21-086

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 21-086

Trade Name Zyprexa Zydis

Generic Name olanzapine orally disintegrating Tabs.

Sponsor Eli Lilly and Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 21-086

CONTENTS

	Included
Approval Letter	✓
Tenative Approval Letter	
Approvable Letter	✓
Final Printed Labeling	✓
Medical Review(s)	
Chemistry Review(s)	✓
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology Biopharmaceutics Review(s)	✓
Bioequivalence Review(s)	
Administrative Document(s) Correspondence	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-086

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-086

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

APR. 6, 2000

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated March 1, 1999, received March 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa Zydis (olanzapine) orally disintegrating tablets.

We acknowledge receipt of your submission dated January 27, 2000. Your submission of January 27, 2000 constituted a complete response to our December 23, 1999 action letter. We also acknowledge your electronic mail of March 21, 2000, providing draft labeling combining the Zyprexa tablet and Zyprexa Zydis orally disintegrating tablet labeling into a single package insert (attached).

This new drug application provides for the use of Zyprexa Zydis (olanzapine) orally disintegrating tablets for the management of the manifestations of psychotic disorders.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling (combined package insert submitted via electronic mail on March 21, 2000, and immediate container and carton labels submitted December 6, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-086." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

You have been advised that the Pediatric Final Rule (63 FR 66632) requires that all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that your Proposed Pediatric Study Request was submitted to NDA 20-592 (Zyprexa tablets) on February 25, 2000 and received February 28, 2000. A formal Written Request will be forwarded to you under separate cover.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-086

APPROVABLE LETTER

Table of Contents

NDA 21-086

Zyprexa Zydis (olanzapine) Orally Disintegrating Tablets

Approvable Package

Volume #1 1 of 1

NDA 21-086

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

DEC 23 1999

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated March 1, 1999, received March 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa Zydis (olanzapine) Orally Disintegrating Tablets.

We acknowledge receipt of your submissions of March 31, 1999, May 5, 1999, and December 6, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

1. Your comment on page 18 of volume 4:1.2 allowing the use of suitable alternative micronization equipment is not acceptable. Specifically, a change in equipment should be supported by studies that assess the effect of the change on this product. Once the studies have been performed, the change is required to be reported in the application according to the provisions in FDAMA. The November 1999 guidance for industry entitled Changes to An Approved NDA or ANDA will provide guidance on how to report these changes. Please provide a commitment stating your intent to file post approval changes according to current regulations.

2. The reprocessing statement for the micronization of the drug substance (p. 21 of volume 4:1.2) indicates that the micronizing conditions may be adjusted to achieve the desired particle size. This is not an acceptable condition for reprocessing. Please note that a change in the processing parameters is considered a change to the application and should be made to conform to the post approval regulations. Please revise your reprocessing commitment accordingly.

3. The container closure information provided for the drug substance (page 23 of volume 4:1.2) is inadequate. Please provide the following as they may apply to the liners: Letters of Authorization for related DMFs, incoming testing and release, sources, materials, safety and compatibility data. In addition, the statement you made on page 23 indicating that the targets are approximate and are subject to acceptable industry standards is not acceptable. Changes made to the materials and controls approved in the application requires reporting and appropriate validation as stated in the regulations. Please provide a commitment stating your intent to file

post approval changes according to current regulations.

4. You state that your stability drug substance container closure system (page 36 of volume 4:1.2) simulates the commercial packaging of the drug substance. [redacted] The commercial container closure system (page 23) does not provide information about the inner liner being heat sealed, only that the three liners are tightly closed. These systems are not similar, and thus, the stability data generated would not be representative of the drug substance in the commercial container closure system. Please explain how you intend to demonstrate that the stability data in the simulated packaging system is representative of data that will be generated in the proposed commercial packaging system.

5. The Olanzapine micronized specifications for stability are not specified in the Section 4.A.I.D. Stability Tests of Volume 4:1.2. Please verify that the stability specifications for the Olanzapine micronized are the same as the release specifications on page 25. If there are any deviations, they should be substantiated by adequate stability data. The test methods and specifications should be clearly indicated in the proposed Stability Protocol for Olanzapine Micronized: Routine Stability Lots (page 73 of vol. 4:1.2). Please revise the protocol with the requested information.

6. Micronized particles have higher energy than the corresponding macroscopic particles, therefore, please provide data from a one time characterization study that verifies the crystalline form I is maintained throughout the retest period.

