CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-483

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-483

Geodon® (ziprasidone hydrochloride) Oral Suspesion

Pfizer, Inc.

Chemistry Review

Donald N. Klein, Ph.D.

HFD-130

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-483 Geodon® (ziprasidone hydrochloride) Oral Suspension.**

2. **CHEM. REVIEW: # 4 for NDA 21-483.**

3. **REVIEW DATE:** December 19, 2005.

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** CMC Reviews # 1, 2, and 3.

6. **SUBMISSION BEING REVIEWED:**

Submissions Reviewed	Document Date
Complete Response (AZ)	9/29/05
Information Request (E-mail)	10/24/05
Response (E-mail)	10/24/05

7. **NAME AND ADDRESS OF APPLICANT:**

Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

8. **DRUG PRODUCT NAME:**

Proprietary:	Geodon®
Nonproprietary/USAN (1994):	ziprasidone hydrochloride
Code Name/Number:	CP-88,059-1
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50.

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

11. **DOSAGE FORM:** Suspension.

12 **STRENGTHS:** 10 mg/mL.

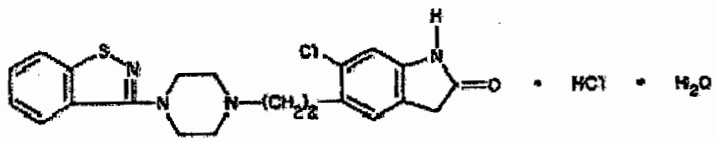
13. **ROUTE OF ADMINISTRATION:** Oral.

14. DISPENSED: _x_ RX __OTC.

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___Yes _x_No.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:
5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone monohydrochloride, monohydrate.

Molecular formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$
Mol. Wt.: 467.41
CAS Registry: 138982-67-9



17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's: Refer to CMC Review # 3.

B. Other Documents: Refer to CMC Review # 3.

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date or Review #	Reviewer or Office
EES	Acceptable	28-NOV-2005	Office of Compliance
FDA Method Validation Report	Suitable for Regulatory Analysis of the drug product	16-AUG-2003 (Review # 2)	Northeast Regional Laboratory
Medical	*pending*	*pending*	Roberta Glass, M.D.
Microbiology	Approval	06-NOV-03	Stephen Langille, Ph.D.
OCPB	*pending*	*pending*	Kofi Kumi, Ph.D.
Environmental Assessment	Acceptable	15-JULY-03	Donald Klein, Ph.D.
Pharm/Tox	*not assigned*	*n/a*	*n/a*

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-483 Geodon® (ziprasidone hydrochloride) Oral Suspension is recommended approval from the CMC standpoint.

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

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

All CMC aspects of the drug product were found acceptable with Review # 3 (Dr. Klein, 11/19/03).

The test methods were validated by the FDA Northeast Regional Laboratory and found suitable for regulatory analysis of the drug product on August 16, 2003. Review # 2 (Dr. Klein, 11/12/03) summarizes the test method validation results.

With this September 29, 2005 Resubmission the five drug product sites were resubmitted for evaluation and found acceptable by Compliance on November 28, 2005.

Drug Substance

All CMC aspects of the drug substance were found acceptable with Review # 3 (Dr. Klein, 11/19/03).

With this September 29, 2005 Resubmission the two drug substance sites were resubmitted for evaluation and found acceptable by Compliance on November 28, 2005.

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

As stated in CMC Review # 3 the oral suspension will be packaged in a [redacted] opaque, [redacted] bottle (labeled fill volume is 60 mL) and in a [redacted] opaque, [redacted] bottle (labeled fill volume is 240 mL). The dose increments (2.5 mg) for the 2 mL Oral Dispenser are 0.25 mL, [redacted] and the dose increments (10 mg) for the 8 mL Oral Dispenser are 1.0 mL. [redacted] The applicant validated both the 2 mL Oral Dispenser and the 8 mL Oral Dispenser. The maximum daily dose is 160 mg, 80 mg BID.

Along with drug product, the patient receives a press-in bottle adapter (PIBA) and an oral dispenser (syringe type): with the 60 mL bottle the patient receives the 2 mL oral dispenser; and with the [redacted] bottle, the patient receives the 8 mL oral dispenser. The PIBA fits both bottles.

The patient is instructed (package insert, carton label, and container label) to shake the oral suspension well before using. The patient inserts the PIBA in the bottle followed by inserting the oral dispenser in the PIBA. Subsequently, the bottle is inverted and the patient pulls back on the oral dispenser handle to the prescribed dose. The patient removes the oral dispenser and delivers the oral suspension into the mouth. The PIBA remains in the bottle. The oral dispenser is then rinsed with water in order to be used again.

C. Basis for Approvable or Not-Approval Recommendation:

NDA 21-483 (Geodon® Oral Suspension, Pfizer, Inc.) is recommended approval.

