CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-919

Chemistry Review(s)

NDA 20-919

Geodon® (ziprasidone mesylate) for Injection

Pfizer Global Research & Development

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

[redacted]

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 20-919(AZ) (Geodon® for Injection, ziprasidone mesylate)**
2. **CHEM. REVIEW #4**
3. **REVIEW DATE:** June 20, 2002
4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS REVIEWS:**

Previous Reviews	Document Date
Review #1	December 8, 1998
Review #2	November 19, 1999
Review #3	January 14, 2000

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
Resubmission-(AZ)	December 21, 2001
Amendment-(BL)	June 7, 2002
Amendment-(BL)	June 12, 2002

7. **NAME AND ADDRESS OF APPLICANT:** Pfizer Global Research & Development
50 Pequot Avenue
New London, CT 06320

8. **DRUG PRODUCT NAME:**

Proprietary:	Geodon® for Injection
Nonproprietary/USAN:	ziprasidone mesylate
Code Name/Number:	CP-88,059
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** N/A

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** acute agitation in psychotic patients

11. **DOSAGE FORM:** Injection

12. **STRENGTHS:** 20 mg/mL

13. **ROUTE OF ADMINISTRATION:** Intramuscular

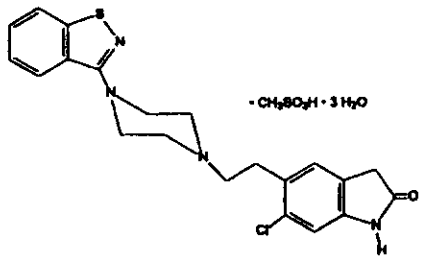
14. **DISPENSED:** XXX RX ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** ___ Yes XXX NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate

$C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$

MW: 563.09



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The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability

From Chemistry point of view, this NDA can be approved.

B. Recommendations on Phase 4(Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable

II. Summary of Chemistry Assessments

A. Description of Drug Product and Drug Substance

With CMC Review #3 dated 1/14/00, R.Seevers, HFD-120, from the CMC standpoint, NDA 20-919 was approved.

It was necessary to compare the 6/7/02 draft Package Insert to the approved package insert for the capsules and to the draft submitted in the 12/21/01 resubmission.

With the help of the EES staff, the inspection update (FUR in EES) was submitted on 4/16/02 for CFN [redacted] This site was submitted because Pat Alcock, Compliance, informed us that we will have to get final update for inspections as the 2 year period from the last inspection will be over on May 11, 2002.

B. Description of How the Drug Product is Intended to be Used

GEODON® for Injection, 20 mg/mL, is to be administered intramuscularly for acute agitation in psychotic patients.

C. Basis for Approvable or Not-Approval Recommendation

NDA 20,919 (Geodon® for Injection, Pfizer Global Research & Development) is recommended for approval based on the following:

- With CMC review # 3 dated January 14, 2000, NDA 20-919 was recommended for approval from the CMC standpoint.
- All facilities involved in the manufacture and control of the drug substance and drug product were found acceptable by Compliance on June 18, 2002.
- Both the draft package insert and the draft labeling are acceptable.

III. Administrative

Reviewer: Donald N. Klein, Ph.D.

Team Leader: Thomas F. Oliver, Ph.D.

Project Manager: Steve Hardeman, R.Ph.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

SUMMARY REVIEW

NDA#: 20-919 **CHEMISTRY REVIEW: # 4** **DATE REVIEWED:** June 20, 2002

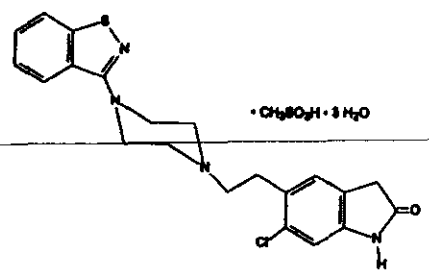
Submission Type	Document Date	CDER Date	Assigned Date
Resubmission-(AZ)	12/21/01	12/21/01	4/12/02
Amendment-(BL)	6/7/02	6/10/02	6/10/02
Amendment-(BL)	6/12/02	6/13/02	6/19/02