7. Three lots of drug substance failed the physical appearance test at the six month accelerated condition due to inappropriate packaging of the stability samples (reference is made to page 40 of volume 4:1.2). The explanation provided is unclear as to what caused the failure. Please clearly indicate and provide an explanation for the inappropriate packaging and explain how this affected the discoloration of the liners, the product contamination on the outside, and the rationalization used to reject these failures.

8. On page 38 of volume 4:1.2, the very last statement discusses a difference between the potency test on stability compared to the potency test at release for the drug substance. Please clearly explain this difference, the reason for the difference, and the correlation between these two tests that will support the comparison of the results measured in two different ways.

9. [redacted]

10. On page 72 of volume 4:1.2, a retest period of 24 months is proposed for the olanzapine

micronized drug substance when stored under warehouse conditions in the proposed storage conditions. Note that both of these situations are different than the conditions used in the supportive stability data studies. Please confirm that the warehouse conditions are consistent with ICH storage conditions and address the issue of the relationship between the simulated stability packaging system with the proposed packaging system (previously addressed in a separate comment).

11. Several places throughout this NDA you use the term "or equivalent" (i.e., page 122 of volume 4:1.2 regarding equipment). Please know that your application approval is based on the information (processes, equipment, etc) that is specified in this application. Please provide a commitment that states any changes made to the application after approval, will be submitted per the requirements in the regulations.

12. In process testing of the crystal form is considered a critical step in the manufacturing process, but yet this test is not performed at release nor is it proposed for stability. The studies provided in this submission do not support the absence of this test. Until a significant body of data exists that demonstrates the different crystal forms do not affect stability or function of the drug product in this dosage form, please commit to performing a release test and an annual stability test for the crystal form [redacted]

13. On page 183 volume 4:1.2, you state that the PVC/PVdC were tested according to USP <661> and permeation was done as per USP <671>, however, you did not provide the data. Please provide this data to support the qualification of the container closure system.

14. Please provide the following additional information to support the qualification of the packaging components and the packaging system: (1) the product code for each packaging component, (2) results for seal integrity or leak testing, (3) representative certificates of analysis for each lot of packaging components used in the manufacture of the bioequivalence lots, and (4) describe the method that will be used to monitor consistency in composition (note: it is not adequate to release components solely on the certificate of analysis).

15. You state that the stability samples in the PVC/PVdC were not debossed, but the commercial samples will be debossed with the appropriate tablet identification. Please explain how you intend to demonstrate that the debossing of the blister and thus the tablet provides the same stability results as the samples that were note debossed.

16. Your proposed stability protocol for routine production lots as specified on page 203 of volume 4:1.2, is not adequate. Specifically, the proposed test intervals of 0, 6, 12, 18, 24, and 36 months are not acceptable. Please revise the test intervals to be 0, 3, 6, 9, 12, 18, 24 months, and yearly thereafter. Additionally, please include the specifications for each of the proposed tests as part of the protocol.

17. [redacted] Please indicate if this is a typo. If this is the true limit, then please explain why

this test is adequate for evaluation of crystal form.

18. In the methods validation section of volume 4:1.3, there is a study for the Determination of the Identity of Olanzapine Micronized by [redacted] However, this test was not specified in the submission. Please clearly indicate the purpose of this test as part of the methods validation.

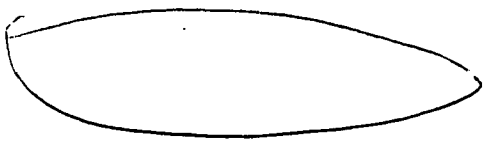
19. With respect to the levels of phenylalanine specified on the proposed labeling and package insert, please provide the calculations that support these levels.

