

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-266

21-267

CHEMISTRY REVIEW(S)

**DIVISION OF SPECIAL PATHOGEN
AND IMMUNOLOGIC DRUG PRODUCTS**

Review of Chemistry, Manufacturing and Controls

NDA #: 21-267

DATE REVIEWED: 09-MAY-2002

CHEMISTRY REVIEW #: 2

REVIEWER: Gene W. Holbert, Ph.D.

<u>SUBMISSION:</u>	<u>DOCUMENT DATE:</u>	<u>CDER DATE:</u>	<u>ASSIGNED DATE:</u>
Original	17-NOV-2000	21-NOV-2000	21-NOV-2000
Amendment	27-JUN-2001	29-JUN-2001	28-JUN-2001
Amendment	28-JUN-2001	29-JUN-2001	29-JUN-2001
Amendment	13-JUL-2001	16-JUL-2001	16-JUL-2001
Amendment	31-JUL-2001	01-AUG-2001	01-AUG-2001
Amendment	27-AUG-2001	28-AUG-2001	28-AUG-2001
Amendment	31-AUG-2001	04-SEP-2001	07-SEP-2001
Amendment	07-SEP-2001	10-SEP-2001	10-SEP-2001
Amendment	23-OCT-2001	24-OCT-2001	24-OCT-2001
Amendment	24-OCT-2001	25-OCT-2001	25-OCT-2001
Amendment	26-OCT-2001	29-OCT-2001	29-OCT-2001
Amendment	22-JAN-2002	23-JAN-2002	23-JAN-2002

NAME & ADDRESS OF SPONSOR:

Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

REPRESENTATIVE:

Maureen H. Garvey, Ph.D.
Director, Regulatory Affairs Department
(212) 733-5688

DRUG PRODUCT NAME:

Proprietary:

VFEND IV

Nonproprietary:

Voriconazole for Injection

Code Name/#:

UK-109,496

Chem.Type/Ther. Class:

1S

PHARMACOLOGICAL CATEGORY: Antifungal (synthetic)

INDICATION:

Invasive aspergillosis, serious *Candida* infections, infections caused by *Scedosporium* spp. and *Fusarium* ss., rare and refractory infections and empirical treatment.

DOSAGE FORM:

Lyophilized powder for IV administration

STRENGTH:

200 mg/vial

ROUTE OF ADMINISTRATION:

IV Infusion

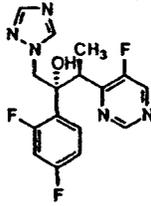
Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME/STRUCTURAL FORMULA: (2*R*, 3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol



Molecular Formula: C₁₆H₁₄F₃N₅O **Molecular Weight:** 349.3 **CAS #:** 137234-62-9

SUPPORTING DOCUMENTS: The application references the following DMFs:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date

RELATED DOCUMENTS: IND

COMMENTS: Pfizer has submitted sufficient information to ensure the identity, strength, quality, purity and potency of voriconazole for injection. However, OC had recommended withholding approval due to deficiencies at the drug product manufacturing site. Consequently, the Division took an Approvable action on 17-DEC-2001. Since then, the manufacturing problems have been resolved and the firm involved has undergone a satisfactory CGMP inspection. On 12-FEB-2002, OC issued an overall recommendation of **Acceptable**.

CONCLUSIONS & RECOMMENDATIONS: The manufacturing problems have been resolved and final labeling negotiations are underway. From the CMC perspective, **APPROVAL** of this NDA is recommended.

Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590: N. Schmuff

NDA 21-267, CMC Review # 2
Pfizer, Inc.

VFEND IV
(voriconazole)

3

cc:

Original: NDA 21-267

HFD-590: N. Schmuff

HFD-590: G. Holbert

HFD-590: J. Saliba

HFD-830: C. Chen

File: N 21-267.000R2.doc

08-MAY-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 1 of 3

Application : NDA 21267/000
Org Code : 590
Priority : 18

Sponsor: PFIZER GLOBAL
50 PEQUOT AVE
NEW LONDON, CT 06320

Stamp Date : 17-NOV-2000
PDUFA Date : 27-MAY-2002
Action Goal :
District Goal: 19-JUL-2001

Brand Name : VFEND (VORICONAZOLE) 20 MG IV
Estab. Name:
Generic Name: VORICONAZOLE
Dosage Form: (INJECTION)
Strength : 200 MG/VIAL

FDA Contacts: J. SALIBA
G. HOLBERT
N. SCHMUFF

Project Manager (HFD-590) 301-827-2423
Review Chemist (HFD-590) 301-827-2399
Team Leader (HFD-590) 301-827-2425

Overall Recommendation: ACCEPTABLE on 12-FEB-2002 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 28-DEC-2001 by P. LEPLER (HFD-324) 301-827-0062
WITHHOLD on 14-NOV-2001 by P. LEPLER (HFD-324) 301-827-0062
WITHHOLD on 29-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment :

DMP No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-00
Decision : ACCEPTABLE
Reason : BASED ON PROFILE
Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-FEB-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1211022 FEI : 1211022
PFIZER INC
EASTERN POINT RD
GROTON, CT 06340

DMP No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

08-MAY-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 2 of 3

FINISHED DOSAGE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-JAN-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION
Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-00
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1819598 FEI : 1819598
PFIZER INC
100 PFIZER DRIVE
TERRE HAUTE, IN 47802
DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-FEB-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610425 FEI : 3002807868
PFIZER LTD
CT139NJ
SANDWICH, KENT, UK
DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-NOV-00
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611016 FEI : 3002807852
PFIZER PHARMACEUTICALS INC
RINGASKIDDY, COUNTY CORK, EI
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

08-MAY-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 3 of 3

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-MAY-01		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

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ON ORIGINAL

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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/

Gene Holbert
5/14/02 02:17:12 PM
CHEMIST

Norman Schmuff
5/15/02 06:53:21 AM
CHEMIST

**DIVISION OF SPECIAL PATHOGEN
AND IMMUNOLOGIC DRUG PRODUCTS**

Review of Chemistry, Manufacturing and Controls

NDA #: 21-267

DATE REVIEWED: 27-SEP-2001

CHEMISTRY REVIEW #: 1

REVIEWER: Gene W. Holbert, Ph.D.

<u>SUBMISSION:</u>	<u>DOCUMENT DATE:</u>	<u>CDER DATE:</u>	<u>ASSIGNED DATE:</u>
Original	17-NOV-2000	21-NOV-2000	21-NOV-2000
Amendment	27-JUN-2001	29-JUN-2001	28-JUN-2001
Amendment	28-JUN-2001	29-JUN-2001	29-JUN-2001
Amendment	13-JUL-2001	16-JUL-2001	16-JUL-2001
Amendment	31-JUL-2001	01-AUG-2001	01-AUG-2001
Amendment	27-AUG-2001	28-AUG-2001	28-AUG-2001
Amendment	31-AUG-2001	04-SEP-2001	07-SEP-2001
Amendment	07-SEP-2001	10-SEP-2001	10-SEP-2001
Amendment	23-OCT-2001	24-OCT-2001	24-OCT-2001
Amendment	24-OCT-2001	25-OCT-2001	25-OCT-2001
Amendment	29-OCT-2001	29-OCT-2001	29-OCT-2001

NAME & ADDRESS OF SPONSOR: Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

REPRESENTATIVE: Maureen H. Garvey, Ph.D.
Director, Regulatory Affairs Department
(212) 733-5688

DRUG PRODUCT NAME:

<u>Proprietary:</u>	VFEND IV
<u>Nonproprietary:</u>	Voriconazole for Injection
<u>Code Name/#:</u>	UK-109,496
<u>Chem.Type/Ther. Class:</u>	1S

PHARMACOLOGICAL CATEGORY: Antifungal (synthetic)

INDICATION: Invasive aspergillosis, serious *Candida* infections, infections caused by *Scedosporium* spp. and *Fusarium* ss., rare and refractory infections and empirical treatment.

