CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-253

CHEMISTRY REVIEW(S)
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253                                DATE REVIEWED: February 27, 2004

CHEMISTRY REVIEW: #6                              REVIEWER: Sherita McLamore, Ph.D.

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NAME and ADDRESS of APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
- Proprietary: Zyprexa®
- Non proprietary/USAN: Olanzapine for injection
- Code Name/Number: n/a
- Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation
for injection

DOSAGE FORM:
- 10 mg

ROUTE of ADMINISTRATION:
- Intramuscular Injection

DISPENSED:
- X Rx
- OTC

SPECIAL PRODUCTS:
- Yes
- X No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:
CA name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C_{17}H_{20}N_{4}S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:

SUPPORTING DOCUMENTS:
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**RELATED DOCUMENTS:**

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996


3. NDA 21-086: Zyprexa®Zydus® antipsychotic agent, Eli Lilly Corporation, Approved April 6, 2000

**OTHER REQUESTS:**

Establishment Evaluation Request 5 sites

| CFN | \( \rightarrow \mid \) acceptable on 07-24-00 |
| CFN | acceptable on 09-25-00 | withhold on 02-26-01 |
| CFN | \( \rightarrow \mid \) acceptable on 03-26-01 |
| CFN | \( \rightarrow \mid \) acceptable on 02-01-01 |

**Overall Recommendation: Acceptable 01-14-04**

Methods Validation Pending

The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, it is recommended that this application should be Approved.

/S/

 Sherita D. McLamore, Ph.D.
  Review Chemist

/S/

 Thomas Oliver, Ph.D.
 Chemistry Team Leader

cc:
Orig. NDA 21-253
HFD-120/Division File
HFD-180/JSimmons
HFD-120/SMcLamore
HFD-120/TOliver
HFD-120/SHardeman

Filename: C:\WINDOWS\DESKTOP\Reviews\NDA's\NDA 21-253-V1.doc
4 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
Application: NDA 21253/000
Sponsor: LILLY

Crg Code: 120
DRUG EPIDEMIOLOGY UNIT DROP CODE 2238

Priority: 3S
INDIANAPOLIS, IN 46285

Stamp Date: 16-JUN-2000
Brand Name: (OLANZAPINE) 10MG

POUSA Date: 03-MAY-2004
VIALS INJ

Action Goal:

District Goal: 15-FEB-2001
Generic Name: OLANZAPINE

Dosage Form: (FOR INJECTION)
Strength: 10 MG

FDA Contacts:
S. HARDEMAN
Project Manager (HFD-120) 301-594-5525

S. MCLAMORE
Review Chemist (HFD-810) 301-594-5359

ID = 115238
Team Leader

Overall Recommendation:
ACCEPTABLE on 14-JAN-2004 by S. FERGUSON (HFD-322) 301-827-9009

on 15-DEC-2003 by J. D AMBROGIO (HFD-322) 301-827-9049

on 16-SEP-2002 by HARTMANS

on 27-MAR-2001 by J. D AMBROGIO (HFD-322) 301-827-9049

Establishment: CFN: ---
FEI: ---

DMF No: ---
AADA: ---

Responsibilities:

Profile: CSN

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-NOV-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

OAI Status: NONE
ELI LILLY CO/TIPPECANCE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

Responsibilities: DRUG SUBSTANCE MANUFACTURER
                  DRUG SUBSTANCE OTHER TESTER
                  DRUG SUBSTANCE RELEASE TESTER

Profile: CSN
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 04-NOV-03
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 9611006
               FEI: 3002806888
               ELI LILLY SA (ELANCO)
               KINSALE, COUNTY CORK, EI

Responsibilities: DRUG SUBSTANCE MANUFACTURER
                  DRUG SUBSTANCE OTHER TESTER
                  DRUG SUBSTANCE RELEASE TESTER

Profile: CSN
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 12-NOV-03
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 1819470
               FEI: 1819470
               LILLY, ELI & CO.
               LILLY CORPORATE CENTER
               INDIANAPOLIS, IN 46285

DMF No: AADA:
Responsibilities:

DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : SVS
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 15-DEC-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Appears This Way
On Original
**Establishment Evaluation Request Summary Report**