D. Administrative:

Reviewer, HFD-130: Donald N. Klein, Ph.D.
Team Leader, HFD-130: Thomas F. Oliver, Ph.D.
Project Manager, HFD-130: Keith Kiedrow, Pharm.D.

10 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/

Donald Klein
12/19/2005 12:34:38 PM
CHEMIST

Thomas Oliver
12/20/2005 09:39:03 AM
CHEMIST

NDA 21-483

Geodon® (ziprasidone hydrochloride) Oral Suspension

Pfizer, Inc.

Chemistry Review

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

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CHEMISTRY REVIEW

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-483 GEODON® (ziprasidone hydrochloride) Oral Suspension**

2. **CHEMISTRY REVIEW # 3**

3. **REVIEW DATE:** November 19, 2003

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** CMC Reviews # 1 and # 2

6. **SUBMISSIONS BEING REVIEWED:**

Submission Reviewed	Document Date
Telecon	12-AUG-03
Complete Response (AZ)	29-SEPT-03
E-mail Response	30-OCT-03
E-mail Response	04-NOV-03
E-mail Submission	10-NOV-03

7. **NAME AND ADDRESS OF APPLICANT:** Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

8. **DRUG PRODUCT NAME:**

Proprietary:	GEODON® Oral Suspension
Nonproprietary/USAN [1994]	ziprasidone hydrochloride
Code Name/Number	CP-88,059-1
Chem. Type/Ther. Class	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

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

11. **DOSAGE FORM:** Suspension

12 **STRENGTHS:** 10 mg/mL

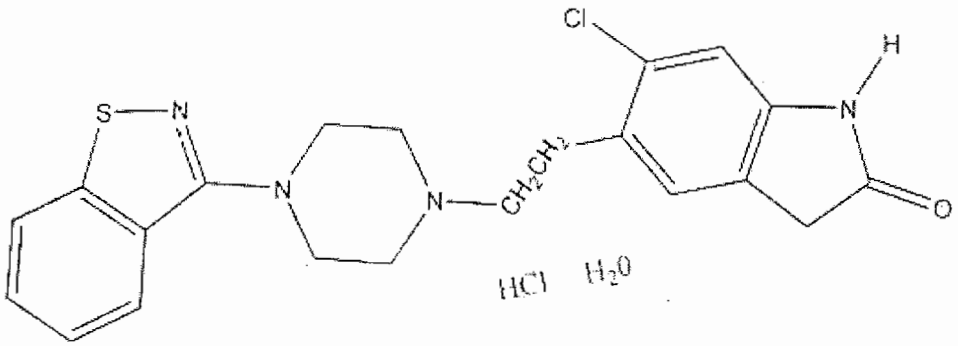
13. **ROUTE OF ADMINISTRATION:** Oral

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-2-indolinone monohydrochloride, monohydrate

Molecular formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$
Molecular Weight: 467.41
CAS Registry # : 136982-67-9



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17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	IV			1	Adequate	05-MAY-03	Flavorant used in the reformulated product
	IV			7	Not applicable	Not applicable	Memo to File dated 5/22/03; original flavorant that has been replaced; D.Klein requested the formulation for background
	III			3, 7	Adequate	26-SEPT-00	Primary packaging; compatibility testing
	III			3	Adequate Adequate	28-SEPT-00 29-APR-02	Primary packaging
	III			3	Adequate	03-APR-01	Primary packaging
	III			3, 7	Adequate	24-MAR-00	Primary packaging; compatibility testing
	III			1, 7	Adequate	28-MAY-03	Liner for closure; compatibility testing
	III			1, 7	Adequate	28-OCT-03	Primary packaging; compatibility testing
	III			1	Adequate	30-MAY-03	Primary packaging
	III			1, 7	Adequate	17-NOV-03	Associated packaging; compatibility testing; validation
	III			3	Adequate	05-MAY-03	Associated packaging; compatibility testing
	II			1,7	Adequate	12-NOV-03	Associated packaging; compatibility testing
	IV			1,7	Adequate	12-NOV-03	Associated packaging; compatibility testing

[1]Action codes for DMF Table:
1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")
[2]Adequate, Inadequate

B. Other Documents:

NDA # or IND #	Applicant	Drug Product	Date Approved or found Satisfactory
NDA 20-825	Pfizer Inc.	Geodon (ziprasidone HCl) Capsules	05-FEB-01
NDA 20-919	Pfizer Inc.	Geodon (ziprasidone mesylate) Injection	21-JUNE-02
NDA 20-990	Pfizer Inc.	Zoloft (sertraline HCl) Oral Concentrate	07-DEC-99
IND 34,629	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	03-MAY-90
IND 49,045	Pfizer Inc.	Ziprasidone HCl / Intramuscular	30-NOV-95
IND 54,297	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	14-NOV-97

