

**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.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Response to AE letter	October 31, 2003	October 31, 2003	November 4, 2003

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

DOSAGE FORM: for injection

STRENGTHS: 10 mg

ROUTE of ADMINISTRATION: Intramuscular Injection

DISPENSED: 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

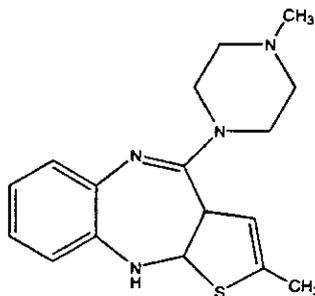
Chemical Formula: C₁₇H₂₀N₄S

Molecular Weight: 312.44

CAS Registry Number:

Laboratory Code: none listed

Chemical Structure:



SUPPORTING DOCUMENTS:

Number/Type	Subject	Holder/Sponsor	Status	Review Date	Letter Date
			Adequate Reviewed by Ravi S. Harapanhalli	8-16-00	5-09-00
			Adequate Reviewed by Joseph Sieczkowski	2-29-00	2-03-00
			Adequate Reviewed by T. A. Broadbent	7-06-98	
			Adequate Reviewed by U. Venkataram	8-25-97	12-13-99
			Adequate Reviewed by R. K. Kasliwal	9-22-99	5-21-00
			Adequate Reviewed by Rajendra Uppoor	8-31-00	12-07-99
			See note in chemistry review # 1	n/a	5-09-00
			See note in chemistry review # 1	n/a	12-08-99

RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996
2. IND 55,342: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved April 4, 1998.
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
 CFN ⤴ withhold on 02-26-01
 CFN ⤴ acceptable on 03-26-01
 CFN ⤴ 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-VI.doc

4 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Establishment : CFN : _____ FEI : _____

DMF No:

ADA:

Responsibilities:

Profile : SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-NOV-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1813682 FEI : 1813682

Appears This Way
On Original

SUMMARY REPORT

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

DMF No:

AADA:

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

DMF No:

AADA:

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

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On Original

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE
TESTER

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)

GMP EI DATED APRIL 18-27, 2000 WAS CLASSIFIED NAI. OC RECOMMENDATION 25-SEP-2000 BASED ON FILE REVIEW ACCEPTABLE DAMBROGIOJ 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

Estab. Comment: DET-DO FACTS ASSIGNMENT # 159771 REQUESTS A PRE-APPROVAL EI OF PROFILES SVS AND CSN REGARDING NDA 21-253. A GMP EI OF SVS, SVL, AND SVT IS ALSO ASSIGNED UNDER THE SAME FACTS NUMBER. A FEB 15, 2001 COMPLETION DATE WAS REQUESTED. (on 02-NOV-2000 by M. ROBINSON (HFR-CE740) 313-226-6260) THIS SITE IS THE MANUFACTURER AND PACKAGER OF THE OLANZAPINE FOR INJECTION [] THIS SITE PROVIDES IN-PROCESS AND RELEASE TESTING FOR FOR THE DRUG SUBSTANCE, THE ACTIVE DRUG PRODUCT [] THIS SITE IS ALSO LISTED AS THE CONDUCTOR OF THE MICROBIOLOGICAL TESTS. (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Table with 5 columns: Milestone Name, Date, Req. Type, Insp. Date, Decision & Reason, Creator. Rows include SUBMITTED TO OC, SUBMITTED TO DO, ASSIGNED INSPECTION, INSPECTION SCHEDULED, INSPECTION PERFORMED, DO RECOMMENDATION.

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 MROBINSO

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 DAMBROGIOJ FACILITY NOT DOING FUNCTION

DETAIL REPORT

BULK DRUG NOT MADE HERE. MADE IN IRELAND PER DISTRICT DO RECOMMENDATION COMMENTS.

Profile: SVS OAI Status: OAI ALERT
 Estab. Comment: SEE COMMENTS FOR CFN 1819470 (PROFILE CSN). (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JUL-2000				MCLAMORES
SUBMITTED TO DO	13-JUL-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	02-NOV-2000	PS			MROBINSO
INSPECTION SCHEDULED	29-JAN-2001		28-FEB-2001		MROBINSO
INSPECTION PERFORMED	23-FEB-2001		23-FEB-2001		MROBINSO
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	MROBINSO
WARNING LETTER 2001-DT-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
 Estab. 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)
 THIS SITE ALSO SUPPLIES THE THE FOLLOWING TWO _____
 _____ (on 12-JUL-2000 by S. MCLAMORE (HFD-810) 301-594-5359)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JUL-2000				MCLAMORES
SUBMITTED TO DO	13-JUL-2000	GMP			FERGUSONS
ASSIGNED INSPECTION	02-NOV-2000	PS			MROBINSO