Microbiology

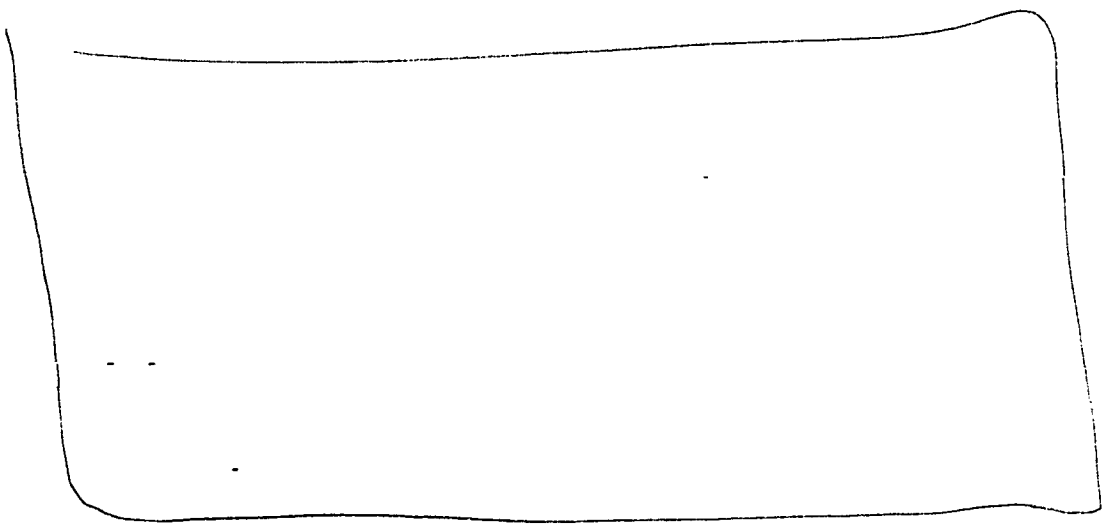
You are encouraged to monitor the bioburden of the olanzapine suspensions during the manufacturing process to control for the development of resistant microbial species with time. This could be accomplished on a skip-lot basis, not necessarily on every production lot.

Biopharmaceutics

Since dissolution data show that the release from all rapidly disintegrating tablet (RDT) lots tested are 100% in 10 minutes, the recommended specification is NLT 80% in 10 minutes for all strengths. Please adopt the following dissolution methodology and specification for all four strengths (5, 10, 15, and 20mg) of olanzapine Zydis tablets:



In addition, it will be necessary for you to submit final printed labeling (FPL) revised as follows:



cc:
Archival NDA 21-086
HFD-120/Div. Files
HFD-120/Hardeman
HFD-120/Laughren/Andreason/Seevers/
HFD-002/ORM
HFD-101/ADRA
HFD-40/DDMAC (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: sdh/December 20, 1999
final: 12/20/99
filename:

APPROVABLE (AE)

12/20/99
HZ 12/21/99
RB 12/21/99
RW 12/20/99

[redacted]

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Steve Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
317.276.2000

December 6, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

PROPOSED PACKAGE LABELING

RE: NDA 21-086, ZYPREXA® ZYDIS® (olanzapine) – Orally Disintegrating Tablets

Enclosed are proposed carton and container labels in final form for the referenced drug. A recent telephone conversation between Mr. Steve Hardeman (FDA) and Drs. Al Webber and Michele Sharp (Eli Lilly and Company) suggested this submission was timely.

Please refer to our March 1, 1999 submission of the referenced NDA. That submission included draft carton and container labels (Vol. 1, beginning on pg. 52).

The enclosure includes: 1) blister label (DV 3487 BLF), 2) child-resistant sachet front panel (DV 3485 SFF), 3) child-resistant sachet back panel (DV 3486 SBF), 4) non child-resistant sachet front panel (DV 3491 SFF), 5) non child-resistant sachet back panel (DV 3492 SBF) 6) child-resistant carton of 30 (DV 3403 DVS) and 7) non child-resistant carton of 100 (DV 3412 DVS) for the 5 mg tablet only. The text found on the 10 mg, 15 mg and 20 mg carton and container labels are identical to the provided 5 mg labeling aside from the dosage strength identification, NDC code, tablet number identification, and phenylalanine amount. In addition, the 10 mg, 15 mg and 20 mg carton and container labels contain color bands different from the 5 mg. These colors are purple, light blue and dark red, respectively.

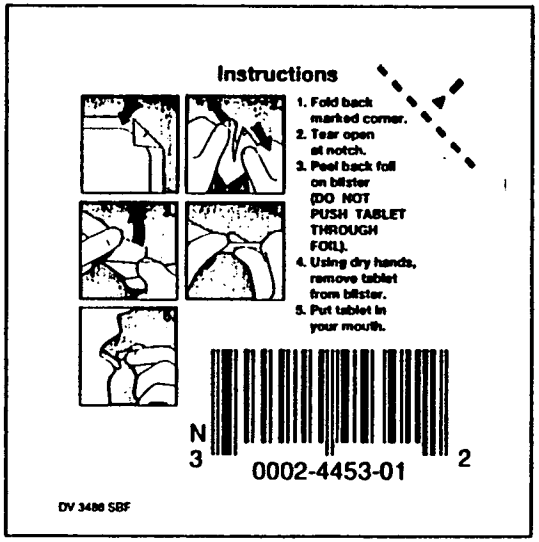
Please call Dr. Michele Sharp at (317) 277-8382 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Enclosures
cc: Mr. Steve Hardeman

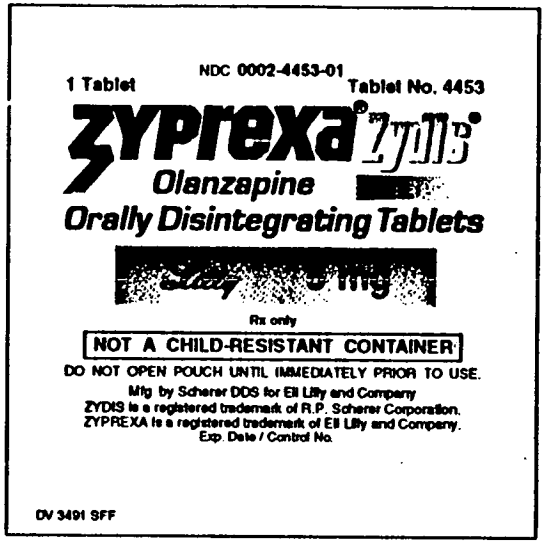


DEVELOPMENTAL COPY ONLY

COLOR ID	
Item Code: DV 3486 SBF Colors:	
BLACK	DV 3486 SBF

LILLY APPROVALS		
Graphics Operator:	N/A	Date:
Proofreader:	N/A	Date:
Label Editor or Label Editor Asst:	LC	Date: 12-2-99
Printing Quality Control:		Date:

PPMQC copy check 12-3 [illegible]



DEVELOPMENTAL COPY ONLY

COLOR ID	Item Code: / Colors:	DV 3491 SFF
	BLACK	DV 3491 SFF
	PURPLE 0526	DV 3491 SFF
	YELLOW 0123	DV 3491 SFF
	BLUE 0299	DV 3491 SFF

LILLY APPROVALS			
	Graphics Operator:	N/A	Date:
	Proofreader:	N/A	Date:
	Label Editor or Label Editor Asst:	RC	Date: 12-2-99
	Printing Quality Control:		Date:

PMGC copy check end 12-3-99

1 Tablet

NDC 0002-4453-01

Tablet No. 4453

ZYPREXA® ZYDIS®

Olanzapine

Orally Disintegrating Tablets

Lilly 5 mg

Rx only

DO NOT OPEN POUCH UNTIL IMMEDIATELY PRIOR TO USE.

Mfg. by Scherer DDS for Eli Lilly and Company

ZYDIS is a registered trademark of R.P. Scherer Corporation.

ZYPREXA is a registered trademark of Eli Lilly and Company.

Exp. Date / Control No.

DV 3485 SFF

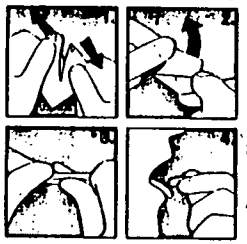
DEVELOPMENTAL COPY ONLY

COLOR ID		
	Item Code:	DV 3485 SFF
	Colors:	
	BLACK	DV 3485 SFF
	PURPLE 0526	DV 3485 SFF
	YELLOW 0123	DV 3485 SFF
	BLUE 0299	DV 3485 SFF

LILLY APPROVALS		
Graphics Operator:	N/A	Date:
Proofreader:	N/A	Date:
Label Editor or Label Editor Asst:	JRC	Date: 12-2-99
Printing Quality Control:		Date:

PPMGC copy check, ... 12-3-99

Instructions



1. Tear open.
2. Peel back foil on blister (DO NOT PUSH TABLET THROUGH FOIL).
3. Using dry hands, remove tablet from blister.
4. Put tablet in your mouth.

N 3 0002-4453-01 2

DV 3492 SBF

DEVELOPMENTAL COPY ONLY

COLOR ID		
Item Code:	DV 3492 SBF	
Colors:		
BLACK	DV 3492 SBF	

LILLY APPROVALS		
Graphics Operator:	N/A	Date:
Proofreader:	N/A	Date:
Label Editor or Label Editor Asst:	RC	Date: 12-2-99
Printing Quality Control:		Date:

APPROX copy check Jml 12-3-99

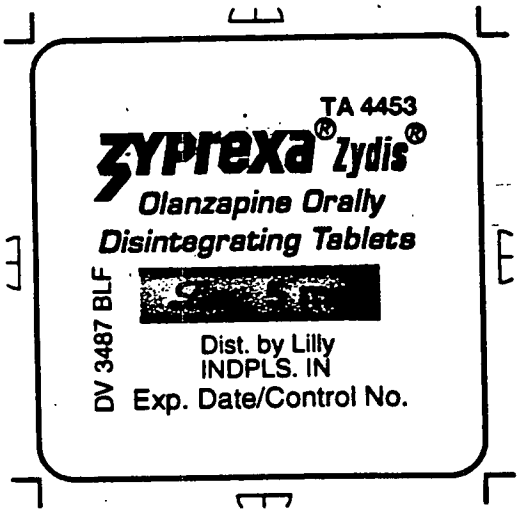
actual size

DEVELOPMENTAL COPY ONLY

COLOR ID		
	Item Code:	DV 3487 BLF
	Colors:	
	BLACK	DV 3487 BLF
	PURPLE 0526	DV 3487 BLF
	YELLOW 0123	DV 3487 BLF

LILLY APPROVALS		
Graphics Operator: N/A	Date:	
Proofreader: N/A	Date:	
Label Editor or Label Editor Asst: Rc	Date: 12-2-99	
Printing Quality Control	Date:	

fpmQC copy check Mul 12-3-99



300% enlarged

NDC 0002-4453-85
30 Tablets Tablets No. 4453

ZYPREXA ZYDIS
Olanzapine
Orally Disintegrating Tablets

Compliance Calendar

Initial Week: Sun Mon Tue Wed Thu Fri Sat

Week One: Sun Mon Tue Wed Thu Fri Sat

Week Two: Sun Mon Tue Wed Thu Fri Sat

Week Three: Sun Mon Tue Wed Thu Fri Sat

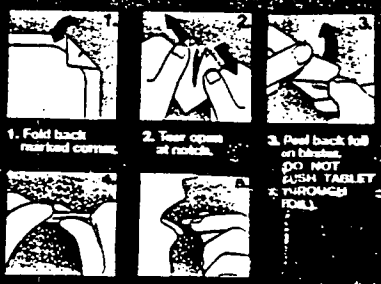
Week Four: Sun Mon Tue Wed Thu Fri Sat

TIME TO REORDER

Lilly

ZYPREXA ZYDIS
Olanzapine
Orally Disintegrating Tablets

DO NOT OPEN POUCH UNTIL IMMEDIATELY PRIOR TO USE.



1. Fold back marked corner.
2. Tear open at notch.
3. Peel back foil on blister. DO NOT PUSH TABLET THROUGH FOIL.
4. Using dry hands, remove tablet from blister.
5. Put tablet in your mouth.

NDC 0002-4453-85
30 Tablets Tablets No. 4453

ZYPREXA ZYDIS
Olanzapine
Orally Disintegrating Tablets

DO NOT OPEN POUCH UNTIL IMMEDIATELY PRIOR TO USE.

Rx only

ZYPREXA
Olanzapine
Orally Disintegrati

ZYDIS is a registered trademark of R.P.

ZYPREXA is a registered trademark of

Manufactured for
Eli Lilly and Co
by Schwarz DDS
Swindon, Unite
SN5 6RU

5 mg

Exp. Date / Control No.

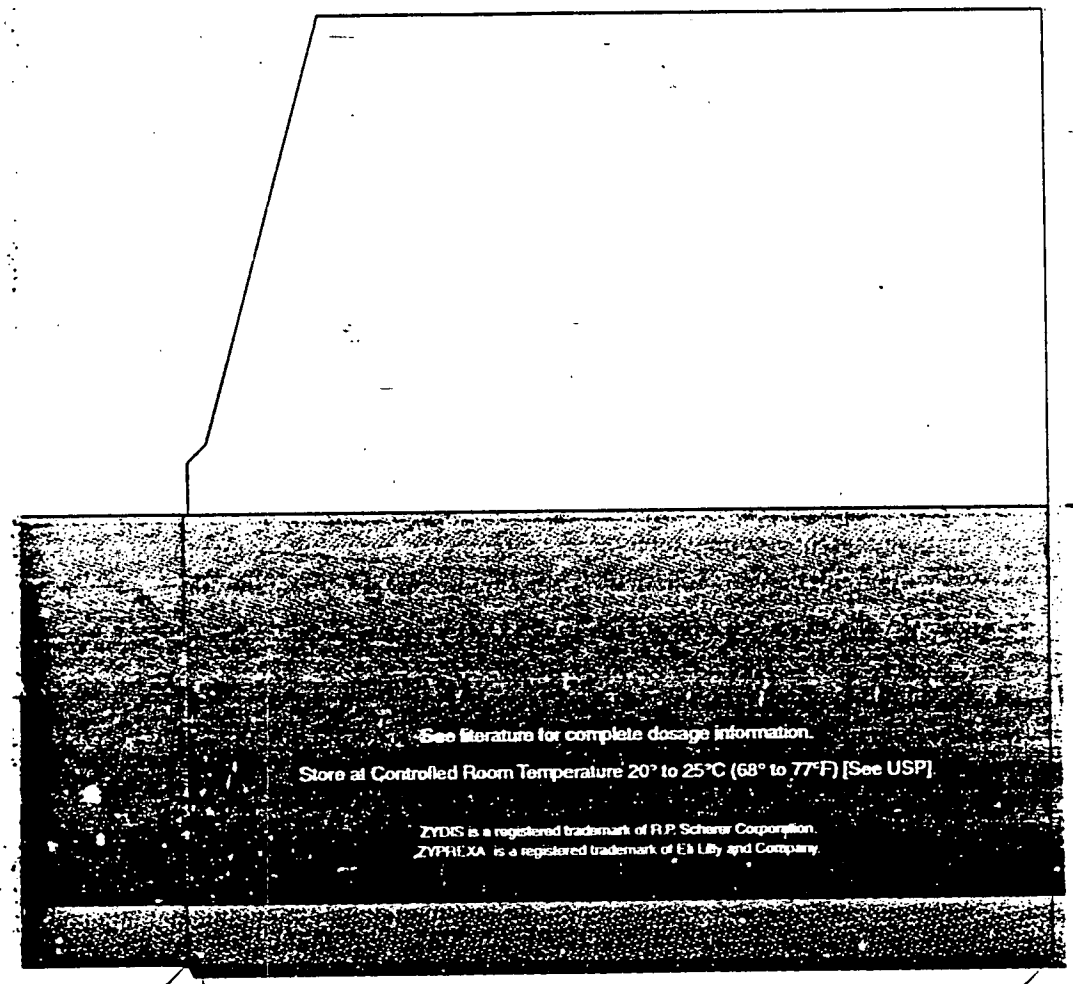
DV 3403 DVS DV 3403 DVS DV 3

N 3 0002-4453-85 2

DEVELOPMENTAL COPY ONLY

RID	Item Code: DV 3403 DVS Colors:	APPROVALS	Graphics Operator: N/A Date: Proofreader: N/A Date:

Label



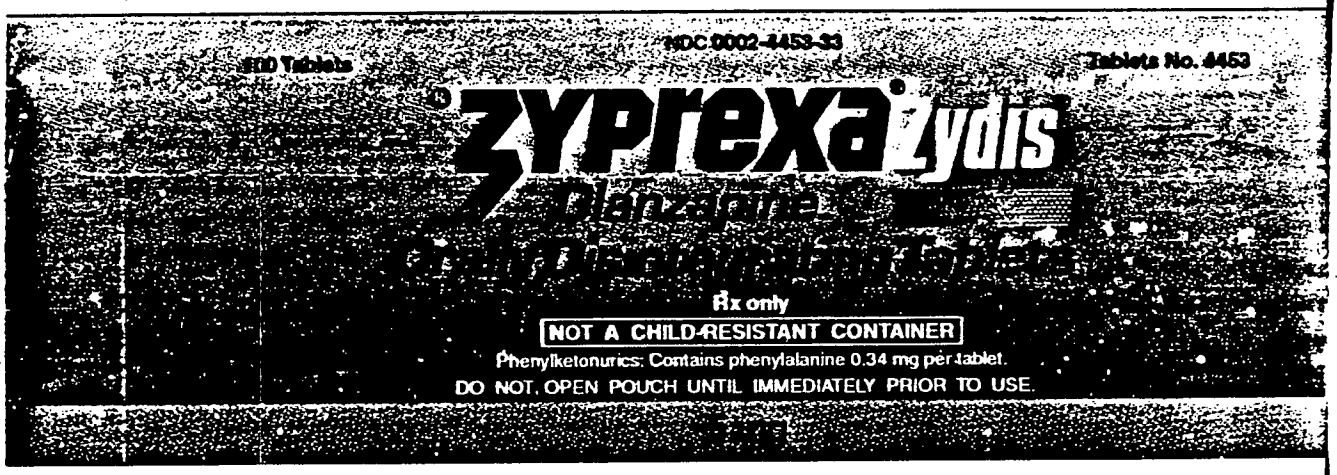
DV 3412 DVS DV 3412 DVS DV 3412 DVS

DEVELOPMENTAL COPY ONLY

COLOR ID	Item Code: DV 3412 DVS
	Colors:
	BLACK DV 3412 DVS
	PURPLE 0526 DV 3412 DVS
	YELLOW 0123 DV 3412 DVS
	BLUE 0299 DV 3412 DVS

LILLY APPROVALS			
	Graphics Operator:	N/A	Date:
	Proofreader:	N/A	Date:
	Label Editor or Label Editor Asst:	gc	Date: 12-2-99
	Printing Quality Control:		Date:

Image acceptable
12-3-99



Expiration Date/Control No.

N 3 0002-4453-33 3

ITEM 13: PATENT INFORMATION

NDA 21-086

ZYPREXA®ZYDIS®

(olanzapine orally disintegrating tablets)

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of olanzapine, as indicated. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act:

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)
5,229,382	April 23, 2011	Compound, method of use, formulation
5,605,897	February 25, 2014	Method of use
5,627,178	April 23, 2011	Method of use
5,736,541	March 24, 2015	Compound, method of use
5,817,655	April 23, 2011	Method of use
5,817,656	April 23, 2011	Method of use
4,371,576	January 29, 2000	Formulation
5,457,895	September 30, 2013	Formulation

U. S. Patent No. 5,229,382 claims a "method of treating an animal, including a human, suffering from or susceptible to psychosis, acute mania or mild anxiety states...." employing olanzapine.

U. S. Patent No. 5,605,897 claims a method of treating a patient suffering from any of a number of listed conditions, including "Bipolar Disorder NOS" employing olanzapine.

U. S. Patent No. 5,627,178 claims a method of treating a patient suffering from any of a number of listed conditions, including "Bipolar Disorder, Mixed, Severe, with Psychotic Features; Bipolar Disorder, Manic, Severe, with Psychotic Features; Bipolar Disorder, Depressed, Severe, with Psychotic Features, Schizophrenia, Catatonic, Schizophrenia Disorganized, Schizophrenia Paranoid, Schizophrenia Undifferentiated, Schizophrenia Residual, Major Depression, Generalized Anxiety Disorder " employing olanzapine.

U. S. Patent No. 5,736,541 claims a method of treating a patient suffering from any of a number of listed conditions including "a psychotic condition" and "mild anxiety" employing an olanzapine polymorph.

U. S. Patent No. 5,817,655 claims a method of treating a patient suffering from any of a number of listed conditions, including "Major Depression" employing olanzapine.

U. S. Patent No. 5,817,656 claims a method of treating a patient suffering from any of a number of listed conditions, including "Bipolar Disorder, Mixed, Severe, without Psychotic Features; Bipolar Disorder, Manic, Severe, without Psychotic Features; Bipolar Disorder, Depressed, Severe, without Psychotic Features" employing olanzapine.

U. S. Patent No. 4,371,576 claims a dosage form which "can be disintegrated by water within ten seconds."

U. S. Patent No. 5,457,895 claims a fast dissolving dosage formulation.

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

3/1/99
Date

Copy sent to Mary Ann Holovac 4/7/00 SHardeman

Copy #2 sent 5/18/00 SHardeman

Exclusivity Checklist

NDA: 21-086

Trade Name: Zyprexa Zydis Orally Disintegrating Tablets

Generic Name: olanzapine

Applicant Name: Lilly

Division: HFD-120

Project Manager: Steven D. Hardeman, R.Ph.

Approval Date: 4/6/00

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA? **Yes** (circled) No

b. Is it an effectiveness supplement? Yes **No** (circled)

c. If yes, what type? (SE1, SE2, etc.)

Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") Yes **No** (circled)

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation: 3 bioequivalence studies (F1D-EW-LOAJ / LOAL / LOAU) were all open-label, crossover in design.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Explanation:

d. Did the applicant request exclusivity? Yes **No** (circled)

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO

DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? Yes (No)

If yes, NDA #

Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? Yes (No)

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. (Yes) No

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety. (Yes) No

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product **Zyprexa Tablets**

NDA # **20-592**

Drug Product

NDA #

Drug Product

NDA #

2. Combination product. Yes (No)

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved Yes No

active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product

NDA #

Drug Product

NDA #

Drug Product

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. Yes (No)

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. ✓

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to Yes No

support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? Yes No

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. Yes No

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? Yes No

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes	No
Investigation #2	Yes	No
Investigation #3	Yes	No

If you have answered "yes" for one or more investigations, identify each such

investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number

Investigation #2 -- NDA Number

Investigation #3 -- NDA Number

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	Yes	No
Investigation #2	Yes	No
Investigation #3	Yes	No

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

Investigation #1 -- NDA Number

Investigation #2 -- NDA Number

Investigation #3 -- NDA Number

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1

Investigation #2

Investigation #3

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes	No
IND#:		
Explain:		
Investigation #2	Yes	No
IND#:		
Explain:		

Investigation #3 Yes No

IND#:

Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 Yes No

IND#:

Explain:

Investigation #2 Yes No

IND#:

Explain:

Investigation #3 Yes No

IND#:

Explain:

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) Yes No

If yes, explain:

Signature of PM/CSO
Date: 12/21/99
/S/
Signature of Division Director
Date: 12/23/99
/S/
cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21086	**Trade Name:**	ZYPREXA ZYDIS(OLANZAPINE) 5/10/15/20/MGTS
Supplement Number:		**Generic Name:**	OLANZAPINE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AE	**Proposed Indication:**	management of the manifestations of psychotic disorders

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
none

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, STEVE HARDEMANS

/S/ 12/21/99

Signature Date

CERTIFICATION

NDA Application No.: **21-086**

Drug Name: **Zyprexa®Zydis®**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Gregory T. Brophy, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: March 1, 1999

MEMORANDUM

DATE: December 23, 1999

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-086

SUBJECT: Action Memo for NDA 21-086, Zyprexa (olanzapine) orally disintegrating tablets

Eli Lilly and Company submitted NDA 21-086 for the use of Zyprexa orally disintegrating tablets (5, 10, 15, and 20 mg strengths) on 3/1/99. The submission contains the results of 3 bioequivalence studies, all single dose cross-over trials, which compared the 5, 10, and 20 mg strengths to the approved tablets (the 15 mg disintegrating tablet was not studied). In addition, the application contains relevant CMC information.

The bioequivalence studies have been reviewed by Dr. Zha0 (review dated 12/7/99). She has concluded that the tested disintegrating tablets are bioequivalent to the marketed tablets, and that the 15 mg disintegrating tablet may also be considered bioequivalent based on compositional proportionality and acceptable dissolution. She recommends that the sponsor adopt specific dissolution specifications.

Melissa Maust, chemist, has reviewed the CMC portion of the application (review dated 12/22/99) and has a number of comments, but recommends that the application be considered Approvable.

I have reviewed Dr. Zhao's and Ms. Maust's reviews, comments, and recommendations, as well as the proposed labeling. I agree that the application is Approvable. In particular, I agree that the sponsor's proposed statement in the Dosage and Administration section instructing prescribers that it would be acceptable to dissolve the disintegrating tablet in liquid prior to administration should be removed.

Given the above considerations, I will issue the attached Approvable letter with draft labeling.

/S/

Russell Katz, M.D.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 6, 2000

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Zyprexa (olanzapine) Zydis orally disintegrating tablets

TO: File NDA 21-086
[Note: This memo should be filed with the 1-27-00 complete response to our 12-23-99 approvable letter.]

Zyprexa (olanzapine) is approved for the treatment of psychosis, and is available as 2.5, 5, 7.5, and 10 mg immediate release tablets. This supplement provides support for an oral rapidly disintegrating tablet in 5, 10, 15, and 20 mg strengths.

The original 3-1-99 application included bioequvalence data demonstrating bioequivalence between the immediate release and Zydis formulations and CMC information. There were no clinical data submitted. We issued an approvable letter on 12-23-99 including a number of CMC deficiencies, dissolution specifications, and proposed changes to labeling.

The 1-27-00 response has been reviewed by Sherita McLamore, Ph.D. (See 3-17-00 review) and has been determined to be an adequate response to all deficiencies noted in our 12-23-99 letter. The labeling has also been modified according to our instructions.

I agree that this NDA can now be approved, and I recommend that we issue the attached approval letter.

cc:
Orig NDA 21-086
HFD-120/DivFile
HFD-120/TLaughren/RKatz/SHardeman

DOC: NDA21086.01