18. STATUS:

Consults / Related Reviews	Recommendation	Date	Reviewer
Compliance/EES	Acceptable	18-JUNE-03	Office of Compliance
Methods Validation	Suitable for regulatory analysis of the drug product	16-AUG-03	Northeast Regional Laboratory Chemists
Microbiology	Approval	06-NOV-03	Stephen Langille, Ph.D.
OCPB	Not Approvable	06-NOV-03	Veneeta Tandon, Ph.D.
EA	Acceptable	15-JULY-03	Donald Klein, Ph.D.
Clinical	*pending*	*pending*	Roberta Glass, M.D.
Pharm/Tox	*not assigned*	*n/a*	*n/a*

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The Chemistry Review for NDA 21-483

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-483 for Geodon® (ziprasidone hydrochloride) Oral Suspension is recommended approval from the CMC standpoint.

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

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

Geodon® Oral Suspension was developed for patients who have difficulty swallowing capsules and allows more flexibility in dose titration. Because the suspension is easily divisible, *i.e.*, 2.5 mg increments with the 2.0 mL dispenser and 10 mg increments with the 8.0 mL dispenser, it will facilitate finer dose titration steps within the approved capsule dose range of 20 mg to 80 mg BID.

Outlined below are the inactive components of the drug product.

1. [redacted]: Polysorbate 80, NF
2. Xanthan Gum, NF
3. Xylitol, NF
4. : Citric Acid, USP; Sodium Citrate, USP
5. Sodium Chloride, USP
6. : Colloidal Silicon Dioxide, NF
7. Artificial Cherry [redacted]
8. Methylparaben, NF; Propylparaben, NF
9. Purified Water, USP

The applicant demonstrated that the in-house testing for Organic Volatile Impurities is equivalent to the current compendial method. This was in response to one of the

July 18, 2003 Not Approvable CMC deficiencies.

[redacted]

With this Response [redacted] the 6 supportive lots' (each lot in the upright position and in the side position) stability data were updated [redacted] to 24 months at the following conditions: 5°C; 25°C/60%RH; and 30°C/60%RH. With the original submission, Pfizer presented the 6 supportive lots' stability data at 40°C/75%RH [redacted]

The 2 primary lots were only in the side position on stability and were updated with this [redacted] Response from [redacted] months to [redacted] months in the following conditions: 25°C/60%RH and 30°C/60%RH. With the original submission, Pfizer presented the 2 primary lots' stability data at 40°C/75%RH [redacted].

The applicant has proposed that the release and the stability specification limits be the same. The Degradation Product [redacted] is a drug substance process impurity and a degradation product in the oral suspension. [redacted] is a drug substance process impurity and is a degradant in the oral suspension, but is not a degradant in the approved Geodon® capsules.

With this [redacted] Response, Pfizer agreed to tighten the [redacted] specification from [redacted] maximum to [redacted] maximum.

The following Drug Master Files were reviewed in support of this [redacted] Response.

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

All of the twelve supporting Drug Master Files have been found adequate for NDA 21-483.

Pfizer submitted acceptable suitability data demonstrating that the primary packaging components and the associated components are compatible with the oral suspension.

The drug product analytical methods have been validated by the FDA Laboratory.

The FDA Northeast Regional Laboratory concluded the analytical methods are suitable for regulatory analysis of the drug product. Refer to the CMC Review # 2.

Based on the updated stability data submitted with this response, a 24 month expiration date is granted.

The Overall Compliance recommendation was acceptable as presented in CMC Review # 1.

Drug Substance

The drug substance is referenced via NDA 20-825, Geodon® (ziprasidone hydrochloride) Capsules, that was approved on February 5, 2001. The drug substance retest date is [redacted] at room temperature. Furthermore, the drug substance reference standard retest date is [redacted] at room temperature.

Summarized from CMC Review # 1: In response to The June 19, 2003, Division of Scientific Investigations (HFD-48) report discusses a CMC question posed to Pfizer regarding Lot 23,638-214-1F of ziprasidone hydrochloride monohydrate which was used as a reference standard for bioanalytical assays performed at [redacted] months after it was manufactured. DSI had requested that the NDA 21-483 Reviewing Chemist evaluate Pfizer's April 4, 2003 response. This request resulted in the following CMC deficiency (7/18/03 NA Letter):

> *Please refer to your April 4, 2003 response to the CMC question via the FDA inspector. In order for the agency to state that Lot QCRS7G184-19QCS (Source: Lot: 32,389-69-1F) is of acceptable identity, strength, quality, purity, and potency, provide the assay results for this drug substance lot. The agency notes that in the event Lot QCRS7G184-19QCS (Source: Lot: 32,389-69-1F) is found acceptable, this acceptance does not establish a new retest date for ziprasidone hydrochloride monohydrate (NDA 20-825).*

Based on the applicant's current analytical procedure that was described in this [redacted] Response, the drug substance reference standard **Lot #23,638-214-F** is not of acceptable identity, strength, quality, purity, and potency [redacted] after it was manufactured. This conclusion is based on the fact that during the review of this [redacted] Response, it was established that the drug substance retest date is [redacted] at room temperature and the drug substance reference standard retest date is [redacted] at room temperature. Utilizing a reference standard [redacted] past it's retest date is not acceptable. Refer to pages 11 – 17 in this CMC Review.