**Application:** NDA 21253/000

**Stamp:** 16-JUN-2000 Regulatory Due: 16-APR-2001

**Priority:** S  
**Org Code:** 120

**Brand Name:** VIALS INJ

**Action Goal:**  
**District Goal:** 15-FEB-2001

**Applicant:** LILLY

**LILLY CORPORATE CENTER**

**DRUG EPIDEMIOLOGY UNIT DROP C**

**INDIANAPOLIS, IN 46285**

**Generic Name:** OLANZAPINE

**Dosage Form:** FIJ (FOR INJECTION)

**Strength:** 10 MG

**Established Name:**

**FDA Contacts:**

- **S. HARDEMAN** (HFD-120)  
  301-594-2850, Project Manager

- **S. MCLAMORE** (HFD-810)  
  301-594-5359, Review Chemist

- **R. SEEVERS** (HFD-120)  
  301-594-2850, Team Leader

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**Overall Recommendation:**

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**Profile:** CSN  
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**Last Milestone:** OC RECOMMENDATION  
**Milestone Date:** 26-FEB-2001  
**Decision:**  
**Reason:**

**Responsibilities:**

- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE RELEASE TESTER
- FINISHED DOSAGE LABELER
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: FACILITY NOT DOING FUNCTION
Profile: SVS OAI Status: OAI ALERT
Last Milestone: DO RECOMMENDATION
Milestone Date: 06-MAR-2001
Decision: 
Reason: PEND REG ACTION - WARNING LT

Establishment: 1813682
ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 02-NOV-2000

Responsibilities: DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER

Establishment: 9611006
ELI LILLY SA (ELANCO)
KINSALE, COUNTY CORK, EI

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-FEB-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE RELEASE TESTER
15-FEB-2001

16-APR-2001

LILLY

S

120

Priority:

Org Code:

Application Comment: APPLICATION IS FOR (OLANZAPINE FOR INJECTION). (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

BASED ON FILE REVIEW

GMP EI DATED APRIL 18-27, 2000 WAS CLASSIFIED NAI.

OC RECOMMENDATION 25-SEP-2000

ACCEPTABLE

DISTRICT RECOMMENDATION

Establishment: 1819470

ELI LILLY AND CO

LILLY CORP CTR/WHITE RIVER PKY/EAST DR

INDIANAPOLIS, IN 46200

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile: CSN

OAI Status: NONE


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BULK ACTIVE PHARMACEUTICAL INGREDIENT IN PROFILE CLASS CSN FOR THE PRODUCT ZYPREXA (OLANZAPINE) IS NOT MADE AT THIS FACILITY. IT'S MADE IN IRELAND.

DO RECOMMENDATION 26-FEB-2001

DRUG NOT MADE HERE

BULK ACTIVE PHARMACEUTICAL INGREDIENT ZYPREXA (OLANZAPINE) IN PROFILE CLASS CSN IS NOT MADE AT THIS FACILITY. IT'S MADE IN IRELAND.

OC RECOMMENDATION 26-FEB-2001

FACILITY NOT DOING FUNCTION
### BULK DRUG NOT MADE HERE. MADE IN IRELAND PER DISTRICT DO RECOMMENDATION

**Profile:** SVS  
**OAI Status:** OAI ALERT

**Establishment Comment:** SEE COMMENTS FOR CFN 1819470 (PROFILE CSN). (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

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**GMP AND PAI EI DATED 1/29-2/23/2001 COVERING PROFILES SVS, SVL, AND SVT REPORTS DEVIATIONS IN PARENTERAL BUILDING ————**

**DO RECOMMENDATION** 06-MAR-2001

**PEND REG ACTION — WARNING LTR**

**WARNING LETTER 2001-01-12 WAS ISSUED ON MARCH 2, 2001.**

---

**Establishment:** 1813682  
**ELI LILLY CO/TIPPECANOE**  
**BOX 685 LILLY RD**  
**LAFAYETTE, IN 47902**

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** CTL  
**OAI Status:** NONE

**Establishment Comment:** THIS PRE-APPROVAL INSPECTION REQUEST HAS BEEN ADDED TO DET-DO FACTS INSPECTION ASSIGNMENT 157443 TO PERFORM A GMP EI CONCERNING CLEANING VALIDATION. (on 02-NOV-2000 by M. ROBINSON (HFR-CE740) 313-226-6260)