DOSAGE FORM:

Lyophilized powder for IV administration

STRENGTH:

200 mg/vial

ROUTE OF ADMINISTRATION:

IV Infusion

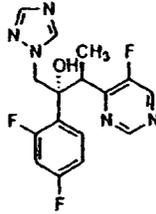
Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

CHEMICAL NAME/STRUCTURAL FORMULA: (2*R*, 3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol



Molecular Formula: C₁₆H₁₄F₃N₅O **Molecular Weight:** 349.3 **CAS #:** 137234-62-9

SUPPORTING DOCUMENTS: The application references the following DMFs:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date

RELATED DOCUMENTS: IND _____

COMMENTS: Please refer to page 3.

CONCLUSIONS & RECOMMENDATIONS: Pfizer has submitted sufficient information to ensure the identity, strength, quality, purity and potency of voriconazole for injection. However, OC has recommended withholding approval due to deficiencies at the drug product manufacturing site. From the CMC standpoint, this application is **APPROVABLE** pending resolution of the manufacturing problems and a satisfactory CGMP inspection of the manufacturer or the identification of another acceptable contract manufacturer.

Gene W. Holbert, Ph.D., Review Chemist

Concurrence:
HFD-590: N. Schmuff

cc:

Original: NDA 21-267

HFD-590: N. Schmuff

HFD-590: G. Holbert

HFD-590: J. Saliba

HFD-830: C. Chen

File: N 21-267.000.doc

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52 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

**DIVISION OF SPECIAL PATHOGEN
AND IMMUNOLOGIC DRUG PRODUCTS**

Review of Chemistry, Manufacturing and Controls

NDA #: 21-266

DATE REVIEWED: 15-NOV-2001

CHEMISTRY REVIEW #: 2

REVIEWER: Gene W. Holbert, Ph.D.

<u>SUBMISSION TYPE:</u>	<u>DOCUMENT DATE:</u>	<u>CDER DATE:</u>	<u>ASSIGNED DATE:</u>
Original	17-NOV-2000	21-NOV-2000	21-NOV-2000
Amendment	27-JUN-2001	29-JUN-2001	28-JUN-2001
Amendment	28-JUN-2001	29-JUN-2001	29-JUN-2001
Amendment	13-JUL-2001	16-JUL-2001	16-JUL-2001
Amendment	31-JUL-2001	01-AUG-2001	01-AUG-2001
Amendment	27-AUG-2001	28-AUG-2001	28-AUG-2001
Amendment	31-AUG-2001	04-SEP-2001	07-SEP-2001
Amendment	07-SEP-2001	10-SEP-2001	10-SEP-2001
Amendment	23-OCT-2001	24-OCT-2001	24-OCT-2001
Amendment	24-OCT-2001	25-OCT-2001	25-OCT-2001

NAME & ADDRESS OF SPONSOR: Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

REPRESENTATIVE: Maureen H. Garvey, Ph.D.
Director, Regulatory Affairs Department
(212) 733-5688

DRUG PRODUCT NAME:

<u>Proprietary:</u>	VFEND
<u>Established:</u>	Voriconazole Tablets
<u>Code Name/#:</u>	UK-109,496
<u>Chem. Type/Ther. Class:</u>	1S

PHARMACOLOGICAL CATEGORY: Antifungal (synthetic)

INDICATION: Invasive aspergillosis, serious Candida infections, infections caused by *Scedosporium* spp. and *Fusarium* ss., rare and refractory infections and empirical treatment.

DOSAGE FORM: Tablets

STRENGTH: 50 and 200 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: Rx OTC

SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FROMULA,
OLECULAR WEIGHT, CAS: (2*R*, 3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol



Molecular Formula: C₁₆H₁₄F₃N₅O **Molecular Weight:** 349.3 **CAS #:** 137234-62-9

SUPPORTING DOCUMENTS: IND _____

The application references the following DMFs:

DMF Type/ Number	Subject	Holder	Status	Review Date	Letter Date
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RELATED DOCUMENTS:

CONSULTS:

REMARKS/COMMENTS: See below.

CONCLUSIONS & RECOMMENDATIONS: Pfizer has submitted sufficient information to ensure the identity, strength, quality, purity and potency of voriconazole tablets. From the CMC

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124 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

standpoint, APPROVAL of this application is recommended.

Gene W. Holbert, Ph.D., Review Chemist

cc:

Original: NDA 21-266
HFD-590 Division File
HFD-590: G. Holbert
HFD-590: J. Saliba
HFD-590: N. Schmuff
HFD-830: C. Chen
R/D Init by: N. Schmuff
File: N 21-266.002.doc

JUN 16 2001

DMF: _____ DMF Type: IV

1. CHEM REVIEW #: 1

2. REVIEW DATE: June 8, 2001

3. DMF INFORMATION REVIEWED:

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Original	August 30, 1999	Volume 22.1 (page 4094)

4. PREVIOUS DOCUMENTS:

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
-------------------------	-------------------------	----------------

5. NAME AND ADDRESS OF DMF HOLDER AND REPRESENTATIVE (S):

Name: _____

Address: _____

Representative: _____

Title: _____

Telephone: _____

Fax: _____

6. ITEM REVIEWED:

Name: _____

Chemical Name: N/A

CAS: N/A

MOLECULAR FORMULA: N/A

MOLECULAR WEIGHT: N/A

7. DMF REFERENCED FOR:

NDA: 21-266

APPLICANT NAME: Pfizer Inc.

LOA DATE: August 30, 1999

DRUG PRODUCT NAME: VFEND (voriconazole) Tablets

DOSAGE FORM: Tablets

STRENGTH: 50 and 200 mg

ROUTE OF ADMINISTRATION: Oral

8. SUPPORTING DOCUMENTS: None

9. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE:

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S
HAVE BEEN PROVIDED:

10. CONSULTS: None

11. REMARKS/COMMENTS: _____ is composed of the
compendial ingredients hydroxypropyl methylcellulose, titanium dioxide, lactose
monohydrate and triacetin. This DMF has been reviewed several times for other items.

12. CONCLUSIONS AND RECOMMENDATIONS: The DMF is adequate for

JSI
Gene W. Holbert, Ph.D.
Review Chemist, HFD-590

JSI 6/16/01
Norman R. Schmuff, Ph.D.
Chemistry Team Leader, HFD-590

CC:
DMF — (2 copies)
HFD-590/Division File NDA 21-266
HFD-590/JSaliba
HFD-590/GHolbert
HFD-590/NSchmuff

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1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

D.V.V

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

IND#: _____

CHEMISTRY REVIEW #: 2

DATE REVIEWED: December 11, 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Telephone conversation	26-Feb-96	----	----
Telephone conversation	05-Mar-1996	----	----
Amendment	11-Jun-96	12-Jun-96	18-Jun-96
Telephone conversation	14-Aug-96	----	----
Amendment	12-Sept-96	16-Sept-96	25-Sep-96

NAME & ADDRESS OF SPONSOR:

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

NAMES:

Generic Name (USAN, BAN):
Code:

Voriconazole
UK-109,496

PHARMACOLOGICAL CATEGORY:

Antifungal

INDICATION:

Treatment of antifungal infections including aspergillosis

DOSAGE FORM/STRENGTH:

Tablets, 50 mg and 200 mg/200 mg/vial

ROUTE OF ADMINISTRATION:

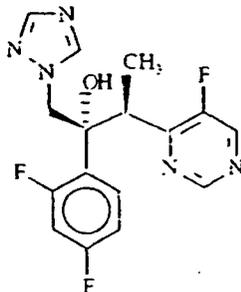
Oral/I.V.