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

As outlined in CMC Review # 1, the oral suspension will be packaged in a [redacted] opaque, [redacted] bottle (labeled fill volume is 60 mL) and in [redacted] opaque, [redacted] bottle (labeled fill volume is 240 mL).

The dose increments (2.5 mg) for the 2 mL Oral Dispenser are 0.25 mL, [redacted] and the dose increments (10 mg) for the 8 mL Oral Dispenser are 1.0 mL [redacted] The applicant validated both the 2 mL Oral Dispenser and the 8 mL Oral Dispenser. The maximum daily dose is 160 mg, 80 mg BID.

Along with drug product, the patient receives a press-in bottle adapter (PIBA) and an oral dispenser (syringe-type): with the 60 mL bottle the patient receives the 2 mL oral dispenser; and with the [redacted] bottle, the patient receives the 8 mL oral dispenser. The PIBA fits both bottles.

The patient is instructed (package insert, carton label, and container label) to shake the oral suspension well before using. The patient inserts the PIBA in the bottle followed by inserting the oral dispenser in the PIBA. Subsequently, the bottle is inverted and the patient pulls back on the oral dispenser handle to the prescribed dose. The patient removes the oral dispenser and delivers the oral suspension into the mouth. The PIBA remains in the bottle. The patient rinses the oral dispenser with water.

B. Basis for Approvable or Not-Approval Recommendation

NDA 21-483 (Geodon® Oral Suspension, Pfizer, Inc.) is recommended approval.

C. Administrative

CMC Reviewer, Neuropharm Team 2: Donald N. Klein, Ph.D.
CMC Team Leader, Neuropharm Team 2: Thomas F. Oliver, Ph.D.
Project Manager: Steve Hardeman, R.Ph.

39 Page(s) Withheld

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_____ Deliberative Process

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/s/

Donald Klein
11/19/03 04:21:11 PM
CHEMIST

Thomas Oliver
11/19/03 04:25:23 PM
CHEMIST

NDA 21-483

Geodon® (ziprasidone hydrochloride) Oral Suspension

Pfizer, Inc.

Chemistry Review

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

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CHEMISTRY NDA REVIEW DATA SHEET

1. NDA 21-483 GEODON® (ziprasidone hydrochloride) Oral Suspension

2. CHEMISTRY REVIEW #2

3. REVIEW DATE: October 17, 2003

4. REVIEWER: Donald N. Klein, Ph.D.

5. PREVIOUS DOCUMENTS: Chemistry Review #1

6. SUBMISSIONS BEING REVIEWED:

Submission Reviewed	Document Date
Method Validation Form	21-APR-03
Memo to File	05-MAY-03
Memo: NDA 21-483 Method Validation, Sample No. 236637	16-AUG-03

7. NAME AND ADDRESS OF APPLICANT: Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

8. DRUG PRODUCT NAME:

Proprietary:	GEODON® Oral Suspension
Nonproprietary/USAN [1994]:	ziprasidone hydrochloride
Code Name/Number:	CP-88,059-1
Chem. Type/Ther. Class:	3S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

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

11. DOSAGE FORM: Suspension

12 STRENGTHS: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. DISPENSED: XXX RX ___OTC

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

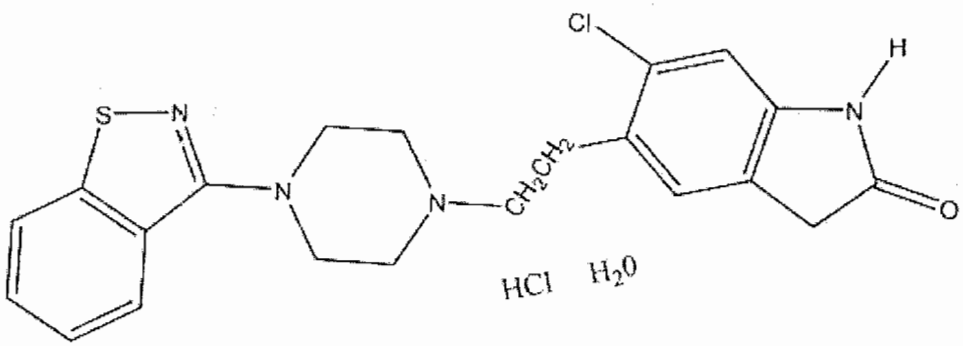
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**