**MCLAMORE (HFD-810) 301-594-5359**

---

**Establishment:** 9611006  
**ELI LILLY SA (ELANCO)**  
**KINSALE, COUNTY CORK, EI**

**DMF No:** AADA:

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
DRUG SUBSTANCE RELEASE TESTER

**Profile:** CTL  
**OAI Status:** NONE

**Establishment Comment:** THIS SITE IS RESPONSIBLE FOR IN PROCESS AND RFELAESE TESTING AS THE DRUG SUBSTANCE. THE APPLICANT ALSO INDICATES THAT The ARE MANUFACTURED AT THIS FACILITY. (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

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Application: NDA 21253/000
Stamp: 16-JUN-2000
Regulatory Due: 16-APR-2001
Applicant: LILLY
Drug Epidemiology Unit Drop Code 2238
Priority: INDIANAPOLIS, IN 46285
Org Code: S
FDA Contacts: S. HARDEMAN (HFD-120)
S. McLAMORE (HFD-810)
R. SEEVERS (HFD-120)

Overall Recommendation:
Establishment: 

DMF No: 
Responsibilities: 
Profile: CSN
OAI Status: NONE
Estab. Comment: 

Milestone Name | Date | Req. TypeInsp. Date | Decision & Reason Creator |
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SUBMITTED TO OC | 12-JUL-2000 | | |
SUBMITTED TO DO | 13-JUL-2000 GMP | | |
DO RECOMMENDATION | 24-JUL-2000 | | |

DALLAS DISTRICT RECOMMENDS APPROVAL OF THIS NDA BASED ON A PREVIOUS PAI CONDUCTED AT ON 6/29-7/22/1999 THAT WAS CLASSIFIED ACCEPTABLE.

OC RECOMMENDATION | 24-JUL-2000 | ACCEPTABLE | DAMBROSOJ DISTRICT RECOMMENDATION |

Establishment: 

DMF No: 
Responsibilities: 
Profile: SVS
OAI Status: NONE
Estab. Comment: 
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/s/
------------------
Sherita McLamore
3/3/04 01:21:13 PM
CHEMIST

Thomas Oliver
3/3/04 02:58:25 PM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253

CHEMISTRY REVIEW: #5

DATE REVIEWED: May 8, 2001

REVIEWER: Sherita McLamore, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Amendment March 9, 2001 March 12, 2001 March 13, 2001

NAME and ADDRESS of APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
Proprietary: Zyprexa®
Non proprietary/USAN: Olanzapine for injection
Code Name/Number: n/a
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation
for injection

DOSAGE FORM:

STRENGTHS:

ROUTE of ADMINISTRATION: Intramuscular Injection

DISPENSED:

SPECIAL PRODUCTS:

X RX OTC
Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C_{17}H_{26}N_{4}S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:
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### RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996
3. NDA 21-086: Zyprexa®-Zydis® antipsychotic agent, Eli Lilly Corporation, Approved April 6, 2000

### OTHER REQUESTS:

Establishment Evaluation Request 5 sites  
- CFN Γ acceptable on 07-24-00  
- CFN acceptable on 09-25-00  
- CFN withhold on 02-26-01  
- CFN acceptable on 03-26-01  
- CFN Λ acceptable on 02-01-01  

**Overall Recommendation:** 103-27-01

Methods Validation Pending  
The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
Microbiology Consult

The microbiology consult was submitted by Dr. Bates (project manager) on June 16, 2000 and was completed by Dr. Bryan Riley on February 16, 2001. The review covers the manufacture of the lyophilized drug product. The applicant submitted a response to the microbiology deficiencies on March 12, 2001. Dr. Riley completed the review of the submission which included the microbiology deficiencies and concluded that the submission was submission is approvable pending the resolution of the microbiology deficiencies which are included in the draft letter.

COMMENTS:

1. Zyprexa® (Olanzapine for Injection) is currently not marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine group of compounds.

3. NDA 20-592 is referenced for the drug substance, Olanzapine. There is no drug substance or drug product USP monograph.

4. Olanzapine was approved (NDA 20-592) as a solid oral dosage form (IR tablet) as Zyprexa® on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

5. The for Injection dosage form is available in 10 mg vials.

6. Olanzapine will not be marketed for pediatric population because safety and effectiveness in pediatric patients has not been established.

