CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50749

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
NDA #: 50-749 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 2-Dec-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Dec-96	31-Dec-96	1-Jan-97
AMENDMENT/AC -Street address for _ Plants	10-Jan-97	13-Jan-97	15-Jan-97
AMENDMENT/AC -Summary of MV package (item 4 of NDA)	24-Jan-97	27-Jan-97	28-Jan-97
AMENDMENT/BC -Response to DRAFT deficiency letter (Review 1)	13-Aug-97	14-Aug-97	14-Aug-97
AMENDMENT/BZ -Update of stability data	27-Aug-97	28-Aug-97	28-Aug-97
AMENDMENT -MV dissolution method	29-Sep-97 (desk copy)		30-Sep-97
AMENDMENT/ -Final draft container label	16/Oct-97	17-Oct-97	17-Oct-97
AMENDMENT/BB Response to Biopharm recommendations for the dissolution method and specifications.	20-Oct-97	21-Oct-97	21-Oct-97
AMENDMENT/ -18 month stability data + Container label revision for storage of reconstituted suspension	07-Nov-97 (desk copy)		08-Nov-97
AMENDMENT -Amendment to Post approval stability protocol	18-Nov-97 (desk copy)		19-Nov-97
AMENDMENT -Response to draft Post-Approval Commitments.	25-Nov-97(desk copy)		26-Nov-97
AMENDMENT -Response to draft Post-Approval Commitments.	26-Nov-97(desk copy)		28-Nov-97

NAME & ADDRESS OF APPLICANT: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Co.
2800 Plymouth Road,
P.O.Box 1047
Ann Arbor, MI 48106-1047

Contact: Dr.Paul Chen
Phone:(313) 996-2623

DRUG PRODUCT NAME

Proprietary:	Omnicef® Oral Suspension
Nonproprietary/USAN:	Cefdinir
Code Names/#'s:	
Chemical Type/ Therapeutic Class:	38

ANDA Suitability Petition/DESI/Patent Status:
N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Anti-infective/ For treatment of mild to moderate infections.

DOSAGE FORM:	Oral Suspension
STRENGTHS:	125 mg/5 mL
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{14}H_{13}N_5O_5S_2$ M.W. 395.42

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(hydroxyamino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2ene-2-carboxylic acid.

SUPPORTING DOCUMENTS:
IND
DMF

DMF

NDA 50-749 Chemistry review 1.

Packaging Components:
DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

EA review completed; Fonsi Issued 6/9/97 - attached to CMC Review 2.

Nomenclature Committee for trade name Omnicef - Not

acceptable to the committee (similar name - Omnipen is a marketed product). As a post-approval commitment, the firm will monitor prescription errors resulting from similarity of different brand names starting with OMNI.

Establishment Inspection - Submitted Date 1/27/97

Methods validation - Completed-November 12, 1997

REMARKS/COMMENTS:
The structure relates to cefixime, the acetate group at the ( ) is replaced by ( )

The drug substance is also known as FK482.

CONCLUSIONS & RECOMMENDATIONS:

Recommend approval of this application for manufacturing and controls under section 505(b) of the Act.

The drug substance is recommended for approval under NDA 50-739.

/S/

Shrikant N. Pagay, Ph.D. 12/2/97
Review Chemist

cc: Orig. NDA 50-749 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/S.Pagay/date
HFD-520/Soreth/Viraghavan/Hamilton
HFD-520/Osterberg
HFD-520/Sheldon
HFD-520/Debellas
HFD-520/Katague R/D Init by: Katague DBK 12/2/97
Filename:N50-749

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
NDA #: 50-749 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 1-Dec-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Dec-96	31-Dec-96	1-Jan-97
AMENDMENT/AC -Street address for Plants	10-Jan-97	13-Jan-97	15-Jan-97
AMENDMENT/AC -Summary of MV package (item 4 of NDA)	24-Jan-97	27-Jan-97	28-Jan-97
AMENDMENT/BC -Response to DRAFT deficiency letter (Review 1)	13-Aug-97	14-Aug-97	14-Aug-97
AMENDMENT/BZ -Update of stability data	27-Aug-97	28-Aug-97	28-Aug-97
AMENDMENT -MV dissolution method	29-Sep-97 (desk copy)		30-Sep-97
AMENDMENT/ -Final draft container label	16/Oct-97	17-Oct-97	17-Oct-97
AMENDMENT/BB Response to Biopharm recommendations for the dissolution method and specifications.	20-Oct-97	21-Oct-97	21-Oct-97
AMENDMENT/ -18 month stability data + Container label revision for storage of reconstituted suspension	07-Nov-97 (desk copy)		08-Nov-97
AMENDMENT -Amendment to Post approval stability protocol	18-Nov-97 (desk copy)		19-Nov-97
AMENDMENT -Response to draft Post-Approval Commitments.	25-Nov-97(desk copy)		26-Nov-97