5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone monohydrochloride, monohydrate

Molecular formula: $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$

Molecular Weight: 467.41

CAS Registry # : 136982-67-9



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17. RELATED/ SUPPORTING DOCUMENTS:
A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
[redacted]	IV	[redacted]	[redacted]	1	Adequate	05-MAY-03	Flavorant used in the reformulated product
	IV			7	Not applicable	Not applicable	Memo to File dated 5/22/03; original flavorant that has been replaced; D.Klein requested the formulation for background
	III			3, 7	Adequate	26-SEPT-00	Primary packaging; compatibility testing
	III			3	Adequate Adequate	28-SEPT-00 29-APR-02	Primary packaging
	III			3	Adequate	03-APR-01	Primary packaging
	III			3, 7	Adequate	24-MAR-00	Primary packaging; compatibility testing
	III			1, 7	Adequate	28-MAY-03	Liner for closure; compatibility testing
	III			1	Adequate	30-MAY-03	Primary packaging
	III			1	Adequate	02-JUNE-03	Primary packaging
	III			7	Will be evaluated in Review #3	Will be evaluated in Review #3	Primary packaging; LOA (dated 5/28/03) was submitted in the 6/3/03 [redacted] compatibility testing
	III			5, 7	Will be evaluated in Review #3	Will be evaluated in Review #3	Associated packaging; The LOA to the DMF was not provided; compatibility testing; validation

[1]Action codes for DMF Table:
1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")
[2]Adequate, Inadequate

B. Other Documents:

NDA # or IND #	Applicant	Drug Product	Date Approved or found Satisfactory
NDA 20-825	Pfizer Inc.	Geodon (ziprasidone HCl) Capsules	05-FEB-01
NDA 20-919	Pfizer Inc.	Geodon (ziprasidone mesylate) Injection	21-JUNE-02
NDA 20-990	Pfizer Inc.	Zoloft (sertraline HCl) Oral Concentrate	07-DEC-99
IND 34,629	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	03-MAY-90
IND 49,045	Pfizer Inc.	Ziprasidone HCl / Intramuscular	30-NOV-95
IND 54,297	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	14-NOV-97

18. **STATUS:**

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer or FDA Laboratory
Compliance/EES	Acceptable	18-JUNE-03	Office of Compliance
Methods Validation	Suitable for regulatory analysis of the drug product	16-AUG-03	Northeast Regional Laboratory Chemists
Microbiology	Approvable	16-JULY-03	Stephen Langille, Ph.D.
DSI	Not Approvable	19-JUNE-03	Martin K. Yau, Ph.D. Charles A. Snipes, Ph.D. Nilufer Tampal, Ph.D.
OCPB	Not Approvable	03-JULY-03	Wendy Chou, Ph.D.
EA	Acceptable	15-JULY-03	Donald Klein, Ph.D.
Clinical	Approval Not Approvable	24-JUNE-03 07-JULY-03	Roberta Glass, M.D. Paul Andreason, M.D.
Pharm/Tox	*not assigned*	*n/a*	*n/a*

The Chemistry Review for NDA 21-483

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-483 for Geodon® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL, analytical methods are recommended approval from the CMC standpoint.

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

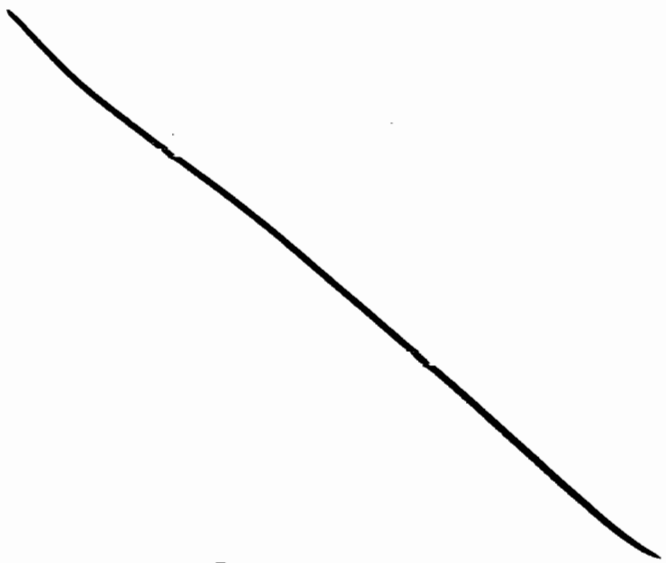
N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product

Drug Product

The following drug product analytical methods and supportive validation data were submitted to the FDA Northeast Regional Laboratory on April 11, 2003.