7. NDA 20-086 for Zyprexa®Zydis® was approved April 6, 2000 as an antipsychotic agent. The dosage form is an orally disintegrating tablet available as a 5-, 10-, 15-, and 20 mg tablet, dosing at 5 to 20 mg once a day.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, it is recommended that this application is __________ based on the _______ recommendation by EES.

\[Signature\]

Sherita D. McLamore, Ph.D.
Review Chemist

\[Signature\]

Robert Seevers, Ph.D.
Chemistry Team Leader

cc:
Orig. NDA 21-253
HFD-120 Division File
HFD-810 C Hoiberg
HFD-180 J Simmons
HFD-120 S McLamore
HFD-120 R Seevers
HFD-120 S Hardeman

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2 Page(s) Withheld

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

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sherita McLamore
5/8/01 11:57:16 AM
CHEMIST

Robert H. Seevers
5/8/01 12:07:19 PM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253
DATE REVIEWED: February 20, 2001
CHEMISTRY REVIEW: #4
REVIEWER: Sherita McLamore, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Amendment March 7, 2001 March 8, 2001 March 9, 2001

NAME and ADDRESS of APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
Proprietary: Zyprexa®
Non proprietary/USAN: Olanzapine for injection
Chemical Name/Number: n/a
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation
for injection
DOSAGE FORM:
STRENGTHS:
10 mg
ROUTE of ADMINISTRATION:
Intramuscular Injection
DISPENSED:
SPECIAL PRODUCTS:

Chemical Name, Structural Formula, Molecular Formula:
CA name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C17H20N4S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:
SUPPORTING DOCUMENTS:

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RELATED DOCUMENTS:


3. NDA 21-086: Zyprexa® Zydis®, antipsychotic agent, Eli Lilly Corporation, Approved April 6, 2000

OTHER REQUESTS:

Establishment Evaluation Request 5 sites

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_Overall Recommendation: _______________ 03-27-01_

Methods Validation Pending

The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
Microbiology Consult

The microbiology consult was submitted by Dr. Bates (project manager) on June 16, 2000 and was completed by Dr. Bryan Riley on February 16, 2001. The review covers the manufacture of the lyophilized drug product. It is the opinion of the microbiology reviewer that the submission is approvable pending the resolution of the microbiology deficiencies which are included in the draft letter. The applicant submitted a response to the microbiology deficiencies on March 12, 2001.

COMMENTS:

1. Zyprexa® (Olanzapine for Injection) is currently not marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine group of compounds.

3. NDA 20-592 is referenced for the drug substance, Olanzapine. There is no drug substance or drug product USP monograph.

4. Olanzapine was approved (NDA 20-592) as a solid oral dosage form (IR tablet) as Zyprexa® on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

5. The for Injection dosage form is available in 10 mg vials.

6. Olanzapine will not be marketed for pediatric population because safety and effectiveness in pediatric patients has not been established.

7. NDA 20-086 for Zyprexa®-Zydis® was approved April 6, 2000 as an antipsychotic agent. The dosage form is an orally disintegrating tablet available as a 5-, 10-, 15-, and 20 mg tablet, dosing at 5 to 20 mg once a day.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, it is recommended that this application is based on the recommendation by EES.

Sherita D. McLamore, Ph.D.
R&D Chemist

Robert Seevers, Ph.D.
Chemistry Team Leader

cc:
Orig. NDA 21-253
HFD-120 Division File
HFD-810/CHOilberg
HFD-180/JSimmons
HFD-120 SMcLamore
HFD-120/RSeevers
HFD-120/SHardeman

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/s/
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Sherita McLamore  
3/28/01 02:47:16 PM
CHEMIST

Robert H. Seevers  
3/28/01 03:31:25 PM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253
DATE REVIEWED: February 20, 2001

CHEMISTRY REVIEW: #3
REVIEWER: Sherita McLamore, Ph.D.