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

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JUL-2000				MCLAMORES
SUBMITTED TO DO	12-JUL-2000	GMP			EGASM

DETAIL REPORT

ASSIGNED INSPECTION	'13-JUL-2000	GMP			EGASM
INSPECTION SCHEDULED	16-AUG-2000		27-SEP-2000		IRIVERA
INSPECTION PERFORMED	28-SEP-2000		27-SEP-2000		IRIVERA
DO RECOMMENDATION	01-FEB-2001			ACCEPTABLE	EGASM
				INSPECTION	
OC RECOMMENDATION	01-FEB-2001			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21253/000	Action Goal:
Stamp: 16-JUN-2000	District Goal: 15-FEB-2001
Regulatory Due: 16-APR-2001	Brand Name: _____ (OLANZAPINE) 10MG
Applicant: LILLY	VIALS INJ
DRUG EPIDEMIOLOGY UNIT DROP CODE 2238	Estab. Name:
Priority: INDIANAPOLIS, IN 46285	Generic Name: OLANZAPINE
Org Code: S	Dosage Form: (FOR INJECTION)
	Strength: 10 MG
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	

Overall Recommendation:

Establishment: _____

DMF No: _____ AADA: _____

Responsibilities: _____

Profile: CSN OAI Status: NONE

Estab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JUL-2000				MCLAMORES
SUBMITTED TO DO	13-JUL-2000	GMP			FERGUSONS
DO RECOMMENDATION	24-JUL-2000			ACCEPTABLE BASED ON FILE REVIEW	JMARTIN1
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 DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: _____

DMF No: _____ AADA: _____

Responsibilities: _____

Profile: SVS OAI Status: NONE

Estab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	12-JUL-2000				MCLAMORES
SUBMITTED TO DO	13-JUL-2000	GMP			FERGUSONS
DO RECOMMENDATION	25-SEP-2000			ACCEPTABLE	MROBINSO

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
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

DATE REVIEWED: May 8, 2001

CHEMISTRY REVIEW: #5

REVIEWER: Sherita McLamore, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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
DOSAGE FORM: for injection

STRENGTHS: 10 mg

ROUTE of ADMINISTRATION: Intramuscular Injection

DISPENSED: 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

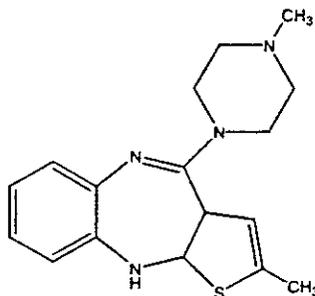
Chemical Formula: C₁₇H₂₀N₄S

Molecular Weight: 312.44

CAS Registry Number:

Laboratory Code: none listed

Chemical Structure:



SUPPORTING DOCUMENTS:

Number/Type	Subject	Holder/Sponsor	Status	Review Date	Letter Date
			Adequate Reviewed by Ravi S. Harapanhalli	8-16-00	5-09-00
			Adequate Reviewed by Joseph Sieczkowski	2-29-00	2-03-00
			Adequate Reviewed by T. A. Broadbent	7-06-98	
			Adequate Reviewed by U. Venkataram	8-25-97	12-13-99
			Adequate Reviewed by R. K. Kasliwal	9-22-99	5-21-00
			Adequate Reviewed by Rajendra Uppoor	8-31-00	12-07-99
			See note in chemistry review # 1	n/a	5-09-00
			See note in chemistry review # 1	n/a	12-08-99

RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996
2. IND 55,342: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved April 4, 1998.
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 L J. 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 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.

/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 JSimmons
HFD-120 SMcLamore
HFD-120 RSeevers
HFD-120 SHardeman

Filename: C:\WINDOWS\DESKTOP\Reviews\NDA's\NDA 21-253-V.doc

2 Page(s) Withheld

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§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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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.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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

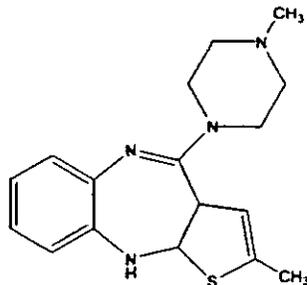
DRUG PRODUCT NAME:

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

PHARMACOLOGICAL CATEGORY/INDICATION: for the rapid control of agitation
DOSAGE FORM: for injection
STRENGTHS: 10 mg
ROUTE of ADMINISTRATION: Intramuscular Injection
DISPENSED: 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: C₁₇H₂₀N₄S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:



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:

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Appears This Way
On Original

CONCLUSIONS and RECOMMENDATIONS:

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

151

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

Filename: C:\WINDOWS\DESKTOP\Reviews\NDA's\NDA 21-253-IV.doc

1 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

/s/

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.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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

DOSAGE FORM: for injection

STRENGTHS: 10 mg

ROUTE of ADMINISTRATION: Intramuscular Injection

DISPENSED: 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

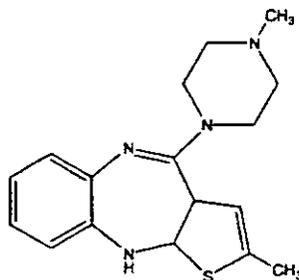
Chemical Formula: C₁₇H₂₀N₄S

Molecular Weight: 312.44

CAS Registry Number:

Laboratory Code: none listed

Chemical Structure:



SUPPORTING DOCUMENTS:

Number/Type	Subject	Holder/Sponsor	Status	Review Date	Letter Date
┌ ├ ├ ├ ├ ├ ├ └			Adequate Reviewed by Ravi S. Harapanhalli	8-16-00	5-09-00
			Adequate Reviewed by Joseph Sieczkowski	2-29-00	2-03-00
			Adequate Reviewed by T. A. Broadbent	7-06-98	
			Adequate Reviewed by U. Venkataram	8-25-97	12-13-99
			Adequate Reviewed by R. K. Kasliwal	9-22-99	5-21-00
			Adequate Reviewed by Rajendra Uppoor	8-31-00	12-07-99
			See note in chemistry review # 1	n/a	5-09-00
			See note in chemistry review # 1	n/a	12-08-99

RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved September 30, 1996
2. IND 55,342: Zyprexa® (olanzapine) Tablets, antipsychotic agent, Eli Lilly Corporation, Approved April 4, 1998.
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
CFN		inspection scheduled 01-29-01
CFN		assigned inspection on 11-2-00
CFN	└	acceptable 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.

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On Original

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/JSIMMONS
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~~
2001

CHEMISTRY REVIEW: #2

REVIEWER: Sherita McLamore, Ph.D.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	January 8, 2000	January 9, 2000	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

DOSAGE FORM: for injection

STRENGTHS: 10 mg

ROUTE of ADMINISTRATION: Intramuscular Injection

DISPENSED: 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

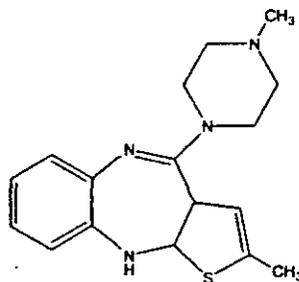
Chemical Formula: C₁₇H₂₀N₄S

Molecular Weight: 312.44

CAS Registry Number:

Laboratory Code: none listed

Chemical Structure:



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.
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Appears This Way
On Original

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/JSimmons
HFD-120/SMcLamore
HFD-120/RSeevers
HFD-120/SHardeman

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/s/

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

Robert H. Seevers
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.

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original Submission	June 15, 2000	June 15, 2000	February 3, 2000
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

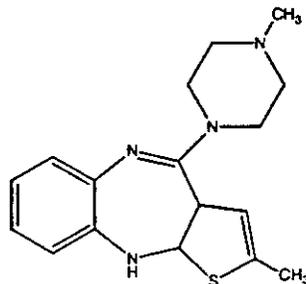
DRUG PRODUCT NAME:

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
DOSAGE FORM: for injection
STRENGTHS: 10 mg
ROUTE of ADMINISTRATION: Intramuscular Injection
DISPENSED: 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: C₁₇H₂₀N₄S
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed
Chemical Structure:



SUPPORTING DOCUMENTS:

Number/Type	Subject	Holder/Sponsor	Status	Review Date	Letter Date
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			Adequate Reviewed by Joseph Sieczkowski	2-29-00	2-03-00
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			Adequate Reviewed by Rajendra Uppoor	8-31-00	12-07-99
			DMF not reviewed. See this review page 24	n/a	5-09-00
			DMF not reviewed. See this review page 24	n/a	12-08-99

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OTHER REQUESTS:

Establishment Evaluation Request 5 sites

CFN	7	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	7	inspection performed on 9-28-00

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: L

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

COMMENTS:

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CONCLUSIONS and RECOMMENDATIONS:

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/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/JSimmons
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/s/

Sherita McLamore
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CHEMIST

Robert H. Seevers
12/6/00 08:55:39 AM
CHEMIST