On August 19, 2003, Dr. Klein received a Memo, dated August 16, 2003, from Ella S. Walker, Supervisory Chemist, Drug Chemistry Branch, Northeast Regional Laboratory, which stated the analysis of Geodon® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL, was performed by the Northeast Regional Laboratory using the firm's method and the samples provided. No analytical problems were encountered with the tests performed. The firm's analytical method appears to be suitable for regulatory analysis of this product.

B. Basis for Approvable or Not-Approval Recommendation

The Geodon® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL, (NDA 21-483) analytical methods are recommended approval based on the August 16, 2003 Memo from the FDA Northeast Regional Laboratory.

C. Administrative

CMC Reviewer, Neuropharm Team 2: Donald N. Klein, Ph.D.
CMC Team Leader, Neuropharm Team 2: Thomas F. Oliver, Ph.D.
Project Manager: Steve Hardeman, R.Ph.

101 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 3

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/s/

Donald Klein
10/23/03 01:14:59 PM
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Thomas Oliver
11/12/03 07:47:22 AM
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NDA 21-483

Geodon® (ziprasidone hydrochloride) Oral Suspension

Pfizer, Inc.

Chemistry Review

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

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-483 GEODON® (ziprasidone hydrochloride) Oral Suspension**

2. **CHEMISTRY REVIEW #1**

3. **REVIEW DATE:** July 15, 2003

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSIONS BEING REVIEWED:**

Submission Reviewed	Document Date
EDR ORIGINAL	26-SEP-02
CMC Information Request	08-OCT-02
(BC) Amendment	17-OCT-02
(BC) Amendment	04-FEB-03
CMC Information Request	21-APR-03
CMC Information Request	08-APR-03
(BC) Amendment	05-MAY-03
CMC Information Request	20-MAY-03
(BC) Amendment	22-MAY-03
(BC) Amendment	03-JUNE-03
CMC Information Request via e-mail	13-JUNE-03
E-mail Response	13-JUNE-03
CMC Information Request via e-mail	16-JUNE-03
CMC Information Request via e-mail	16-JUNE-03
(BC) Amendment	16-JUNE-03
E-mail Responses	17-JUNE-03
CMC Information Requests via e-mail	18-JUNE-03
(BC) Amendment	18-JUNE-03
(BC) Amendment	25-JUNE-03
E-mail Response	26-JUNE-03
CMC Information Request via e-mail	07-JUL-03
CMC Information Request via e-mail	09-JUL-03
E-mail Response	09-JUL-03
(BC) Amendment	27-JUNE-03
(BC) Amendment	07-JULY-03

7. **NAME AND ADDRESS OF APPLICANT:** Pfizer, Inc.
50 Pequot Avenue
New London, CT 06320

8. **DRUG PRODUCT NAME:**

Proprietary:	GEODON® Oral Suspension
Nonproprietary/USAN [1994]:	ziprasidone hydrochloride
Code Name/Number:	CP-88,059-1
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50

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

11. **DOSAGE FORM:** Suspension

12 **STRENGTHS:** 10 mg/mL

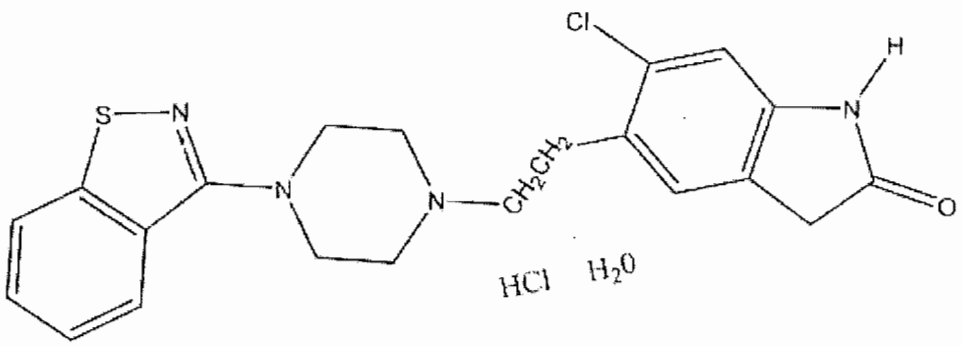
13. **ROUTE OF ADMINISTRATION:** Oral

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-2-indolinone monohydrochloride, monohydrate

Molecular formula: $C_{21}H_{21}ClN_4OS$. HCl . H_2O
Molecular Weight: 467.41
CAS Registry # : CAS-138982-67-9