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE
Amendment  February 1, 2001  February 2, 2001  February 3, 2001

NAME and ADDRESS of APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
Proprietary: Zyprexa®
Non proprietary/USAN: Olanzapine for injection
Code Name/Number: n/a
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation for injection
DOSAGE FORM:
STRENGTHS: 10 mg
ROUTE of ADMINISTRATION: Intramuscular Injection
DISPENSED: X RX OTC Yes No
SPECIAL PRODUCTS:

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:
CA name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C_{17}H_{20}N_{4}S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:
**SUPPORTING DOCUMENTS:**

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**RELATED DOCUMENTS:**

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996


3. NDA 21-086: Zyprexa® Zydus® antipsychotic agent, Eli Lilly Corporation, Approved April 5, 2000

**OTHER REQUESTS:**

Establishment Evaluation Request 5 sites
- CFN acceptable on 07-24-00
- CFN acceptable on 09-25-00
- CFN inspection scheduled 01-29-01
- CFN assigned inspection on 11-2-00
- CFN unacceptable on 02-01-01

Methods Validation Pending

The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
Microbiology Consult

The microbiology consult was submitted by Dr. Bates (project manager) on June 16, 2000 and was completed by Dr. Bryan Riley on February 16, 2001. The review covers the manufacture of the lyophilized drug product. It is the opinion of the microbiology reviewer that the submission is approvable pending the resolution of the microbiology deficiencies which are included in the draft letter.

COMMENTS:

1. Zyprexa (Olanzapine for Injection) is currently not marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine group of compounds.

3. NDA 20-592 is referenced for the drug substance, Olanzapine. There is no drug substance or drug product USP monograph.

4. Olanzapine was approved (NDA 20-592) as a solid oral dosage form (IR tablet) as Zyprexa® on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

5. The for Injection dosage form is available in 10 mg vials.

6. Olanzapine will not be marketed for pediatric population because safety and effectiveness in pediatric patients has not been established.

7. NDA 20-086 for Zyprexa®Zydis® was approved April 6, 2000 as an antipsychotic agent. The dosage form is an orally disintegrating tablet available as a 5-, 10-, 15-, and 20 mg tablet, dosing at 5 to 20 mg once a day.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, the application is Approvable with specific comments to be communicated to the firm (see draft letter comments at the end of this review).

/S/

Sherita D. McLamore, Ph.D.
Review Chemist

/S/

Robert Seevers, Ph.D.
Chemistry Team Leader

cc:
Orig NDA 21-253
HFD-120/Division File
HFD-810/Choiberg
HFD-180/ISimmons
HFD-120/SMcLamore
HFD-120/RSeevers
HFD-120/SHardeman

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/s/

Sherita McLamore
2/27/01 12:05:32 PM
CHEMIST

Robert H. Seevers
2/27/01 02:51:48 PM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253
DATE REVIEWED: January 18, 2000

CHEMISTRY REVIEW: #2
REVIEWER: Sherita McLamore, Ph.D.

SUBMISSION TYPE: Amendment
DOCUMENT DATE: January 8, 2000
CDER DATE: January 9, 2000
ASSIGNED DATE: January 8, 2000

NAME and ADDRESS of APPLICANT:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:
Proprietary: Zyprexa™
Non proprietary/USAN: Olanzapine for injection
Code Name/Number: n/a
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation for injection

DOSAGE FORM:
STRENGTHS: 10 mg

ROUTE of ADMINISTRATION:
Intramuscular Injection

DISPENSED: X RX OTC

SPECIAL PRODUCTS:
Yes

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:
CA name: 2-methyl-4-(4-methyl-1-piperaziny)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C_{17}H_{20}N_{4}S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:
SUPPORTING DOCUMENTS:

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RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996
3. NDA 21-086: Zyprexa® Zydis® antipsychotic agent, Eli Lilly Corporation, Approved April 6, 2000

OTHER REQUESTS:

Establishment Evaluation Request 5 sites

- CFN acceptable on 07-24-00
- CFN acceptable on 09-25-00
- Assigned inspection on 11-2-00
- Assigned inspection on 11-2-00
- Inspection performed on 09-28-00

Methods Validation Pending

The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
Evaluation of: Microbiological examination test and bacterial endotoxin test for drug substance; Bacteria endotoxin test for drug substance; Bacterial endotoxin test and sterility test for the drug product.

Submitted by Doris Bates (project manager) on June 16, 2000

COMMENTS:

1. Zyprexa® (Olanzapine for Injection) is currently not marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine group of compounds.

3. NDA 20-592 is referenced for the drug substance, Olanzapine. There is no drug substance or drug product USP monograph.

4. Olanzapine was approved (NDA 20-592) as a solid oral dosage form (IR tablet) as Zyprexa® on September 30, 1996 for the treatment of the manifestations of psychotic disorders.