NAME & ADDRESS OF APPLICANT: Pfizer Global Research & Development
50 Pequot Avenue
New London, CT 06320

DRUG PRODUCT NAME:
Proprietary: GEODON® for Injection
Nonproprietary/Established/USAN: ziprasidone mesylate
Code Name/#: CP-88,059
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: acute agitation in psychotic patients
DOSAGE FORM: intramuscular injection
STRENGTHS: 20 mg/mL
ROUTE OF ADMINISTRATION: intramuscular
DISPENSED: X Rx ___ OTC
SPECICAL PRODUCTS: ___ YES X NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate
CAS # 185021-64-1
$C_{21}H_{21}ClN_4OS\ CH_3SO_3H\ 3H_2O$; MW: 563.09



SUPPORTING DOCUMENTS: DMF ( )

REVIEW NOTES:

1. BACKGROUND:

With CMC Review #3 dated 1/14/00, R.Seevers, HFD-120, from the CMC standpoint, NDA 20-919 is Approved.

2. ESTABLISHMENT INSPECTION:

a. With the help of the EES staff, the inspection update (FUR in EES) was submitted on 4/16/02 for CFN [ ]. This site was submitted because Pat Alcock, Compliance, informed us that we will have to get final update for inspections as the 2 year period from the last inspection will be over on May 11, 2002.

CFN [ ]

b. EER is attached.

EVALUATION:

1. On 6/18/02, the OC Recommendation for CFN [ ] was acceptable.
2. On 6/18/02 the Overall OC recommendation is Acceptable.

3. PACKAGING INSERT: 6/7/02 Amendment-(BL); 6/12/02 Amendment-(BL);

EVALUATION:

1. I compared the 6/7/02 Package Insert to the approved package insert for the capsules and to the draft submitted in the 12/21/01 resubmission. The following sections are acceptable from the CMC point of view:

    a. DESCRIPTION
    b. Preparation for Administration
    c. HOW SUPPLIED

2. ~~The proposed label in the 6/12/02 amendment is acceptable.~~

20-JUN-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 20919/000
Org Code : 120
Priority : 3S

Sponsor: PFIZER CENT RES
EASTERN POINT RD
GROTON, CT 06340

Stamp Date : 17-DEC-1997
PDUFA Date : 21-JUN-2002
Action Goal :
District Goal: 17-AUG-1998

Brand Name : ZELDOX IM (ZIPRASIDONE MESYLATE) 20MG/ML
Estab. Name:
Generic Name: ZIPRASIDONE MESYLATE
Dosage Form: (INJECTION)
Strength : 20 MG/ML

FDA Contacts: S. HARDEMAN — Project Manager (HFD-120) — 301-594-2850
D. BATES — Review Chemist (HFD-120) — 301-594-5536
ID = 115238 — Team Leader

Overall Recommendation: ACCEPTABLE on 18-JUN-2002by J. D AMBROGIO(HFD-324) 301-827-0062

ACCEPTABLE on 11-MAY-1999by J. D AMBROGIO(HFD-324) 301-827-0062

WITHHOLD on 02-NOV-1998by J. D AMBROGIO(HFD-324) 301-827-0062

Establishment : CFN : [ ] FEI : [ ]

DMF No: AADA:

Responsibilities: [ ]

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-APR-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

Establishment : CFN : [ ] FEI : [ ]

DMF No: AADA:

Responsibilities: [ ]

Profile : SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-JUN-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [ ] FEI : [ ]

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-APR-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

Establishment : CFN : [redacted] FEI : [redacted]
[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-APR-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-APR-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2410924 FEI : 2410924
PFIZER INC
630 FLUSHING AVE
BROOKLYN, NY 11206

MF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-APR-02		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

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

/s/

Donald Klein
6/20/02 10:18:22 AM
CHEMIST

REVISIONS MADE

Thomas Oliver
6/20/02 10:22:17 AM
CHEMIST

JAN 14 2000

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

NDA#: 20-919

CHEMISTRY REVIEW: # 3 **DATE REVIEWED:** 14-JAN-2000

Submission Type	Document Date	CDER Date	Assigned Date
Amendment	22-NOV-1999	22-NOV-1999	22-NOV-1999