17. RELATED/ SUPPORTING DOCUMENTS:
A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	IV			1	Adequate	05-MAY-03	Flavorant used in the reformulated product
	IV			7	Not applicable	Not applicable	Memo to File dated 5/22/03; original flavorant that has been replaced; D.Klein requested the formulation for background
	III			3, 7	Adequate	26-SEPT-00	Primary packaging; compatibility testing
	III			3	Adequate Adequate	28-SEPT-00 29-APR-02	Primary packaging
	III			3	Adequate	03-APR-01	Primary packaging
	III			3, 7	Adequate	24-MAR-00	Primary packaging; compatibility testing
	III			1, 7	Adequate	28-MAY-03	Liner for closure; compatibility testing
	III			1	Adequate	30-MAY-03	Primary packaging
	III			1	Adequate	02-JUNE-03	Primary packaging
	III			7	Will be evaluated in Review #2	Will be evaluated in Review #2	Primary packaging; LOA (dated 5/28/03) was submitted in the 6/3/03 [redacted] compatibility testing
	III			5, 7	Will be evaluated in Review #2	Will be evaluated in Review #2	Associated packaging; The LOA to the DMF was not provided; compatibility testing; validation

[1]Action codes for DMF Table:
1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")
[2]Adequate, Inadequate

B. Other Documents:

NDA# or IND #	Applicant	Drug Product	Date Approved or found Satisfactory
NDA 20-825	Pfizer Inc.	Geodon (ziprasidone HCl) Capsules	05-FEB-01
NDA 20-919	Pfizer Inc.	Geodon (ziprasidone mesylate) Injection	21-JUNE-02
NDA 20-990	Pfizer Inc.	Zoloft (sertraline HCl) Oral Concentrate	07-DEC-99
IND 34,629	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	03-MAY-90
IND 49,045	Pfizer Inc.	Ziprasidone HCl / Intramuscular	30-NOV-95
IND 54,297	Pfizer Inc.	Ziprasidone HCl (CP-88,059-1) Oral	14-NOV-97

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer or Laboratory Chemist
Compliance/EES	Acceptable	18-JUNE-03	Office of Compliance
Methods Validation	*Submitted to FDA lab for validation on 4/11/03*	*pending*	Susan W. Ting, B.S.
Microbiology	*Consult submitted on 4/4/03*	*pending*	Stephen Langille, Ph.D.
DSI	Not Approvable	19-JUNE-03	Martin K. Yau, Ph.D. Charles A. Snipes, Ph.D. Nilufer Tampal, Ph.D.
OCPB	Not Approvable	03-JULY-03	Wendy Chou, Ph.D.
EA	Acceptable	15-JULY-03	Donald Klein, Ph.D.
Clinical	Approval Not Approvable	24-JUNE-03 07-JULY-03	Roberta Glass, M.D. Paul Andreason, M.D.
Pharm/Tox	*not assigned*	*n/a*	*n/a*

The Chemistry Review for NDA 21-483

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-483 for Geodon® (ziprasidone hydrochloride) Oral Suspension is recommended approvable from the CMC standpoint. The approval for the CMC of this NDA is contingent on adequate responses to the CMC deficiencies related to the drug product as outlined in this review.

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

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

Geodon® Oral Suspension was developed for patients who have difficulty swallowing capsules and allows more flexibility in dose titration. Because the suspension is easily divisible, *i.e.*, 2.5 mg increments with the 2 mL dispenser and 10 mg increments with the 8 mL dispenser, it will facilitate finer dose titration steps within the approved capsule dose range of 20 mg to 80 mg BID.

Outlined below are the inactive components of the drug product.

1. [redacted] Polysorbate 80, NF
2. [redacted] : Xanthan Gum, NF
3. Xylitol, NF
4. · Citric Acid, USP; Sodium Citrate, USP
5. Sodium Chloride, USP
6. · Colloidal Silicon Dioxide, NF
7. Artificial Cherry SN080109, Food Grade
8. Methylparaben, NF; Propylparaben, NF
9. : Purified Water, USP

During the stability data (1998) through [redacted] months storage for Lot G-416-X98-21A-SIDA in support of clinical lot ED-G-416-X98 the container closure system was leaking at the time of the studies. Subsequently, Pfizer changed to the [redacted] closure liner that prevents leaking. The [redacted] liner was reviewed in support of this NDA.

The applicant developed two analytical methods ([redacted] method and [redacted] method) for detecting the impurities in the drug product for release and for stability testing. Test Method [redacted] is capable of detecting the drug substance specified and unspecified impurities present in the drug product and Test Method [redacted] is capable of detecting [redacted] impurities in the oral suspension. The applicant conducted [redacted] degradation studies and found that the drug product (final formulation) is very stable at room temperature.

The applicant conducted an in-use stability study of two different lots (original formulation) of the drug product. Based on [redacted] of the proposed specifications, this study evaluated the stability of the drug product under simulated patient use conditions. The study simulated the withdrawal of two doses per day from the bottles [redacted] through the maximum 60-day in-use period.