CHEMICAL NAME/STRUCTURAL FORMULA:

Chemical Name: (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol.

Molecular Formula: C₁₆H₁₄N₅F₃O

Molecular Weight: 349.3



RE: IND ~~_____~~ - Voriconazole Tablets
IND ~~_____~~ - Voriconazole Lyophilized Powder
Information Amendments - Chemistry, Manufacturing and Controls
DRAFT LETTER. Continued.

cc:

Richard Midwood
Food and Drug Administration
Boston NE Region
One Montvale Ave.
Stoneham, MA 02180

~~_____~~
~~_____~~
~~_____~~

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6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

proteins and decreased bilirubin concentration and urinary volume. These effects were all reversed after the one-month recovery period.

Study no: 91030

Volume # 14

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: February, 1991

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R1. Purity, 97.3 %.

Formulation/vehicle: methylcellulose 4000 cps containing _____ and HCL.

This study was designed to assess the reversibility of the adrenal and liver changes seen in the previous one-month study. Groups of 5 male and 5 female Sprague Dawley rats were treated orally for one month with UK-109,496 at 0, 10 and 30 mg/kg and then were either sacrificed or kept untreated for another month. The compound was suspended in a 0.5% aqueous solution of methylcellulose 4000 cps containing _____ acidified with _____ HCl and administered at a standard volume of 10 ml/kg bodyweight. Control rats received vehicle only. Clinical observations were restricted to recording mortality and body weights were recorded weekly. Clinical chemistry and hematology were assessed at the end of the study or after the reversibility period. Animals were then sacrificed and necropsied. Liver and adrenals were weighed and subjected to histopathological examination.

Induction of P450, increased liver weights, centrilobular hypertrophy and proliferation of smooth endoplasmic reticulum, increased plasma proteins and decreased bilirubin concentration and urinary volume were all reversed after the one month recovery period. The increases in adrenal weights, seen in the previous one-month study, were not seen in this (smaller) study.

**APPEARS THIS WAY
ON ORIGINAL**

4. Study title: Three-month dietary prechronic toxicity study in Sprague Dawley rats.
Key study findings: Reduced body weight, food consumption, white blood cell counts, lymphocyte counts, serum triglycerides, bilirubin, creatinine and glucose. Increased cholesterol, total proteins, albumin, AST levels, ALT levels, liver weights, kidney weights, testicular weight.

Also observed: centrilobular hepatocellular hypertrophy, fatty change, hepatocellular necrosis, increased cytochrome P450.

Study no: 95-96-11

Volumes # 15-16

Conducting laboratory and location: Drug Safety Evaluation. Central Research. Pfizer Pharmaceuticals Inc. 5-2 Taketoyo-cho, Chita-gun, Aichi, Japan

Date of study initiation: July 1995

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R14.

Formulation/vehicle: Drug-diet mixtures were prepared by bag-blending the voriconazole with an aliquot of diet and then combining this mixture with large amounts of diet in a V-blender.

Groups of Sprague Dawley rats, 10 rats/sex/group, were fed with a diet supplemented with appropriate quantities of voriconazole to result in an average daily intake of 50, 100 or 150 mg/kg. Animals were housed individually and kept in a 12-hour light/dark cycle. Animals had free access to food and water. Records were kept of clinical signs, body weight, food consumption, hematology, serum chemistry, urinalysis, histopathology of liver, heart, kidney, lungs as well as hepatic cytochrome P450 content. Nine supplementary rats /sex/dose level were used for plasma drug level determinations, while a control group of 10 rats/sex received an unsupplemented diet. Plasma drug levels were measured at 1200, 1600, 2000 and 2400h on day 63 at 0400 and 0800 h on day 64.

There was no mortality during this study. At all dose levels, there were significant decreases in body weight, compared to the control animals. At 50, 100 and 150 mg/kg voriconazole, body weight gain was reduced by 4, 16 and 20 % and body weight was reduced by 3, 9 and 11% in males. For females, the corresponding reductions in body weight gain were 21, 23 and 28 % and the reductions in body weights were 9, 9 and 11 %. Mean food consumption was generally lower in the treated groups when compared to controls but the reductions were not always significant, and when they were, they ranged from 8 to 15 %. The relationship between reduced food consumption and reductions in body weights/ body weight gains remains unclear. Since food consumption was reduced, the delivered dose of drug must have been less than estimated, perhaps by as much as 15 %. However, the reduction in body weight may have compensated for this effect.

Drug administration was also associated with decreased hemoglobin content, hematocrit, red blood cell count, mean cell volume and mean cell hemoglobin, but these changes were generally mild (<13 %). White blood cell counts were significantly decreased (up to - 28 %) and correlated with mildly decreased lymphocyte counts in males. Other changes included decreased serum triglycerides (up to -87 % in high dose males), increased cholesterol (up to 117 % increase in high dose females) and decreased bilirubin (up to 85 % decreased). Total proteins increased by up to 16 %, albumin increased by up to 19 %, BUN increased by up to 28 % and creatinine decreased by up to 25 %. Glucose decreased by up to 27 %. There were positive

reactions for proteins and ketones in the urine of some animals. AST levels were increased in males (by 49 and 75 % respectively at 50 and 150 mg/kg/day) and ALT levels were increased by 33 % at 150 mg/kg/day.

Necropsy findings included enlarged livers, dose related increases in liver weight (34 to 132 % increase in relative liver weights), increased relative kidney weights (up to 20 %), and increased relative testicular weights (up to 17%). Hepatic centrilobular hypertrophy was seen in all treated animals and the increase in the size of the centrilobular hepatocytes was dose-related (see Table 6). Fatty change was observed at all dose levels and ranged from the micro vacuolation of midzonal hepatocytes with a few macro vacuolated hepatocytes to the micro vacuolation of midzonal to perilobular hepatocytes, with a moderate number of macro vacuolated hepatocytes. Other liver changes included slight multifocal hepatocellular necrosis in centrilobular areas, seen in 3/10 high dose males, and subcapsular liver necrosis, seen in 4/20 mid- and 2/20 high- dose animals. Hepatic microsomal cytochrome P450 was increased at all doses and ranged from 2-3 times control levels at the lowest dose, to 4-5 times control at the highest dose.

Table 6. Incidence of microscopic observations in liver (10/sex/group examined)

Finding	Control	50 mg/kg	100 mg/kg	150 mg/kg
Infiltration, mononuclear cells	7 (5m,2f)	4 (2m,2f)	4 (2m,2f)	3 (3m)
Centrilobular hypertrophy	0	20	20	20
Necrosis, centrilobular	0	0	0	3(m)
Necrosis, subcapsular	0	0	4(1m,3f)	2(1m,1f)
Fatty change, focal	0	0	0	1
Fatty change	0	8 (7m,1f)	13(9m,4f)	12 (10m,4f)

AUC values over the 24-hour period increased with dose level, but were superproportional at 150 mg/kg (see Table 7).

Table 7. AUC values over 24 hours (µg.h/ml) for UK-109,496

Dose	Males	Females
50	8.9	13

100	23	19
150	61	40

Summary

Several toxic effects, notably multifocal liver necrosis were associated with 100 and 150 mg/kg doses of voriconazole, administered to rats for three months.

Conclusion

Voriconazole was associated with multifocal liver necrosis in the 100 and 150 mg/kg doses after three months of dosing. The animals also demonstrated decreased weight and decreased weight gain at these doses. Other studies (see 6 month study in rats) have shown that there is greater bioavailability of drug and less liver necrosis when drug is administered by gavage, compared to the dietary route.

5. Study title: Six-month oral toxicity study in Sprague Dawley rats-with reversibility at 10 mg/kg.

Key study findings: Decreased hemoglobin, RBC count, packed cell volume, red cell distribution width, platelet volume, lymphocyte count, total white cell count. Increased mean corpuscular hemoglobin, and platelet count. Decreased bilirubin levels, increased cholesterol, increased albumin, total protein, calcium, decreased chloride levels. Increased liver, kidney and adrenal weights. Centrilobular hypertrophy, thyroid hypertrophy, nephropathy, atrophy of the exocrine pancreas and vacuolation of the pituitary.

Study no: 91085

Volume # 16

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: September 1991

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R3. Purity, 100%

Formulation/vehicle: methylcellulose 4000 cps containing _____ and HCL.

Groups of Sprague Dawley rats, 20 per sex per dose group, were treated orally (by esophageal intubation) with UK-109,496 at 3, 10 and 50 mg/kg on a daily basis for six months. Drug was formulated in an aqueous solution of methylcellulose and _____, acidified with _____ hydrochloric acid and administered in a volume of 10 ml/kg. Control rats (20 rats/sex) received vehicle alone over the same period. Records were kept of body weights, food consumption, ophthalmology, hematology, clinical chemistries and plasma drug levels. Rats surviving to the end of the study were sacrificed and subjected to necropsy. Adrenals, brain,

heart, kidneys, liver, spleen and testes were weighed and a complete panel of organs subjected to histopathological examination. The liver was examined using electron microscopy. In a supplementary experiment, designed to assess the reversibility of any toxic effects seen after six months, 10 rats/sex were treated with 0 or 10 mg/kg/day for 6 months after which they were allowed to recover for two months before sacrifice. In a second supplementary experiment, groups of 5 animals/sex/dose level were treated for six months and used to determine drug levels. On days 1 and 176 of the study, blood was collected for plasma drug level assays at 0200, 0500, 1000 and 2400h after dosing.

Mortality

There were no deaths during this study that could be ascribed to the drug substance. No animals from the high dose group died. Deaths in the other dose groups were as follows: Control group: 3/60, low dose group: 1/50, mid dose group: 3/70 animals.

Clinical signs observed in all dose groups (including control animals) included brown deposits on the muzzle or around the eyes (chromodacryorrhoea) and cutaneous lesions (alopecia, crusts, irritation or cutaneous outgrowths). Since these findings were also detected in control animals, they may be related to the excipient.

Other changes included decreases in hemoglobin, red blood cell count, packed cell volumes, red cell distribution width, mean corpuscular volume, platelet volume, lymphocyte count and total white cell count. There were also increases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration and platelet count (although the low dose females had slightly lower platelet counts). Bilirubin levels were decreased up to 50%. Reductions were observed in alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase although these changes were generally transient and moderate. Cholesterol was increased in high dose females, but it was decreased in some males. The drug was also associated with an increase in albumin, total protein, and calcium. Decreases were seen in chloride levels. Potassium levels decreased in females and increased in males. A slight decrease in cholesterol level was still detectable in males, two months after the end of treatment. Drug was also associated with decreased urine pH, increased urine density and decreased urine volume. Except where otherwise noted, these changes were mild (generally less than 20%) and were usually reversible.

Post-mortem changes included increased liver weights (males and females) and increased kidney weights (females). Adrenal weights increased (+15-24%) in females and decreased (-16%) in males, while cardiac weights increased in females (+9%) and decreased in males (-9%). None of these changes were present at the end of the recovery period.

Histologically, rats showed dose-related increases in the incidence and severity of hepatic centrilobular hypertrophy, which, in the high dose animals, extended to midzonal and periportal regions. High dose animals also showed hypertrophy of thyroid follicular cells. There was also a mild dose-related increase in the incidence and severity of chronic progressive nephropathy.

Other changes, seen only in males, included focal atrophy of the exocrine pancreas (1/20, 5/20 and 5/20 males at the low, mid and high doses, respectively) and vacuolation of the pituitary (1/20 and 3/20 at the low and high doses, respectively).

Pharmacokinetics

On day One, plasma UK 109,496 concentrations were maximal 2 or 5 hours after dosing and were generally higher in females than in males. At 24 hours, no drug was detected at the low and mid doses and only very low levels (0.07 to 3.68 µg/ml) were noted at the high dose. Mean AUC's (2-10 hours) were 3.3 and 1.6 fold higher in females than in males at the low and mid doses, respectively, and increased superproportionately to dose in males but not in females. On day 176, drug concentrations were lower and declined more rapidly than on day one, with no drug detected 24 hours after dosing. AUC's were lower on day 176 compared to day one (25% at the low dose and 60 to 80% at the high dose). Drug exposures were higher in females than in males at all dose levels and were approximately proportional to dose.

Table 8. Mean AUC (2-10 h) values µg.h/ml on day 1

Dose (mg/kg)	Males	Females
3	2.8	9.3
10	24	39
50	199	189

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Table 9. Mean AUC (2-10 h) values µg.h/ml on day 176

Dose (mg/kg)	Males	Females
3	2.1	6.8
10	9.4	23
50	48	73

Mean AUC values were higher in females than in males at the two lower doses on day 1 and at all doses on day 176. Mean AUC values were also lower on day 176 compared to day 1. Since the drug has been shown in other studies to induce its own metabolism, this result is not entirely unexpected.

The liver remains the main site of toxic effects after six months of therapy with UK-109,496. A number of the post-mortem changes (such as increased liver weights and kidney weights) were not present at the end of the recovery period. Other effects noted included thyroid follicular cell hypertrophy, nephropathy, focal atrophy of the exocrine pancreas and vacuolation of the pituitary.

6. Study title: UK- 109,496: 3 month dietary prechronic toxicity in CD-1 mice.

Key study findings: Increased aspartate aminotransferase and alanine aminotransferase, increased liver weights, increased triglycerides, hepatocellular hypertrophy, hepatocellular fatty changes, necrosis of the liver and hepatic microsomal cytochrome P450 increases.

Study no: 92104

Volume # 15

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: November 1990

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R1.

Formulation/vehicle: Voriconazole was admixed with the diet

CD-1 mice, 10/sex/group were fed for three months with a diet supplemented with appropriate amounts of UK-109,496 to result in an average daily intake of 50, 100 or 150 mg/kg. Animals were housed individually and were subjected to a twelve-hour light/dark cycle. Records were kept of mortality, clinical signs, body weight, food and water consumption, hematology, clinical chemistries, necropsy findings, select organs weights, histopathology findings (heart, kidney, lungs, liver, pancreas, ovary) cytochrome P450 contents and electron microscopy of liver. Food consumption was measured automatically using an electronic balance connected to a computer. Plasma drug levels were determined in 18 supplementary mice/sex/dose level on day 80 at 0400, 0800, 1200, 1600, 2000 and 2400h.

Mortality

One high dose animal from the main study was found dead on day 42. No cause of death was recorded, but the mouse died without any premonitory sign. One low dose animal from the pharmacokinetics study section died from an anesthesia accident.

Toxicity

The liver was the target organ of UK-109,496 toxicity. Low dose UK-109,496 (50 mg/kg) was associated with decreased neutrophil counts (-44%) and decreased monocytes (-46%), increased aspartate aminotransferase and alanine aminotransferase (females only, see Table 6), increased liver weights (+26 %) , hepatocellular hypertrophy, mild hepatocellular fatty changes, subcapsular necrosis of the liver (2/20 low dose animals) and hepatic microsomal cytochrome P450 increases.

At the higher doses, toxicity also included increased neutrophils (+55 %) and monocytes (+39 %) and increased triglycerides (+73 % in high dose males). Livers were enlarged, pale or marbled with single cell necrosis, proliferation of smooth endoplasmic reticulum and accumulation of cytoplasmic vacuoles. Occasionally, there were differences in the susceptibility between males and females. See table 7 for a summary of the microscopic observations in the liver.

Table 6. Increases in aminotransferase activity in treated females (% control)

Dose (mg/kg)	ALAT increase (% control)	ASAT increase (% control)
50	+40 %	+35 %
100	+65 %	+31 %
150	+106%	+53 %

Table 7 Incidence summary of microscopic observations in liver

Finding	Control	50 mg/kg	100 mg/kg	150 mg/kg
Infiltration, mononuclear cells	0	0	1m	0
Centrilobular hypertrophy	0	8m	17(9m,8f)	17(10m,7f)
Necrosis, single cell	0	0	0	3(m)
Necrosis, subcapsular	0	2(1m,1f)	2(f)	1(f)

Cystic change, hepatocellular	0	0	0	1f
Mitoses	0	0	0	1m
Fatty change	0	4(1m,3f)	17(9m,8f)	17(8m,9f)

Ten males and ten females were examined per group. m-males, f-females

All the necrosis in the male rats was described as minimal. At 50 mg/kg, there was minimal subcapsular necrosis and at 150 mg/kg, minimal single cell necrosis. In the females, the 50 mg/kg dose produced moderate subcapsular necrosis, while the lesion at the two higher doses were described as mild.

Table 8 shows the exposure of the animals over 24 hours.

Table 8. UK-109,496 AUC values over 24 hours, males versus females

Dose (mg/kg)	AUC _{0-24h} (µg.h/ml)	
	Male	Female
50	3	4
100	7	14
150	30	32

Drug exposure increases with dose, but is greater in females than in males. The increase in exposure with dose is superproportional at 150 mg/kg/day in males and at 100 and 150 mg/kg/day in females.

Conclusion: The liver was the target organ of UK-109,496 toxicity. Increased aspartate aminotransferase and alanine aminotransferase, increased liver weights, hepatocellular hypertrophy, hepatocellular fatty changes, necrosis of the liver and hepatic microsomal cytochrome P450 increases were among the toxicities associated with UK-109,496 administration for three months in the diet.

7. Study title: UK-109,496: One month oral toxicity in beagle dogs.

Key study findings: Increased alkaline phosphatase, decreased cholesterol levels, decreased plasma fibrinogen levels, QT prolongation, ophthalmic lesions, (depigmented streaks in the non-tapetum), endocardiosis, mydriasis, salivation, emesis, anorexia, lack of feces, depression, prostration, dryness of the nose, mucopurulent exudates, weight loss, decreased heart rates, markedly increased hemoglobin, red blood cell count and packed cell volume and moderately

increased prothrombin times. Decreased calcium, potassium, glucose and total proteins. Increased aspartate and alanine aminotransferase. Increased liver, spleen, adrenal and renal weights and decreased testicular weights. Thick black bile, pancreas embedded in a gelatinous material, discolored kidneys, small spleen, testes and prostate, and red zones on the endocardium, fatty liver, tubular vacuolation of the kidney, atrophy of the salivary glands, thymic atrophy, testicular tubular atrophy, focal acute vasculitis (brain) and bone marrow atrophy.

Study no: 90145

Volume # 14

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: November 1991

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R1.

Formulation/vehicle: methylcellulose 4000 cps containing _____ and HCL.

Groups of 3 male and 3 female beagle dogs received single daily oral doses of 3, 6, and 12 mg/kg UK-109,496 for one month. Groups of 3 dogs/sex received 24 mg/kg for 14 or 16 days before the animals died or were sacrificed. The compound was suspended in an aqueous solution of methylcellulose 4000 cps containing _____ and administered at a standard volume of 1 ml/kg bodyweight. Control groups received 1 ml/kg of vehicle over the one-month period. Records were kept of clinical signs, food intake, body weight, cardiovascular measurements, ophthalmology, hematology, clinical chemistry and plasma drug levels. At the end of the study all animals were sacrificed and subjected to necropsy. A full histopathology panel of organs underwent histopathological examination and the brain, heart, kidneys liver ovaries, spleen, testes and adrenals were weighed. Cytochrome P450 levels were measured in the liver, which was also examined by electron microscopy. On days 1 and 16, the dogs were bled at 2, 5, 8, and 24 hours after dosing for plasma drug level determination.

Mortality

At the 24 mg/kg dose, one female dog was found dead on day 13 (before dosing) and another (female) on day 17. Another (male) dog was sacrificed in a moribund condition on day 17.

While dogs treated at 3 mg/kg showed only minor rises in alkaline phosphatase, the next higher dose (6 mg/kg) was also associated with decreased cholesterol levels. At 12 mg/kg, additional toxic effects included a moderate decrease in plasma fibrinogen levels and QT interval values exceeding the upper limit of the normal range of 240 milliseconds in two dogs. A bilateral lesion, seen on ophthalmoscopic examination, which was situated on the fundus and consisted of depigmented streaks in the non-tapetum, was only seen in one animal at 12 mg/kg. Also at 12 mg/kg, three of six animals had endocardiosis. Dogs receiving the highest dose, 24 mg/kg,

showed mydriasis, salivation, emesis, anorexia, lack of feces, depression, prostration, dryness of the nose, mucopurulent exudates, weight loss, decreased heart rates (30% decreased), markedly increased hemoglobin, red blood cell count and packed cell volume and moderately increased prothrombin times. In addition, decreased calcium (-20%), potassium (-30 to -40%) and glucose (-30 to -70%) and total proteins (-10 to -50%) as well as increased aspartate and alanine aminotransferase were observed. High-dose animals also had increased liver, spleen, adrenal and renal weights and decreased testicular weights. Other findings included thick black bile, pancreas embedded in a gelatinous material, discolored kidneys, small spleen, testes and prostate, and red zones on the endocardium, fatty liver, tubular vacuolation of the kidney, atrophy of the salivary glands, thymic atrophy, testicular tubular atrophy, focal acute vasculitis (brain) and bone marrow atrophy.

Toxicokinetics

Drug exposure was measured after the first and sixteenth doses at 2, 5, 8 and 24 hours after dosing. Drug levels were approximately dose-related and repeated administration led to reduced exposure after 3, 6, and 12 mg/kg. Treatment at the higher dose (24 mg/kg) resulted in drug accumulation. On a biochemical level, treatment with 3, 6, or 12 mg/kg produced an increase (of similar magnitude), in the hepatic cytochrome P450 content, while the degree of induction appeared to be less at 24 mg/kg (see Tables 10 and 11)

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Table 10. Range of maximal drug concentrations ($\mu\text{g/ml}$) in beagle dogs on days 1 and 16

Dose (mg/kg)	Day 1. Range of maximal drug concentrations ($\mu\text{g/ml}$)	Day 16. Range of maximal drug concentrations ($\mu\text{g/ml}$)
3		
6		
12		
24		

Table 11. Mean AUC (2-24h) ($\mu\text{g}\cdot\text{h/ml}$) after repeated exposure to UK-109,496 on Days 1 and 16.

Dose (mg/kg)	AUC (2-24h) (µg.h/ml)	
	Day 1	Day 16
3	24	14
6	64	43
12	170	124
24	332	867

Conclusion:

Adverse effects were seen in the dogs after 30 days of treatment with voriconazole at 3 mg/kg/day. This is equivalent to a human dose of 1.6 mg/kg for one month. At the higher doses toxic effects of this drug include changes in the eyes, liver and heart.

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8. Study title: 6-month oral toxicity study in beagle dogs, with reversibility at 8 mg/kg. Key study findings: Absence of stool, anorexia, depression, body weight loss, premature ventricular contractions, right deviation of the QRS axis, increased platelet counts and plateletcrit, increase in activated partial thromboplastin time (APTT), alkaline phosphatase (+518%), elevated alanine aminotransferase activity, decreased mean albumin levels, decreased calcium, decreased total protein and decreased mean cholesterol. Increase liver weight. Enlarged and/or dark/marbled/white livers. Hepatic centrilobular hypertrophy, multinucleated hepatocytes, subcapsular hemorrhage, single cell necrosis. Vacuolation of the zona fasciculata of the adrenal glands and tubular giant cells within the seminiferous tubules. Moderate proliferation of smooth endoplasmic reticulum, with displacement of nucleus and organelles to the periphery of the cell. Increase in the specific content of hepatic microsomal cytochrome P450.

Study no: 91084

Volume # 17

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboisè, Cedex, France.

Date of study initiation: September 1991

GLP compliance: Yes

QA report: Yes

Drug batch number :R3.

Formulation/vehicle: methylcellulose 4000 cps containing _____ and HCL.

Groups of beagle dogs, four/sex/dose group were treated with oral UK109 at doses of 4, 8 and 12 mg/kg/day (capsules) for six months. The high-dose group was initially treated with 15 mg/kg for 8 days but this dose caused unacceptable levels of adverse reactions. The dose was therefore stopped and, after a six-day recovery period, animals were treated with 12 mg/kg from day 15 onwards. Control animals were given two placebo capsules per day over the same period. To determine the reversibility of observed changes, supplementary groups of two dogs/sex were treated at 0 and 8 mg/kg for six months after which treatment was withdrawn and animals observed for two months before sacrifice. Records were kept of clinical signs, food intake, body weights, cardiovascular findings, ophthalmology, hematology, clinical chemistry of plasma and urine, necropsy findings, organ weights, histopathology, cytochrome P450 measurements and liver electron microscopy findings.

Mortality

There were no deaths during this study.

Toxicity

Clinical signs were severe in the animals treated with 15 mg/kg/day. Effects included absence of stool (first observed between 3-6 days after dosing began), anorexia (starting on day 5), depression (starting on day 8) and body weight loss (between days 1 and 7). Later, the dose was reduced to 12 mg/kg/day, the growth of these dogs resumed at a rate similar to that of controls, and fully compensated for their initial rate loss by day 50. There were sporadic (although statistically significant) variations in body weights in all dose groups, but these changes were generally in the 10% range. There were no significant changes in cardiovascular parameters that seemed drug-related. One (mid-dose group) animal showed premature ventricular contractions and another (low dose group) animal showed a right deviation of the QRS axis.

In females, significant changes were observed in platelet counts (<47% increase), plateletcrit (<29% increase) mean platelet volume (<12 % decrease). These findings, along with a statistically significant increase in activated partial thromboplastin time (APTT) were comparable to values in concurrent controls two months after cessation of treatment. The main treatment-related change in plasma chemistry was an increase in mean plasma alkaline phosphatase in most treatment groups, which was dose-dependent and rose as high as 518 % of control at the high dose. Other changes included moderately elevated alanine aminotransferase

activity, decreased mean albumin levels, decreased calcium, decreased total protein and decreased mean cholesterol. Plasma chemistry was normal at the end of the two-month reversibility period.

A dose-related increase in absolute (<83% increase) and relative (<73% increase) liver weight was observed in both sexes. Livers occasionally appeared enlarged and/or dark or marbled. One high-dose animal presented with a large white area which was firm. On a microscopic examination, all treated animals except one low dose female presented with hepatic centrilobular hypertrophy. In the mid and high-dose groups, this was accompanied by a dose related increase in the number of multinucleated hepatocytes. Foci of subcapsular hemorrhage and single cell necrosis were observed in a few hepatocytes. Liver changes were reversible after two months. Other histopathological changes included vacuolation of the outer part of the zona fasciculata of the adrenal glands in high dose animals and tubular giant cells within the seminiferous tubules.

Electron microscopy demonstrated moderate proliferation of smooth endoplasmic reticulum, with displacement of nucleus and organelles to the periphery of the cell.

Treatment of dogs with 8 mg/kg UK-109,496 caused an increase in the specific content of hepatic microsomal cytochrome P450.

Conclusion:

The administration of UK-109,496 to dogs for 6 months at doses up to 8 mg/kg/day produced changes in the liver which were reversible after a two-month recovery period. This dose is equivalent to a human dose of 4.3 mg/kg/day for six months. The sponsor neglected to assess the reversibility of the lesions at the high dose. Premature ventricular contractions were noted.

9. Study title: Twelve-month oral toxicity study (capsules) in beagle dogs.

Key study findings: mean arterial pressure increase, heart rate increase, decreased P wave amplitude, increased alkaline phosphatase, increased alanine aminotransferase, increased liver weights, centrilobular hypertrophy, multinucleated hepatocytes, single cell necrosis, decreased albumin, vacuolation of the adrenal zona fasciculata.

Study # 96107

Volume # 18

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: June 26, 1997

GLP compliance: Yes

QA report: Yes

Drug batch number: R18. Purity, 100 %.

Formulation/vehicle: Voriconazole was formulated in capsules containing lactose, maize starch, aerosil 200 and magnesium stearate.

Groups of 4 male and 4 female beagle dogs received single daily oral doses of 4, 8, and 12 mg/kg UK-109,496 for twelve months. Control groups received placebo capsules. Records were kept of mortality, clinical signs, food intake, body weight, cardiovascular measurements, ophthalmology, hematology, urinalysis, clinical chemistry and plasma drug levels. At the end of the study all animals were sacrificed and subjected to necropsy. Internal organs were subjected to histopathological examination and the brain, heart kidneys, pituitary, liver, spleen, ovaries/testes and adrenals were weighed. On days 8 and 260, the dogs were bled at 2, 5, 10, and 24 hours after dosing for plasma drug level determination.

Mortality

There were no deaths during the study.

Toxicity

Voriconazole administration was associated with slight decreases in body weight (up to 5% decreases) during the first 8 days of dosing but body weights returned to day 1 values by day 43. Thereafter, males continued to gain weight normally, but females had reduced bodyweight gain so that at the end of the study, female animals weighed about 10% less than control animals.

