring the label up to current standards. The DUPLEX® container system is an integral part of 2 previously approved applications: NDA 50-779 for cefazolin and NDA 50-580 for cefuroxime.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendations on labeling: The results of the genetic toxicology studies should be included in the label.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-792

Review number: 1

Sequence number/date/type of submission: 9/30/03

Information to sponsor: Yes

Sponsor and/or agent: B. Braun Medical Inc., Irvine, CA

Reviewer name: Terry S. Peters, D.V.M.

Division name: Anti-Infective Drug Products

HFD #: 520

Review completion date: 2/12/04

Drug:

Trade name: Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX® Container

Generic name: Cefotaxime and dextrose

Drug class: Cephalosporin antibiotic

Indication: "Treatment of serious infections due to susceptible organisms"

Clinical formulation: 1 or 2 gms of cefotaxime/container

Route of administration: Intravenous

Studies reviewed within this submission:

- 1) Guinea Pig Maximization Test; — # 91363- 91378
- 2) Determination of the Toxicity in Mice of 4.8% Dextrose Filled Duplex Container Following Daily Intravenous Administration; — # P0598017
- 3) Mutagenicity Test of Cefotaxime Sodium; J. Toxicol. Sci. 1988; 13(1): 245-256

3.4.3 Repeat-dose toxicity

Study title: Determination of the Toxicity in Mice of 4.8% Dextrose Filled Duplex Container Following Daily Intravenous Administration

Key study findings: No significant treatment-related differences from controls were found in any of the parameters evaluated.

Study no.: — Study #P0598017

Conducting laboratory and location: E J

Date of study initiation: 6/5/98

GLP compliance: Yes

QA report: yes

Drug, lot #, and % purity: 4.8% Dextrose drawn from DUPLEX® container. The control for the study was 5% Dextrose drawn from a glass container.

Methods

Doses: 48 hours prior to administration, the container was activated and incubated at 70° C. The control solution was treated similarly.

Species/strain: ICR mice

Number/sex/group or time point (main study): 10/sex

Route, formulation, volume, and infusion rate: I.V. dosing q.d. at 50 mL/kg/d at a rate of 1 mL/minute into the tail vein.

Satellite groups used for toxicokinetics or recovery: None

Age: Males: 25 days old; females: 32 days old

Observation times and results

Mortality: Once/day. There were no premature decedents.

Clinical signs: Once/day. There were no significant clinical signs reported.

Body weights: Daily. No significant treatment-related effects were noted.

Food consumption: Daily. No significant treatment-related effects were appreciated.

Ophthalmoscopy: Not performed

EKG: Not performed

Hematology: On Day 29 under ketamine/xylazine anesthesia. Unfortunately, 31/40 samples had clots in them so no evaluation for hematology was possible. In the remaining

animals, no significant adverse effects on hematologic parameters were determined.

Clinical chemistry: On Day 29 under ketamine/xylazine anesthesia. Samples were evaluated for Ca, albumin, globulin, BUN, ALT, AST, Cl and phosphorus. Total bilirubin values were higher for test males than controls but 2 test article animals had "marked hemolysis" which probably affected the outcome. No other significant treatment-related effects were found.

Urinalysis: Not performed

Gross pathology: All animals at termination. No gross apparent treatment-related lesions were discussed.

Organ weights: Adrenals, brain, heart, kidney, liver, ovaries, spleen and testes. Test article females had statistically significant lower mean relative brain, kidney and liver weights than controls but these differences were not biologically significant.

Histopathology: Adequate Battery: yes

Peer review: no

There were no significant treatment-related lesions reported in the animals on study.

3.4.4. Genetic toxicology

Study title: Mutagenicity Test of Cefotaxime Sodium; J. Toxicol. Sci. 1988; 13(1): 245-256

Key findings: Cefotaxime did not elicit an increase in chromosomal aberrations in this assay.

Study no.: Literature reference only

Conducting laboratory and location: Taiho Pharmaceutical Co., Ltd., Tokushima, Japan

Date of study initiation: Paper published in 1988

GLP compliance: Not specified

Drug, lot #, and % purity: THR-221, lot D034

Strains/species/cell line: Cultured Chinese hamster lung cells

Doses used in definitive study: 0, 0.75, 1.5, 3.0 and 6.0 mg/mL with or without metabolic activation

Basis of dose selection: Preliminary studies to determine cell survival and inhibition of growth.

Negative controls: Saline

Positive controls: 0.005 mg/mL ENNG (*N*-ethyl-*N*-nitro-*N*-nitrosoguanidine) and DMN (*N*-nitrosodimethylamine)

Incubation and sampling times: Cells were seeded into petri dishes and 200 μ l of test compound was added. Cultures were incubated for 24 to 48 hours and Colcemid was added 2 hrs. prior to harvest. After harvest, the cells were treated with potassium chloride and incubated for 15 minutes. The cells were then fixed and slides were prepared for analysis after Giemsa staining. 100 metaphases/concentration were

evaluated.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The positive and negative controls performed as expected so the study is considered valid given the information provided.

Study outcome: There were no significant differences from the negative controls in the number of chromosomal aberrations found at any dose level. No increase in polyploidy was reported. In this assay in Chinese hamster lung cells, cefotaxime did not elicit chromosomal aberrations.

3.4.8 Special toxicology studies

Study title: Guinea Pig Maximization Test

Key study findings: Neither the direct product-contact (laminated foil or clear film) nor the indirect product-contact (clear barrier film, peelable barrier film or set port) from the Duplex® container elicited more than a grade I irritation and

Study no.: 91363- 91378

Conducting laboratory and location: C

J

Date of study initiation: 9/10/97- 10/22/97

GLP compliance: No compliance statement in the submission

QA reports: No

Drug, lot #, and % purity: Lot J117004J- TSR No. 47794

Study design: This was a standard maximization assay using Hartley guinea pigs. Ten animals were treated with the various test extracts and 2 were vehicle controls treated with cottonseed oil.

A shaved area was created over the shoulder region. On Day 1, three paired injections were made into the shaved areas: 0.1 mL Freund's Complete Adjuvant (2 sites), 0.1 mL test sample or control (2 sites) and 0.1 mL of test sample or control vehicle mixed 1:1 with Freund's Complete Adjuvant.

On Day 6, the animals were re-shaved and 10% sodium lauryl sulfate in petrolatum was massaged into each area.

On Day 7, filter paper soaked in test article/vehicle was placed over the shaved area and covered with an occlusive bandage that was removed on Day 9.

On Day 21, animals' flanks were shaved and filter paper soaked in test article/vehicle was placed over this area and an occlusive bandage was applied. The bandages were removed on Day 22.

On Days 22 and 23, the animals were examined for redness and swelling.

Results: None of the components elicited significant irritation or sensitization.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: This application is approvable from a pharmacology/toxicology standpoint.

Unresolved toxicology issues (if any): None

Suggested labeling: The results of the chromosomal aberration assay should be included in the label.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

Deputy Division Director Signature: _____
Concurrence Yes ___ No ___

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

/s/

Terry Peters
2/13/04 06:40:47 AM
PHARMACOLOGIST

Robert Osterberg
2/17/04 09:10:00 AM
PHARMACOLOGIST

Lillian Gavrilovich
2/18/04 06:24:37 PM
MEDICAL OFFICER