CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-086

CHEMISTRY REVIEW(S)

MAR 17 2000

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA **21-086** *CHEM REVIEW:* **#2** *REVIEW DATE:* **March 17, 2000**

SUBMISSION TYPE	*DOCUMENT DATE*	*CDER DATE*	*ASSIGNED DATE*
Initial Submission	March 1, 1999	March 2, 1999	March 15, 1999
Amendment	March 31, 1999	April 1, 1999	April 5, 1999
Amendment	December 6, 1999	December 8, 1999	December 13, 1999
Response	January 27, 2000	January 28, 2000	February 8, 2000

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

DRUG PRODUCT NAME:
Proprietary: Zyprexa®Zydis®
Non proprietary/USAN: Olanzapine
Code Name/Number: none
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Antipsychotic
DOSAGE FORM: orally disintegrating tablets
STRENGTHS: 5, 10, 15, 20 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: _X__ RX ___OTC
SPECIAL PRODUCTS: ____Yes __X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA name: 2-methyl-4-(4-methyl-1-piperazinly)-10H-thieno[2,3-b][1,5]benzodiazepine
USAN name: Olanzapine
Chemical Formula: $C_{17}H_{20}N_4S$
Molecular Weight: 312.44
CAS Registry Number:
Laboratory Code: none listed

Microbiology Consult	*Acceptable* Submitted on 12-10-99, refer to attached email and section B. Drug Product 7. Microbiology of the review

COMMENTS:

1. Zyprexa orally disintegrating tablets are not currently marketed in any country.

2. Olanzapine is an antipsychotic agent that belongs to the thienobenzodiazepine class.

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 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.

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

7. No clinical studies are included in this NDA. Three bioequivalence studies have been conducted to support the approval of this new dosage form. The study designs were all single dose, open-label studies with a crossover design and with a washout period of 13 days between treatments. All strengths except the 15 mg tablet were used in the BE studies. Biopharm review stated that the results of the bio provided support the bioequivalence of the oral lyophilizates with the approved reference listed drug, olanzapine film coated tablets.

8. The batches of product manufactured in the aluminum blister packages are included only for supporting data. This firm has made it very clear that these packages aren't for commercial distribution and they are not intended to be part of the approved container closure system for this product.

CONCLUSIONS:

From a CMC perspective, it is recommended that this application be **APPROVED.**

/S/

Sherita D. McLamore, Ph.D.
Review Chemist, HFD-120

3-17-00
Date

/S/

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

3/17/00
Date

cc:

Orig. NDA 21-086
HFD-120/Division File
HFD-810/J. Simmons
HFD-810/H. Patel
HFD-120/M. McLamore
HFD-120/R. Seevers
HFD-120/S. Hardeman

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA **21-086** *CHEM REVIEW*: **#1** *REVIEW DATE*: **01-JUN-99**

SUBMISSION TYPE	*DOCUMENT DATE*	*CDER DATE*	*ASSIGNED DATE*
Initial Submission	March 1, 1999	March 2, 1999	March 15, 1999
Amendment	March 31, 1999	April 1, 1999	April 5, 1999
Amendment	December 6, 1999	December 8, 1999	December 13, 1999

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

DRUG PRODUCT NAME:
Proprietary: Zyprexa®Zydis®
Non proprietary/USAN: Olanzapine
Code Name/Number: none
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: antipsychotic
DOSAGE FORM: orally disintegrating tablets
STRENGTHS: 5, 10, 15, 20 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: _X__ RX ___OTC
SPECIAL PRODUCTS: ____Yes __X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:

CA name: 2-methyl-4-(4-methyl-1-piperazinly)-10H-thieno[2,3-b][1,5]benzodiazepine
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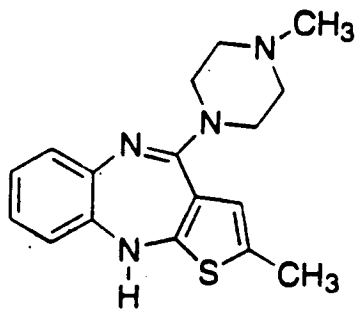

SUPPORTING DOCUMENTS:

TYPE/ NUMBER	SUBJECT	HOLDER/ SPONSOR	STATUS	REVIEW DATE	LETTER DATE
NDA 20-592	Zyprexa (olanzapine) Tablets	Eli Lilly	Approved on 09-30-96	Not applicable	Not applicable

[redacted]

RELATED DOCUMENTS:

1. NDA 20-592: Zyprexa (olanzapine) Tablets, antipyschotic, Eli Lilly, Approved on 09-30-96

[redacted]

OTHER REQUESTS:

Establishment Evaluation Request 7 sites — Submitted on 03-25-99

[redacted]

Methods Validation *Pending* — The following test methods will be submitted to the FDA laboratories after review issues are resolved: assay/potency; Crystal Form via Raman; Related Substances; and Dissolution

Dissolution Specification and Test Method: *Refer to Biopharm review dated 12-07-99*

Microbiology Consult	*Acceptable* Submitted on 12-10-99, refer to attached email and section B. Drug Product 7. Microbiology of the review

APPEARS THIS WAY
ON ORIGINAL

COMMENTS:

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CONCLUSIONS:

- For the CMC section of the submission, it is Approvable with specific comments to be communicated to the firm. See draft comments at the end of this review.

/S/

Melissa Maust
Review Chemist, HFD-120

/S/

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

cc:

Orig. NDA 20-186
HFD-120/Division File
HFD-810/J. Simmons
HFD-810/H. Patel
HFD-120/M. Maust
HFD-120/R. Seevers
HFD-120/S. Hardeman

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