Cardiovascular effects

Voriconazole administration was associated with increased mean arterial pressure (MAP) (+20%) compared to predose values on day 355. On day 12, heart rate was decreased (by as much as 26 %) and P wave amplitude was sporadically decreased (by up to about 30%) in some animals compared to predose values.

Hematology

Platelet counts were increased between 12 % at the low dose on day 93 and 57 % on day 365. Alkaline phosphatase was increased at all doses on days 93 and 275 (see Table 12 below)

Table 12. Percentage increase in alkaline phosphatase on days 93 and 275 of voriconazole treatment

	4 mg/kg	8 mg/kg	12 mg/kg
Day 93	+63%	+129%	+300%
Day 275	+95%	+176%	+618%

Alanine aminotransferase levels were increased (by less than two-fold) at low and mid doses, but were increased by as much as 7 fold at the high dose. Albumin concentrations were decreased at the mid dose (by as much as 16%) and by as much as 23% at the high dose.

Plasma Drug levels

Exposure to voriconazole increased superproportionally with dose and AUC's were higher in males than in females. Exposure levels were similar over time at the mid and low doses but were lower on day 260 than on day 8 for the high dose.

Table 13: Pharmacokinetics of voriconazole

Dose (mg/kg)	AUC _{0-24h} (µg.h/ml)			
	Day 8		Day 260	
	Males	Females	Males	Females
4	30	22	31	27
8	84	56	87	72
12	741	221	161	131

Postmortem findings

Voriconazole produced increases in relative and absolute liver weights at all doses tested. Increases ranged from 22% at the low dose to 66% at the high dose. The effect was slightly greater in males (+51 and +66% at the mid and high doses) than in females (+ 37 and + 58%). Livers were enlarged and discolored. All dogs (except one low dose dog) showed centrilobular hypertrophy of the liver. Liver enlargement was associated at the high dose with multinucleated hepatocytes, single cell necrosis, intracytoplasmic acicular crystals and vacuolation of the gall bladder epithelium. Subcapsular hemorrhage or fibrosis often correlated with the discoloration and was observed at the high dose and mid dose.

Toxic effects included vacuolation of the adrenal zona fasciculata and was seen in all dose groups (1/8 low -, 2/8 mid- and 4/8 high-dose animals). Vacuolation was sometimes multifocal and randomly distributed and vacuoles were large, displacing the nucleus at the periphery of the cell. Testicular atrophy was seen in one control, two low dose, 1 mid dose and 2 high dose males.

Conclusions

Treatment of dogs with oral voriconazole at 4, 8 and 12 mg/kg/day resulted in toxic effects in the liver, kidney and heart. Effects included MAP increase, heart rate increase, decreased P wave amplitude, increased alkaline phosphatase, increased alanine aminotransferase, increased liver weights, centrilobular hypertrophy, multinucleated hepatocytes, single cell

necrosis, decreased albumin and vacuolation of the adrenal zona fasciculata. NOAEL was less than 4 mg/kg, equivalent to a dose of less than 2.2 mg/kg, based on body surface area conversions.

Intravenous Studies

10. Study title: Single dose intravenous toxicity in CD1 mice and Sprague Dawley rats.

Key study findings: Minimum lethal dose was greater than 100 mg/kg for both species.

Equivalent to human doses between >8 mg/kg

Study numbers 91090 and 91091

Volume # 13

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: September 1991

GLP compliance: Yes

QA report: Yes

Drug lot # 953-47

Formulation/vehicle: Voriconazole was dissolved in an aqueous solution of hydroxypropyl-beta-cyclodextrin

Groups of rats and mice (5 animals/sex/dose group) were treated with 50 and 100 mg/kg of voriconazole, intravenously. Drug (10 mg/ml) was dissolved in an aqueous solution of hydroxypropyl-beta-cyclodextrin (HPBCD 160 mg/ml). Drug was injected at a dose of 5 ml/kg and 10 ml/kg to achieve doses of 50 and 100 mg/kg respectively. Records were kept of clinical signs, mortality and bodyweight for 14 days.

There was no mortality. Both species showed staggering and incoordination of the hind limbs at both doses. Other clinical signs in rats included salivation and tremors. Mice also showed restlessness and extended limbs.

Conclusion

The minimum lethal dose in both species was > 100 mg/kg. These doses are equivalent to human doses between >8 or >16 mg/kg (based on mouse and rat data, respectively).

11. Study title: Single dose intravenous toxicity in CD1 mice and Sprague Dawley rats.

Key study findings: Minimum lethal dose was greater than 100 mg/kg for both species.

Equivalent to human doses between >8 mg/kg

Study # 93100/93101.

Volume # 13

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: January 1994

GLP compliance: Yes

QA report: Yes

Drug, lot # R8

Formulation/vehicle: Voriconazole was dissolved in an aqueous solution of beta-cyclodextrin sulphobutyl ether SBECD

Groups of Sprague Dawley rats [CrI:COBS-VAF-CD(SD)BR(France)] and CD1 mice [CrI:COBS-VAF-CD1(ICR)BR(France)], 5 animals/sex/dose group, were treated with single doses of voriconazole (50 or 100 mg/kg), intravenously. Drug (10 mg/ml) was dissolved in an aqueous solution of beta-cyclodextrin sulphobutyl ether (SBECD) and injected at a dose of 5 ml/kg or 10 ml/kg to achieve doses of 50 or 100 mg/kg. Records were kept of clinical signs, mortality and bodyweight for 14 days after which animals were sacrificed and necropsied.

There was no mortality. In mice, the 50 mg/kg dose of UK,109-496-496 resulted in staggering and at 100 mg/kg, mice showed increased activity, convulsions, rigid, extended limbs, hunched posture, piloerection. In the rats, the 50 mg/kg dose produced tremors while 100 mg/kg resulted in decreased activity, increased salivation, rigid extended limbs, slow lateral head movements.

Conclusion

The minimum lethal dose in both species was > 100 mg/kg. This dose is equivalent to human dose of 8 or 16 mg/kg (based on body surface area comparisons of mouse and rat data, respectively).

12. Study title: 14-day intravenous range-finding toxicity in Sprague Dawley rats.

Key study findings: Toxic effects included decrease in water consumption, mild centrilobular hypertrophy in the liver, proliferation of the smooth endoplasmic reticulum and P450 induction, vacuolation of kidney proximal tubules.

Study # 90150

Volume # 21

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: November 1990

GLP compliance: Yes

QA report: Yes

Drug lot # R1

Formulation/vehicle: Voriconazole was dissolved in an aqueous solution of HPBCD

Groups of Sprague Dawley rats, 5 rats/sex/dose group, were treated with 5, 10 and 20 mg/kg of UK,109 intravenously. Drug was dissolved in an aqueous solution of HPBCD. A control group of rats received vehicle. Three supplementary groups of rats were used to determine plasma drug levels on days 1 and 13.

There was no mortality. Toxic effects included a temporary decrease in water consumption in high dose males during the first week, mild centrilobular hypertrophy in the liver in high dose animals, proliferation of the smooth endoplasmic reticulum and P450 induction (1.5 times control levels). Injection site inflammation and granulomas, as well as vacuolation of kidney proximal tubules were probably excipient-related, as they were also seen in controls.

Pharmacokinetics

Plasma drug levels increased to levels slightly higher than would be predicted from a dose proportional model (see Table 14).

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Table 14. Mean plasma voriconazole levels one hour postdose: relationship to dose and duration of therapy.