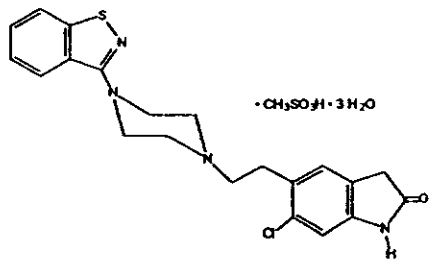
NAME & ADDRESS OF APPLICANT: Pfizer, Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:
Proprietary: ZELDOX IM™
Nonproprietary/Established/USAN: ziprasidone mesylate, (INN, ziprasidone)
Code Name/#: CP-88,059-27
Chem. Type/Ther. Class: 1S

DESI / Patent Status: no DESI issues. patent 4,831,031; exp. 02 MAR 2007

PHARMACOLOGICAL CATEGORY/INDICATION: antipsychotic
DOSAGE FORM: intramuscular injection
STRENGTHS: 20 mg/mL
ROUTE OF ADMINISTRATION: intramuscular
DISPENSED: XXX Rx ___ OTC
SPECICAL PRODUCTS: ___ YES XXX NO

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, CAS NUMBER:
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate (CAS)
CAS # 185021-64-1
$C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$, mw 563.09



SUPPORTING DOCUMENTS: DMF [ ]
Sulfobutylether beta-cyclodextrin (Pfizer)

CONSULTS: None

EIR: The original Withhold recommendation of 11/2/98, based on deficiencies at [ ] Site, was changed to an overall Acceptable recommendation on 5/11/99, based on a re-inspection of that site.

REMARKS/COMMENTS: A related NDA (20-825) for ziprasidone hydrochloride capsules was Not Approved on June 17, 1998 due to clinical concerns. This NDA was Not Approved on December 17, 1998 for the same clinical concerns as well as for several CMC deficiencies. The firm's responded to those CMC issues on 5/4/99; see CR #2. Two final issues were communicated to the firm on 11/22/99. This review is of the firm's response.

CONCLUSIONS & RECOMMENDATIONS:

The firm has satisfactorily responded to the remaining CMC issues. The application may be Approved from a CMC standpoint.

cc: Orig. NDA
HFD-120/Division File
HFD-120/RSeevers/
HFD-120/SHardeman/
HFD-810/HPatel
HFD-810/ JSimmons

/S/ 11/14/00
Robert H. Seevers, Ph.D., Chemistry Team Leader

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X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

NOV 19 1999

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

NDA#: 20-919

CHEMISTRY REVIEW: # 2 **DATE REVIEWED:** 19-NOV-1999

Submission Type	Document Date	CDER Date	Assigned Date
Amendment	04-MAY-1999	05-MAY-1999	07-MAY-1999

NAME & ADDRESS OF APPLICANT: Pfizer, Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:
Proprietary: ZELDOX IM™
Nonproprietary/Established/USAN: ziprasidone mesylate, (INN, ziprasidone)
Code Name/#: CP-88,059-27
Chem. Type/Ther. Class: 1S

DESI / Patent Status: no DESI issues. patent 4,831,031; exp. 02 MAR 2007

PHARMACOLOGICAL CATEGORY/INDICATION: antipsychotic
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SPECICAL PRODUCTS: ___ YES XXX NO

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CAS # 185021-64-1
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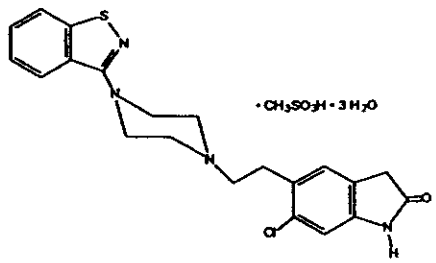

SUPPORTING DOCUMENTS: DMF [redacted]
Sulfobutylether beta-cyclodextrin (Pfizer)

CONSULTS: None

EIR: The original Withhold recommendation of 11/2/98, based on deficiencies at [redacted] Site, was changed to an overall Acceptable recommendation on 5/11/99, based on a re-inspection of that site.

REMARKS/COMMENTS: A related NDA (20-825) for ziprasidone hydrochloride capsules was Not Approved on June 17, 1998 due to clinical concerns. This NDA was Not Approved on December 17, 1998 for the same clinical concerns as well as for several CMC deficiencies. The firm's repsonse to those CMC issues is the subject of the present review.

CONCLUSIONS & RECOMMENDATIONS:

The firm has satisfactorily responded to the majority of CMC deficiencies raised in the original (12/17/98) Not Approval letter. The application is Approveable with regard to chemistry. See Draft letter for comments to be conveyed to the Sponsor.

cc: Orig. NDA
HFD-120/Division File
HFD-120/RSeevers/
HFD-120/SHardeman/
HFD-810/HPatel
HFD-810/ JSimmons

/S/
11/19/99
Robert H. Seevers, Ph.D., Chemistry Team Leader

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

NDA#: 20-919

CHEMISTRY REVIEW: # 1 **DATE REVIEWED:** 01-DEC-1999

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	*17-DEC-1997*	*17-DEC-1997*	*17-FEB-1998*
Amendment	20-NOV-1998	23-NOV-1998	23-NOV-1998

NAME & ADDRESS OF APPLICANT: Pfizer, Inc.
Eastern Point Road
Groton, CT 06340

DRUG PRODUCT NAME:
Proprietary: ZELDOX IM™
Nonproprietary/Established/USAN: ziprasidone mesylate, (INN, ziprasidone)
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Chem. Type/Ther. Class: 1S

DESI / Patent Status: no DESI issues. patent 4,831,031; exp. 02 MAR 2007

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STRENGTHS: 20 mg/mL
ROUTE OF ADMINISTRATION: intramuscular
DISPENSED: XXX Rx ___ OTC
SPECICAL PRODUCTS: ___ YES XXX NO

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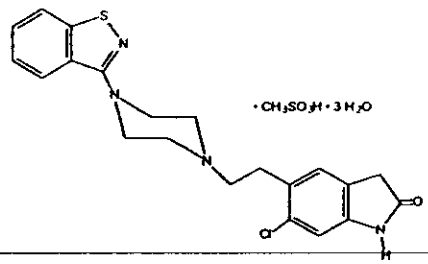
5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate (CAS)
CAS # 185021-64-1
$C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$, mw 563.09



SUPPORTING DOCUMENTS: DMF [ ]
Sulfobutylether beta-cyclodextrin (Pfizer)

CONSULTS: EA: not required:
Tier 0 emissions; categorical exclusion granted.
Micro: submitted June 2, 1998, returned October 15, 1998 with an approval recommendation.
Methods Validation: Initiated

EIR: Requested 02-APR-1998; returned November 2, 1998 with an overall Withold recommendation due to CGMP deficiencies at the [redacted] site.

REMARKS/COMMENTS: A related NDA (20-825) for ziprasidone hydrochloride capsules was Not Approved on June 17, 1998 due to Clinical concerns.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is Not Approvable due to the following issues:

1. The firm has stated that it may make modifications to the drug substance manufacturing process and notify the agency later in annual reports. This is not acceptable; appropriate supplements, either prior approval or changes being effected should be used to report manufacturing changes.

2. The Drug Master File for the manufacture of sulfobutylethter β-cyclodextrin is not adequate to support this NDA.

3. The [redacted] site for the sulfobutylethter β-cyclodextrin failed its inspection due to multiple CGMP deficiencies, resulting in a Withold reccomendation.

There are other, less significant CMC deficiencies; see draft letter.

cc: Orig. NDA
HFD-120/Division File
HFD-120/RSeevers/
HFD-120/SHardeman/CSO
HFD-810/JSimmons
HFD-810/CHoiberg

/S/ 12.8.98

/S/ 11/30/98

Robert H. Seevers, Ph.D., Chemistry Team Leader

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