With the original submission the applicant submitted 6 lots of supportive batches (original formulation) and 2 primary batches' Certificate of Analysis (final formulation). All these drug product batches were manufactured using the commercial process [redacted] of maximum scale) and used similar equipment, operating principles, and controls.

The 6 supportive lots (each lot in the upright position and in the side position) were studied at the following conditions: 5°C [redacted] months); 25°C/60%RH [redacted] months); 30°C/60%RH [redacted] months); and 40°C/75%RH [redacted] months).

The 2 primary lots were only in the side position on stability and were studied in the following conditions: 25°C/60%RH [redacted] months); 30°C/60%RH [redacted] months); and 40°C/75%RH [redacted] months). The [redacted] month primary stability data was submitted in the 2/4/03 amendment and the [redacted] month stability data was submitted in the 5/22/03 amendment.

The applicant has proposed that the release and the stability specification limits be the same. The applicant has only submitted [redacted] months of primary stability data. The applicant needs to submit updated stability data (primary and supportive) in order for the proposed specification limits (Assay, pH, [redacted] Unspecified Degradation

Products, Total Degradation Products) to be evaluated. The Degradation Product [redacted] is a drug substance process impurity and a degradation product in the oral suspension. [redacted] is a drug substance process impurity and is a degradant in the oral suspension, but is not a degradant in the approved Geodon® capsules.

The Overall Compliance recommendation was acceptable.

Drug Substance

Ziprasidone hydrochloride monohydrate (CP-88,059-1) is the hydrochloride salt of a benzisothiazolylpiperazine that was developed for the treatment of psychotic disorders. Ziprasidone's activity is primarily due to the parent drug. Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i's of 4.8, 7.2, 0.4, 1.3, 3.4, 3, and 10 nM, respectively), and moderate affinity for the histamine H1 receptor (K_i = 47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown.

The drug substance specifications were approved in NDA 20-825. However, during the review of NDA 21-483, it was uncovered that Pfizer had not submitted the supportive structural data for the [redacted] impurity. The [redacted] characterization data has since been submitted to NDA 21-483, and the characterization data will be submitted to NDA 20-825 via Annual Report.

Pfizer used 3 different drug substance lots in the preparation of the supportive stability data (6 different batches) and used 2 different drug substance lots in the manufacture of the primary stability data (2 different batches).

The drug substance retest date is [redacted] at room temperature.

The two drug substance sites were found acceptable by Compliance.

The June 19, 2003, Division of Scientific Investigations (HFD-48) report discusses a CMC question posed to Pfizer regarding Lot 23,638-214-1F of ziprasidone hydrochloride monohydrate which was used as a reference standard for bioanalytical assays performed at [redacted] months after it was manufactured. DSI had requested that the NDA 21-483 Reviewing Chemist evaluate Pfizer's April 4, 2003 response. Refer to the drug substance's Specification section (pages 21 –23) of this review for the evaluation.

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

The oral suspension will be packaged in a [redacted] opaque, [redacted] bottle (labeled fill volume is 60 mL) and in a [redacted], opaque, [redacted] bottle (labeled fill volume is 240 mL).

The dose increments (2.5 mg) for the 2 mL Oral Dispenser are 0.25 mL [redacted] and the dose increments (10 mg) for the

8 mL Oral Dispenser are 1.0 mL, [redacted] The applicant validated both the 2 mL Oral Dispenser and the 8 mL Oral Dispenser. The maximum daily dose is 160 mg, 80 mg BID.

Along with drug product, the patient receives a press-in bottle adapter (PIBA) and an oral dispenser (syringe-type): with the 60 mL bottle the patient receives the 2 mL oral dispenser; and with the [redacted] bottle, the patient receives the 8 mL oral dispenser. The PIBA fits both bottles.

The patient is instructed (package insert, carton label, and container label) to shake the oral suspension well before using. The patient inserts the PIBA in the bottle followed by inserting the oral dispenser in the PIBA. Subsequently, the bottle is inverted and the patient pulls back on the oral dispenser handle to the prescribed dose. The patient removes the oral dispenser and delivers the oral suspension into the mouth. The PIBA remains in the bottle. The patient rinses the oral dispenser with water.

The container closure system met the requirements described in 16 CFR 1700.20 for child resistance.

At this time, a 24 month expiration date cannot be granted.

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-483 (Geodon® Oral Suspension, Pfizer, Inc.) is recommended approvable based on the CMC concerns relating to the drug product. The deficiencies are detailed in the draft deficiency letter at the end of this review.

D. Administrative

Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Managers: Steve Hardeman, R.Ph. and Paul David, R.Ph.

77 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 4

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/s/

Donald Klein
7/15/03 08:08:02 PM
CHEMIST

Thomas Oliver
7/16/03 07:23:23 AM
CHEMIST
The wording for two of the CMC issues has
been slightly modified for the letter