Dose (mg/kg)	Concentrations ($\mu\text{g/ml}$)	
	Day 1	Day 13
5	1.64	1.37
10	4.90	3.84
20	12.0	7.85

AUC's increased with dose but were lower on day 13 than on day 1, suggesting that the metabolism of the drug was enhanced by repeated dosing (see Table 15, below).

Table 15. Pharmacokinetics of voriconazole: AUC values and their relationship to dose and number of doses.

Dose (mg/kg)	AUC's (µg.h/ml)	
	Day 1	Day 13
5	5.05	4.23
10	16.9	12.9
20	46.0	25.7

Conclusion

Liver is the major target organ of intravenous voriconazole toxicity and the drug induces its own metabolism.

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13. Study title: 1-month intravenous toxicity in Sprague Dawley rats.

Key study findings: Increased plateletcrit and platelet count, increased protein, decreased bilirubin. Slight decrease in pH, increased liver weights, centrilobular hypertrophy, renal tubular vacuolation ascribed to the vehicle. Injection site lesions and lung granuloma.

Study 91076

Volume 21

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: July 1991

GLP compliance: Yes

QA report: Yes

Drug, lot # 953-47

Formulation/vehicle: Voriconazole was dissolved in an aqueous solution of HPBCD

Rats (10 males and 10 females/dose) were treated with 2, 5, and 10 mg/kg of voriconazole, intravenously for 28 or 29 days. A vehicle control group received HPBCD only, a saline control group received saline. Records were kept of mortality, clinical signs, food and

water intake, body weights, ophthalmology, plasma chemistry, hematology, urinalysis, gross necropsy findings, organ weights and histopathology findings.

Mortality

One high dose female died on day 10 of the study. This animal convulsed during handling (before dosing) and died.

Toxicity

A slight increase in the RBC distribution width (increased 6 and 8% in mid and high dose females respectively) was not considered to be toxicologically significant. Other changes seen in high dose females included mildly increased plateletcrit (+17 %) and platelet count (+15 %), increased protein (+6%) and decreased bilirubin (-29%). A slight decrease in pH was observed in high-dose males (7.2 vs 7.8)

Liver weights were slightly increased in mid and high dose females (+ 8 and 12 % respectively). Minimal centrilobular hypertrophy (hepatocytes enlarged by a factor less than 1.5) was observed in three high dose females.

Multifocal renal tubular vacuolation of proximal tubules was found in all animals which received 160 mg/kg HPBCD with or without voriconazole and so this was ascribed to the vehicle. Injection site lesions and lung granuloma also seemed to be unrelated to the drug since they were also found in control animals.

Conclusion

Liver is the primary target organ during a 28 day administration. The NOAEL (2 mg/kg) was determined to be equivalent to a human dose of 0.32 mg/kg/day for 28 days. Female rats seem to be more sensitive to the toxic effects of the drug.

14. Study title: 1-month intravenous toxicity in Sprague Dawley rats with one-month reversibility at 10 mg/kg.

Key study findings: Increased plateletcrit and platelet count, increased protein, decreased bilirubin. Slight decrease in pH, increased liver weights, centrilobular hypertrophy, renal tubular vacuolation ascribed to the vehicle. Injection site lesions and lung granuloma.

Study # 93096

Volume # 22

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: January 1994

GLP compliance: Yes

QA report: Yes

Drug, lot # 953-47

Formulation/vehicle: Voriconazole was dissolved in an aqueous solution of HPBCD

Sprague Dawley rats, (10 males and 10 females/dose group) were treated with 2, 5, and 10 mg/kg of UK,109 intravenously for 28 or 29 days. Drug was dissolved in an aqueous solution beta cyclodextrin sulphobutyl ether (160 mg/ml) and animals treated with 1 ml/kg. A vehicle control group received 160 mg/kg SBECD only. Records were kept of mortality, clinical signs, body weights, food and water consumption, ophthalmologic examinations, hematology, clinical chemistry and urinalysis. To determine the reversibility of any liver changes, two supplementary groups of rats received 0 or 10 mg/kg of voriconazole and were retained for one month after cessation of therapy.

No animals died during this study. Toxic effects included hair loss, which occurred after cessation of therapy in high dose rats. Mean corpuscular hemoglobin was decreased by 2% on day 29 and by 4 % at end of recovery in high dose females.

Lymphocytes were decreased at end of treatment by 18% in the supplemental group of high dose males, but not in the main high dose group. This decrease was not seen at the end of the recovery period.

There was one high dose female which had a macroscopically enlarged mandibular lymph node, but the imprint of this lymph node and the bone marrow smear were unremarkable. Decreases in bilirubin (-25%) and triglyceride (-30%) were observed in high dose males along with increased urine density which paralleled a decreased urine volume. The few changes persisting at the end of the reversibility period were on the order of 10 % or below.

Liver weights increased in mid and high dose animals (7-15%). This was associated with minimal hypertrophy of the centrilobular hepatocytes in 5/10 males and 6/10 females. These changes were not observed after the reversibility period. Adrenal weights decreased (-18 %) in high dose males and increased (+16 %) in females. Kidney weight increased (+11 %) in high dose females. Testes and heart weights decreased slightly during the study (<10 %) while they were slightly increased (+9 %) at the end of the reversibility period. The relevance of these slight changes is unclear since they were not dose dependent.

Conclusion

Liver is the primary target organ of this drug which produces reversible centrilobular hypertrophy upon repeated administration. The drug also has effects in the adrenals, heart, testicles and kidneys. The NOAEL was determined to be 2 mg/kg, which is equivalent to a human dose of 0.32 mg/kg/day for 28 days.

15. Study title: 1 month intravenous toxicity in Sprague Dawley rats. An investigation of the effects of two degradation products.

Key study findings: Increased liver weights, renal tubular vacuolation remained the predominant toxic effects of voriconazole in the presence of the degradation products

Study # 92006

Volume # 21

Conducting laboratory and location: Pfizer Centre de Recherche. 37401 Amboise, Cedex, France.

Date of study initiation: January 8, 1992

GLP compliance: Yes

QA report: Yes

Drug, lot #, % purity: Drug batch number R5. Purity, 94.7 %.

Formulation/vehicle: Voriconazole was formulated in hydroxypropyl- β -cyclodextrin (10 mg/ml) and diluted with saline as required every day.

Rats (10 males and 10 females/dose) were treated with 2, 5, and 10 mg/kg of voriconazole, intravenously for 28 or 29 days. The degradation products were present in the formulation at 1.9 and 3.4 % respectively. A vehicle control group received HPBCD (160 mg/kg) only, a saline control group received saline. Records were kept of mortality, clinical signs, food and water intake, body weights, ophthalmology, plasma chemistry, hematology, urinalysis, gross necropsy findings, organ weights and histopathology findings.

Mortality

There were no deaths during this study.

Toxicity

In high dose males, voriconazole was associated with decreased white cell counts (-14%), decreased lymphocytes count (-17 %), decreased triglycerides (-34%). In high dose females only, there was a slight (8%) increase in total protein.

Saline control males only had higher body weights at the end of the study compared to HPBCD controls.

Mid- and high dose females had increased relative liver weights (+10 and 14% respectively) while high dose males showed an average 8% increase. Control animals (which received 160 mg/kg HPBCD) had a greater incidence of pale/marbled kidneys (10 of 20 animals), than saline control or drug-treated animals (1 to 3 of 20).

Multifocal tubular vacuolation of the proximal tubules was observed only in groups receiving HPBCD. Large vacuoles replaced the entire tubular cytoplasm and occasionally, acicular eosinophilic pseudocrystals were present. In some animals, the main feature was