NAME & ADDRESS OF APPLICANT: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Co.
2800 Plymouth Road,
P.O.Box 1047
Ann Arbor, MI 48106-1047

Contact: Dr.Paul Chen
Phone:(313) 996-2623

DRUG PRODUCT NAME
Proprietary: Omnicef® Oral Suspension
Nonproprietary/USAN: Cefdinir
Code Names/#'s:
Chemical Type/
Therapeutic Class: 3S

ANDA Suitability Petition/DESI/Patent Status:
N/A
PHARMACOLOGICAL CATEGORY/INDICATION: Anti-infective/ For treatment of mild to moderate infections.

DOSAGE FORM:	Oral Suspension
STRENGTHS:	125 mg/5 mL
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{14}H_{13}N_5O_5S_2$ M.W. 395.42

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(hydroxyamino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2ene-2-carboxylic acid.

SUPPORTING DOCUMENTS:
IND
DMF

DMF

NDA 50-749 Chemistry review 1.

Packaging Components:
DMF

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 505(b) of the Act.

The establishment inspection is pending.

The firm was requested in a meeting on November 21, 1997 to consider the recommendation listed under list of Chemistry Deficiencies and Comments

/S/

Shrikant N. Pagay, Ph.D. 12/1/97
Review Chemist

cc: Orig. NDA 50-749 (other NDA's may be included if appropriate)
HFD-520/Division File
HFD-520/S.Pagay/date
HFD-520/Soreth/Viraghavan/Hamilton
HFD-520/Osterberg
HFD-520/Sheldon
HFD-520/Debellas
HFD-520/Katague R/D Init by: Katague DBK 12/1/97
Filename:N50-749

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
NDA #: 50-749 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 5-June-97

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	30-Dec-96	31-Dec-96	1-Jan-97
AMENDMENT/AC	10-Jan-97	13-Jan-97	15-Jan-97
AMENDMENT/AC	24-Jan-97	27-Jan-97	28-Jan-97

NAME & ADDRESS OF APPLICANT: Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Co.
2800 Plymouth Road,
P.O.Box 1047
Ann Arbor, MI 48106-1047

Contact: Dr.Paul Chen
Phone:(313) 996-2623

DRUG PRODUCT NAME
Proprietary: Omnicef® Oral Suspension
Nonproprietary/USAN: Cefdinir
Code Names/#'s:
Chemical Type/
Therapeutic Class: 3S

ANDA Suitability Petition/DESI/Patent Status:
N/A
PHARMACOLOGICAL CATEGORY/INDICATION: Anti-infective/ For treatment of mild to moderate infections.

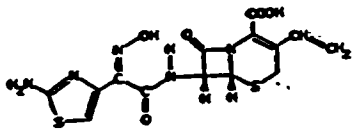
DOSAGE FORM: Oral Suspension
STRENGTHS: 125 mg/5 mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{14}H_{13}N_5O_5S_2$ M.W. 395.42

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(hydroxyamino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2ene-2-carboxylic acid

Figure 1: Cefdinir Structural Formula



SUPPORTING DOCUMENTS:
IND /
DMF

DMF

Packaging Components:
DMF /

RELATED DOCUMENTS (if applicable): None

CONSULTS:

EA review completed; Fonsi Issued 6/9/97

Nomenclature Committee for trade name Omnicef - Not acceptable to the committee (similar name - Omnipen is a marketed product). Clinical and Project management plans to overrule the recommendation.

Establishment Inspection - Submitted Date 1/27/97. Thre drug substance facilities are acceptable (2/5/97). The drug product is pending.

Methods validation - Submitted Date 2/12/97

REMARKS/COMMENTS:
The structure relates to cefixime, the acetate group at the / is replaced by /

50 and 100 mg cefdinir capsules were approved in Japan in 1991.

The drug substance is also known as FK482.

All deficiencies for each Section (example: item 1, 2 etc.) of the Drug Substance and the Drug product are listed at the end of respective sections and compiled

CONCLUSIONS & RECOMMENDATIONS:

The application is not approvable for manufacturing and controls under section 507 of the Act. Specific items which are not approvable are identified under the following headings: Drug Substance [Specifications and Analytical methods]; Drug Product [Manufacturer, Specifications and Methods for Drug Product, Container/Closure System, Stability]; Investigational Formulations and Labeling.

Please note that the drug substance related issues based on DMF/ /and related DMF's/ ((intermediates) were addressed to the DMF holder.

The establishment inspection, methods validation and approval of the brand name are pending.

/S/

Shrikant N. Pagay, Ph.D. 7/17/97
Review Chemist

cc: Orig. NDA 50-749 (other NDA's may be included if appropriate)
HFD-520/Division File Filename: N50-749
HFD-520/S.Pagay
HFD-520/Soreth/Viraghavan/Hamilton
HFD-520/Osterberg
HFD-520/Altaie
HFD-520/DuVall-Miller
HFD-520/Katague R/D Init by: Katague DBK 7/21/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50749

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

OMNICEF®
(CEFDINIR)
Powder for Oral Suspension
NDA 50-749

Warner-Lambert Company
(Parke-Davis)

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Anti-infective Drug Products
(HFD-520)

FINDING OF NO SIGNIFICANT IMPACT

NDA 50-749

OMNICEF®
(CEFDINIR)
Powder for Oral Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Omnicef®, Warner-Lambert Company (Parke-Davis Pharmaceutical Research) has prepared an environmental assessment (attached) in accordance with [21 CFR 25.31a(a)], which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements*.

Cefdinir is a chemically synthesized drug which is administered as a powder for oral suspension in the treatment of patients with mild to moderate infections. The drug substance will be manufactured by Fujisawa Pharmaceutical Co. Ltd. The drug product will be manufactured by Eli Lilly Industries, Inc., in Carolina, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Cefdinir may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Rejected or returned drug product will be disposed of at a licensed high temperature incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to

hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/S/

June 3, 1997

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

/S/

6/3/97

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Date

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

Copies:

HFD-520

Beth Duvall-Miller CSO/PM
Original to NDA 50-749, through Beth Duvall-Miller CSO/PM
Division File for NDA 50-749

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger

file name: c:\fonsi\50749e01.fcb

ITEM 3.6.

Freedom of Information Version of Environmental Assessment for Cefdinir Powder for Oral Suspension

NDA 50-749

TABLE OF CONTENTS

(Page 1 of 2)

Page

NOTES TO REVIEWER 1

1. DATE 2

2. NAME OF APPLICANT 2

3. ADDRESS OF APPLICANT 2

4. DESCRIPTION OF THE PROPOSED ACTION 2
4.1. Description of the Proposed Action 2
4.2. Need for the Action 2
4.3. Locations Where the Products Will be Produced 3

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION 5
5.1. Chemical Names 5
5.2. Synonym Names 5
5.3. Structural Formula 6
5.4. Description 6
5.5. List of Potential Impurities 6
5.6. Ultraviolet Spectrum 7

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT 8
6.1. Materials Emitted Into the Air in Lilly Carolina, Puerto Rico Plant 8
6.2. Materials Disposed as Solid Waste in Lilly Carolina, Puerto Rico Plant . . . 9
6.3. Materials Disposed as Liquid in Lilly Carolina, Puerto Rico Plant 9
6.4. Materials Disposed Into the Sewage Treatment System in Lilly Carolina, Puerto Rico Plant 9
6.5. Materials Disposed of as Hazardous Waste 10

TABLE OF CONTENTS

(Page 2 of 2)

Page

6.6. Maximum Expected Emitted Concentration 10

12. LIST OF PREPARERS OF THE ENVIRONMENTAL ASSESSMENT 12

13. CERTIFICATION 13

14. REFERENCES 14

15. APPENDICES 15

APPENDIX 1. Material Safety Data Sheet for Cefdinir
APPENDIX 2. UV Spectrum of Cefdinir (Confidential)
APPENDIX 3. Certification of Environmental Compliance, Drug Substance
APPENDIX 4. Certification of Compliance, Drug Product
APPENDIX 5. Manufacturing Flow Charts for Cefdinir Suspension (Confidential)

NOTES TO REVIEWER

Cefdinir is licensed from Fujisawa Pharmaceutical Co, Osaka, Japan and developed by Parke-Davis, a Division of Warner-Lambert Company. Fujisawa remains as the manufacturer and supplier of the drug substance. Cefdinir is related to an approved drug, cefixime. The structure of cefdinir differs from that of cefixime only at the oxime moiety where an acetate group is replaced by a hydrogen atom to yield cefdinir.

Parke-Davis has developed cefdinir into capsule (300 mg) and oral powder for suspension (125 mg/5 mL) for the treatment of patients with mild to moderate infections.

Both dosage forms are manufactured by our contract manufacturer, Eli Lilly at the Carolina, Puerto Rico plant.

This report was prepared for cefdinir oral suspension following the guidelines issued November 1995, by the Center for Drug Evaluation and Research titled, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements." We have calculated in Section 6 that the expected environmental concentration of the drug substance is , which is less than the threshold of 1 ppb. We therefore are not including the following sections:

7. Fate of Emitted Substances in the Environment
8. Environmental Effects of Released Substances
9. Use of Resources and Energy
10. Mitigation Measures
11. Alternatives to the Proposed Action

ENVIRONMENTAL ASSESSMENT FOR CEFDINIR CAPSULE

1. DATE

April 25, 1997

2. NAME OF APPLICANT

Warner-Lambert Company

3. ADDRESS OF APPLICANT

201 Tabor Road
Morris Plains, NJ 07950

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Description of the Proposed Action

Warner-Lambert has filed a New Drug Applications (NDA) for Omnicef™ (cefdinir) powder for oral suspension. The drug substance is cefdinir. The NDA requests approval of cefdinir powder for oral suspension for the treatment of patients with mild to moderate infections.

4.2. Need for the Action

Approval of this application will result in production and distribution of Omnicef in the US. Approval will offer patients in the US an effective therapy for treatment of mild to moderate infections in hospitals, clinics, and homes. Because of the

therapeutic benefits associated with its availability and use, approval is sought and preferable to nonapproval.

4.3. Locations Where the Products Will be Produced

Bulk drug substance will be manufactured at the following facility:

Fujisawa Pharmaceutical Co, Ltd
1-6, 2-Chome, Kaskima
Yodogawa-Ku
Osaka, Japan 53

This facility is located in the central part of Osaka. The facility is FDA approved and was inspected several times in the past. Please refer to Fujisawa Type I, Drug Master File (DMF) 9457 for this manufacturing facility. For detailed information on the manufacture and controls of cefdinir drug substance, please reference the Fujisawa Type II, DMF 8489.

The drug products will be manufactured at our contract manufacturer:

Eli Lilly Industries, Inc
KM 13.1
65th Infantry Road
Carolina, PR 00985

Returned and unused drug product will be returned via the Warner-Lambert Drug Distribution System. Material with inadequate shelf-life remaining for distribution will be sent to the following facilities:

Warner-Lambert Company
400 W Lincoln Avenue
Lititz, PA 17543

or

The Ballentine Group
Munsonhurst Road
Franklin, NJ 07416

Returned products will be destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations. Material that does not meet specifications will be either reprocessed at the manufacturing sites specified and submitted as a supplement to the NDA or destroyed by high temperature (1800°F-2200°F) incineration in accordance with all applicable environmental regulations. Permit numbers, issuance date, expiration date, and permitting authority of the incinerators are tabulated below:

Incinerators for the Disposal of Returned or Unused Drug Product

Incinerator:	Lancaster County Solid Waste Management Authority (Conoy Township, Pennsylvania)
Permit Number:	400592
Permit Issuance Date:	02/22/89
Permit Expiration Date:	03/31/09
Permitting Authority:	Commonwealth of Pennsylvania Department of Environmental Resources, Bureau of Waste Management (Harrisburg Regional Office)
Incinerator:	Dutchess County Resource Recovery Agency (Poughkeepsie, New York)
Permit Number:	3-1346-00019/00005-0
Permit Issuance Date:	10/21/93 (Effective Date)
Permit Expiration Date:	10/21/98
Permitting Authority:	New York State Department of Environmental Conservation (New Paltz, New York)
Incinerator:	Adirondack Resource Recovery Associates (Glens Falls, New York)
Permit Number:	5-5344-00001/00006-1

Permit Issuance Date: 02/08/95 (Effective Date)
Permit Expiration Date: 02/07/00
Permitting Authority: New York State Department of Environmental Conservation (Warrensburg, New York)

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

5.1. Chemical Names

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

CAS Registry 91832-40-5

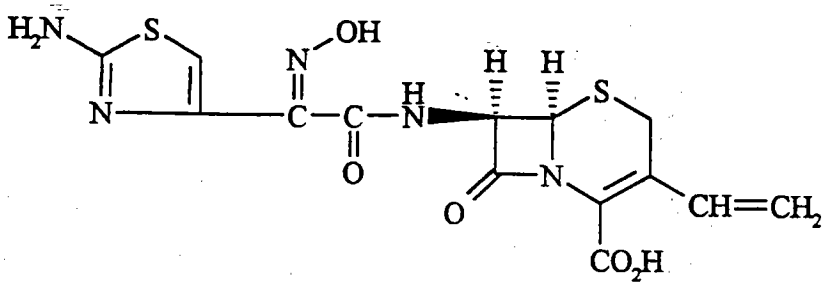
5.2. Synonym Names

Omnicef

Cefdinir

FK-482, CI-983

5.3. Structural Formula



Molecular Weight: 395.42

5.4. Description

White to slightly brownish yellow or off-white solid

5.5. List of Potential Impurities

Cefdinir is a semisynthetic β-lactam antibiotic of the cephalosporin class; therefore, it has the following potential impurities:

(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyimino-N-[(3RS,5aR,6R)-1,4,5a,6-tetrahydro-3-methyl-1,7-dioxo-3H,7H-azeto[2,1-b]furo[3,4-d][1,3]thiazin-6-yl]acetamide

(R)-2-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-2-[(2RS,5RS)-1,2,5,7-tetrahydro-5-methyl-7-oxo-4H-furo[3,4-d][1,3]thiazin-2-yl]acetic acid

(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyimino-N-[[(2R,5RS)-1,2,5,7-tetrahydro-5-methyl-7-oxo-4H-furo[3,4-d][1,3]thiazin-2-yl]methyl]acetamide

(Z)-2-(2-amino-4-thiazolyl)-N-(2,2-dihydroxyethyl)-2-hydroxyiminoacetamide

(R)-2-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-2-[(2R)-4-carboxy-5-[(Z)-ethylidene]-5,6-dihydro-2H-1,3-thiazin-2-yl]acetic acid

(6R,7S)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(6R,7R)-7-[(E)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

N-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetyl]glycine

benzhydryl (6R,7R)-7-[(Z)-4-chloro-2-hydroxyimino-3-oxobutanamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

benzhydryl (6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(6R,7R)-7-[2-(2-amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

(6R,7R)-7-(4-hydroxy-3-isoxazolecarboxamide)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

A material safety data sheet (MSDS) for cefdinir is provided in Appendix 1.

5.6. Ultraviolet Spectrum

The UV-VIS spectrum of cefdinir in 0.1M phosphate buffer pH 7.0 at a concentration of about 0.01 mg/mL is shown in Appendix 2. The spectrum exhibits absorption maxima at 286 and 223 nm, and an absorption minimum at 248 nm.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

Cefdinir drug substance is manufactured at Fujisawa's Osaka, Japan plant. Substances (please reference Fujisawa DMF 8498) introduced into the environment during manufacturing of cefdinir meet the local environmental regulations. The certification of compliance is provided in Appendix 3.

Cefdinir drug product (powder for oral suspension) is manufactured at our contract manufacturer, Eli Lilly Industries, Inc, KM 12.6, 65th Infantry Road, Carolina, PR 00985. The certification of compliance is provided in Appendix 4.

6.1. Materials Emitted Into the Air in Lilly Carolina, Puerto Rico Plant

The air-borne particulates to be emitted from the cefdinir manufacturing process most likely consist of traces of the dry powders used during the formulation. Since the control equipment for particulate emissions consists of Dust Collectors and HEPA filters, the dust generated during the process (probable range of 100 to 1 μ) will be captured and the stack emissions will be a negligible amount of powder particles mostly in the range of less than 10 μ (not visible to human eye). HEPA filters, besides those located at the exit of the main duct collectors, are also connected to the wall intake in the cefdinir manufacturing area to assure that the work area will be free from nuisance dust.

For the cefdinir manufacturing area, an air emission permit (PFE-16-0792-0939-I-O, expiration: expected in 1998) was approved by the Environmental Quality Board (EQB), Commonwealth of Puerto Rico. This permit authorizes the manufacture of trial lots of 16 oral suspension and 2 capsule batches at Lilly's PR03 plant. The limit of particulate will be established for future batches when enough data have been collected. Refer to Appendix 5 for the manufacturing flow charts for cefdinir suspension.

6.2. Materials Disposed as Solid Waste in Lilly Carolina, Puerto Rico Plant

The solid wastes primarily consist of packaging waste, inspection failures, quality control failures and cleanup residues, personal protective equipment, and assay remainings. These wastes are considered nonhazardous and therefore will be incinerated at a local (non-Lilly) facility. The Environmental Quality Board does not assign identification to nonhazardous waste generators.

6.3. Materials Disposed as Liquid in Lilly Carolina, Puerto Rico Plant

The main nonhazardous liquid waste generated during the cefdinir manufacture will be remainings from assays like the particle size analysis in the Technical Services Laboratory. The liquid waste will not be treated at Lilly's Carolina Plant but will be transferred to Lilly's PR04 plant at Mayaqüez, Puerto Rico for incineration.

6.4. Materials Disposed Into the Sewage Treatment System in Lilly Carolina, Puerto Rico Plant

The wastewater that will reach the sewage treatment system is composed primarily of the equipment washwater generated during cleaning after the manufacturing process. This wastewater consists almost entirely of water with trace amounts of the drug product materials. The wastewater from this plant is transferred by pumping to Lilly's PR01 wastewater treatment plant.

The Lilly PR01 wastewater treatment plant complex consists of a standard Zum-Attisholz 2-stage activated sludge treatment system which is composed of 2 aeration basins with clarification, flow equalization, aerobic waste sludge digestion and thickening. The treated wastewater is then pumped to Puerto Rico Sewers and Aqueduct Authority's (PRASA) Regional plant for final treatment and disposal.

The stabilized waste sludge is transferred in trucks to Lilly's PR02 wastewater treatment plant for dewatering by means of a belt press. The dry sludge is then transferred in dumpsters to the Carolina Municipal Landfill for final disposal. The dry sludge is a nonhazardous waste.

The 2 wastewater treatment plant complexes at Lilly's Carolina plant have a combined wastewater discharge permit granted by the PRASA. The permit number is GDA-88-102-027 (expiration: 08/24/97). The authorized maximum wastewater discharge is 542,025 gallons per day. The estimated actual daily discharge from Lilly's facilities is 325,000 gallons.

6.5. Materials Disposed of as Hazardous Waste

The hazardous waste that will be generated as a result of the cefdinir manufacture will be mainly from the analytical laboratory activities. The waste primarily consists of residues from laboratory testing. The PR03 plant (EPA) identification number is PRD 980436067. The hazardous waste will be transported, by a licensed hauler, to Lilly's PR04 Mayaqüez plant to be incinerated. The EPA permit number for this incinerator is PRD091024786. The permit expired in 1994; renewal was submitted and is being processing now. The air emission permit for this plant is PFE-50-0496-0436-I-II-III-0. The expiration is February 2002.

6.6. Maximum Expected Emitted Concentration (EEC)

Calculation of a maximum EEC is based on release of the drug substance uniformly within the US using the equation presented by the Pharmaceutical Research and Manufacturers of America in their guidance document for preparation of environmental assessments and an estimated fifth-year production of of cefdinir.

$$\text{ppm (in US environment)} = \text{lbs/year} \times (8.9 \times 10^{-9})$$
$$\text{derived from ppm} = (A)(B)(C)(D)(E)(F)$$

where:
- A = Pounds produced divided by 1 year (fifth-year production estimate).
- B = One year divided by 365 days (length of year).
- C = One day-person divided by 150 gallons (average daily water use per person in US).
- D = One divided by 246,000,000 persons (population of US).
- E = One gallon divided by 8.34 pounds (weight of a gallon of water).
- F = 1,000,000 (conversion to parts per million).

The maximum expected emitted concentration in the US as a result of drug product use is calculated to be:

ppm (in US environment) =
ppb (in US environment) =

Calculations were performed in order to estimate the worst-case concentration of cefdinir that could possibly be present in the US. The estimate assumes that all cefdinir capsule and oral for suspension produced for sale in the US (based on fifth-year postapproval production estimates,) will be administered to patients and disposed of directly into sewage systems. This calculation overestimates the environmental concentration of cefdinir in at least 2 ways: (1) It assumes that all the cefdinir produced will be sold and used by patients, and that none will be left unsold, unused by patients, or will expire or be returned for disposal outside sewage treatment systems, and (2) It assumes that all of the cefdinir capsule and oral suspension administered to patients will be excreted into sewage treatment systems without hydrolysis and biodegradation. Nonetheless, is calculated to be the maximum expected environmental concentration in the US following the estimate presented above.

12. LIST OF PREPARERS OF THE ENVIRONMENTAL ASSESSMENT

1. Paul R. Chen
   Senior Manager
   Worldwide Regulatory Affairs

2. Sean Brennan
   Senior Director
   Worldwide Regulatory Affairs

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge for the preparation of the environmental assessment.

Date: 4/25/97

Signature: Sean Brennan Sean Brennan

Title: Senior Director, Worldwide Regulatory Affairs

14. REFERENCES

1. Environmental Assessment Technical Assistance Handbook.

2. Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Application and Supplements.

15. APPENDICES

APPENDIX 1. Material Safety Data Sheet for Cefdinir
APPENDIX 2. UV Spectrum of Cefdinir.(Confidential)
APPENDIX 3. Certification of Environmental Compliance, Drug Substance
APPENDIX 4. Certification of Compliance, Drug Product (Confidential)
APPENDIX 5. Manufacturing Flow Charts for Cefdinir Suspension

APPENDIX 1
Material Safety Data Sheet for Cefdinir

KNR950043

Material Safety Data Sheet for FK482

December, 1995

Fujisawa Pharmaceutical Co., Ltd.

Osaka, Japan

MATERIAL SAFETY DATA SHEET

Name: Cefdinir (oral cephalosporin)

I. Product Identification

Manufacturer's Name & Address:

Fujisawa Pharmaceutical Co., Ltd.
1-6, Kashima 2-chome, Yodogawa-ku,
Osaka 532, Japan

Product #: FR080482
CAS #: 91832-40-5
Molecular Formula: $C_{14}H_{13}N_5O_5S_2$

II. Toxicity Hazards

Toxicity Information:

- Mouse; i.v. LD_{50} > 2,000 mg/kg
  p.o. LD_{50} > 5,600 mg/kg
- Rabbit renal toxicity; 100 - 1,000 mg/kg p.o. negative
- Mutagenicity; Ames - negative
  Micronucleus - negative

III. Health Hazard Data

Acute Affects:

- may be harmful by inhalation, ingestion, or skin absorption
- may cause allergic reaction
- may cause irritation

First Aid:

- If swallowed, induce vomiting, wash out mouth with water. Call a physician.
- In case of skin contact, flush with copious amounts of water.
- If inhaled, remove to fresh air and rest. Call a physician.
- In case of contact with eyes, flush with copious amounts of water. Call a physician.

IV. Physical Data

Appearance and Odor:

- White to light yellowish white crystalline powder
- Slightly characteristic odor

V. Fire and Explosion Hazard Data

Extinguishing Media:

- Water spray
- Dry chemical powder

Special Firefighting Procedures: None

Unusual Fire and Explosion Hazards: None

VI. Reactivity Data

Stability: Stable

Conditions to Avoid: High humidity condition

Incompatibilities: No data

Hazardous Combustion or Decomposition Products:
Oxides of sulfur and nitrogen

Hazardous Polymerization: will not occur

VII. Spill or Leak Procedures

Steps to be Taken if Material is Released or Spilled:

- Wear protective equipment.
- Wipe or sweep up, place in a bag and hold for waste disposal.
- Avoid rasing dust.
- Ventilate area and wash spill site after material pick up is complete.

Waste Disposal Method:
Burn as industrial waste or dispose with activated sludge.

VIII. Precautions to be Taken in Handling and Storage

Wear chemical-resistant gloves, safety goggles and dust-protective mask.

Hazardous Label Statements

May cause sensitization by inhalation and skin contact.

Storage and Handling Information for Package Label

Store in a cool dry place.

APPENDIX 3
Certification of Environmental Compliance, Drug Substance

May 26. 1994

Letter addressed to Osaka Plant of Fujisawa Pharmaceutical Co.. Ltd.

Osaka Municipal Government hereby certify that the waste water from Osaka Plant of Fujisawa Pharmaceutical Co.. Ltd. to the public sewage system has been always within the limits of water pollution materials provided in the Sewerage Law by nation issued in 1958. (Japanese law No. 79)

Address of Osaka Plant

1-6. 2-chome. Kashima. Yodogawaku Osaka. Japan

Sincerely yours.

M. Fukuchi

Masakazu Fukuchi

Manager.

Water Quality Control Department

Management Division

Sewage Works Bureau

Osaka Municipal Government

Japan

June 9. 1994

Letter addressed to Osaka Plant of Fujisawa Pharmaceutical Co., Ltd.

Osaka City Government hereby certify that the result of environmental inspection for Osaka Plant of Fujisawa Pharmaceutical Co., Ltd. has been within the limits of Environmental Regulations for prevention of air pollution provided in the Japanese law No. 97 issued by nation in 1968 and Osaka Municipal ordinance No. 1 in 1971. and each value provided in the reports so far submitted by Osaka Plant to the City Government has been always within the limit provided in the above Environmental Regulations.

Address of Osaka Plant

1-6. 2-chome. Kashima. Yodogawaku Osaka. Japan

Sincerely yours.

Toshio Hiraoka

Toshio Hiraoka
Director Engineer and Manager of
Environmental Pollution Control Department
Environment and Public Health Bureau
Osaka City Government
Japan

Fujisawa Pharmaceutical Co., Ltd.
Quality Assurance & Control
Manufacturing Group
1-6, Kashima 2-chome, Yodogawa-ku, Osaka 532, Japan
Telephone:(06)885-5161
Facsimile:(06)885-9313

Fujisawa

Statement of Commitment

We, Fujisawa Pharmaceutical Co. Ltd., hereby declare that Osaka plant located in Osaka-City, Osaka 532, Japan, will be operated in compliance with all applicable Japanese Environmental Laws, Osaka Prefectural Pollution Laws and the agreement with the local authority and the environmental controls within the working area will be in full compliance with Japanese Industrial Safety and Health Law.

K. Nishimura

Kenichi Nishimura
Plant Director
Osaka Plant

Date : October 31, 1995

APPENDIX 4
Certification of Compliance, Drug Product

Cefdinir
Suspension

Lilly

Eli Lilly Industries, Inc.

P.O. Box 1199
Carolina, Puerto Rico 00986-1199
(787) 257-5555

APR - 9

March 25, 1997

Mr. Paul Chen, Senior Manager
Regulatory Affairs
Parke-Davis Research Division
Warner Lambert Company
2800 Plymouth Rd.
Ann Arbor, Michigan 48105

Re: Confirmation of Compliance with Local, State, and Federal Regulations relevant to Manufacturing of Omnicef™ at Eli Lilly Industries, Inc. Carolina, PR

Dear Mr. Chen:

This letter of confirmation is provided in answer to the request in connection with the Omnicef™ submission to the U.S. Food and Drug Administration. The request was for official confirmation that Eli Lilly Industries, Inc. and the facility that will make this product will comply with relevant local, state and federal environmental laws and regulations.

Omnicef™ will be formulated at the PR-03 plantsite of Eli Lilly Industries, Inc. located at Km. 12.6, State Road #3, Carolina, Puerto Rico. Our facility will comply with federal, state and local environmental laws and regulations relevant to the manufacturing of Omnicef™ and with the permits issued to our facility.

Cordially,

ELI LILLY INDUSTRIES, INC.

Aileen Ocasio
Officer, Health, Safety and Environmental Affairs

AO:mos