5. The for injection dosage form is available in 10 mg vials.

6. Olanzapine will not be marketed for pediatric population because safety and effectiveness in pediatric patients has not been established.

7. NDA 20-086 for Zyprexa® (Zydis®) was approved April 6, 2000 as an antipsychotic agent. The dosage form is an orally disintegrating tablet available as a 5-, 10-, 15-, and 20 mg tablet, dosing at 5 to 20 mg once a day.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, the application is Approvable with specific comments to be communicated to the firm (see draft letter comments at the end of this review).

Sherita D. McLamore, Ph.D.
Review Chemist

Robert Seevers, Ph.D.
Chemistry Team Leader

cc:
Orig. NDA 21-253
HFD-120/Division File
HFD-810/CHoiberg
HFD-180/JSimmons
HFD-120/SMcLamore
HFD-120/RSeevers
HFD-120/SHardeman

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/s/
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Sherita McLamore
1/22/01 01:27:21 PM
CHEMIST

Robert H. Severs
1/22/01 04:01:27 PM
CHEMIST
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA NUMBER: 21-253

DATE REVIEWED: November 20, 2000

CHEMISTRY REVIEW: #1

REVIEWER: Sherita McLamore, Ph.D.

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE
Amendment October 16, 2000 October 17, 2000 October 17, 2000

NAME and ADDRESS of APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

DRUG PRODUCT NAME:

Proprietary: Zyprexa®
Non proprietary/USAN: Olanzapine for injection
Code Name/Number: n/a
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION:
for the rapid control of agitation for injection

DOSAGE FORM:

STRENGTHS:

10 mg

ROUTE of ADMINISTRATION:

Intramuscular Injection

DISPENSED:

X RX  OTC

SPECIAL PRODUCTS:

Yes  No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA name: 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: C_{17}H_{20}N_{4}S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:

![Chemical Structure Image]
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### RELATED DOCUMENTS:

1. **NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent**, Eli Lilly Corporation, Approved September 30, 1996


### OTHER REQUESTS:

Establishment Evaluation Request 5 sites: CFN acceptable on 07-24-00

CFN acceptable on 09-25-00

CFN assigned inspection on 11-2-00

CFN assigned inspection on 11-2-00

CFN inspection performed on 09-28-00

Methods Validation Pending

The following test methods will be submitted to the FDA laboratories after all review issues are resolved: determination of related substances by HPLC; determination of potency by HPLC and assay by UV.
Microbiology Consult

Evaluation of: Microbiological examination test and bacterial endotoxin test for drug substance; Bacteria endotoxin test for drug substance; Bacterial endotoxin test and sterility test for the drug product.

Submitted by Doris Bates (project manager) on June 16, 2000

COMMENTS:

1. Zyprexa® (Olanzapine for Injection) is currently not marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine group of compounds.

3. NDA 20-592 is referenced for the drug substance, Olanzapine. There is no drug substance or drug product USP monograph.

4. Olanzapine was approved (NDA 20-592) as a solid oral dosage form (IR tablet) as Zyprexa® on September 30, 1995 for the treatment of the manifestations of psychotic disorders.

5. The oral dosage form is available in 10 mg vials.

6. Olanzapine will not be marketed for pediatric population because safety and effectiveness in pediatric patients has not been established.

7. NDA 20-086 for Zyprexa®Zydus® was approved April 6, 2000 as an antipsychotic agent. The dosage form is an orally disintegrating tablet available as a 5-, 10-, 15-, and 20 mg tablet, dosing at 5 to 20 mg once a day.
CONCLUSIONS and RECOMMENDATIONS:

From a CMC perspective, the application is Approvable with specific comments to be communicated to the firm (see draft letter comments at the end of this review).

/\S/\-

Sherita D. McLamore, Ph.D.
Review Chemist

/\S/\-

Robert Seever, Ph.D.
Chemistry Team Leader

cc:
Orig. NDA 21-253
HFD-120/Division File
HFD-810/CHOiberg
HFD-180/JSimmons
HFD-120/SMcLamore
HFD-120/RSeever
HFD-120/SHardeman

Filename: C:\WINDOWS\DESKTOP\Reviews\NDA's\NDA 21-253.doc
32 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable