

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592Orig1s040s041

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 020592

SUPPL # 040 & 041

HFD # 130

Trade Name Zyprexa tablets

Generic Name olanzapine

Applicant Name Eli Lilly and Company

Approval Date, If Known 12/4/2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE5

c) 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

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.

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:

d) Did the applicant request exclusivity?

YES NO

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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).

NDA# 020592

Zyprexa (olanzapine) tablets

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(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:

F1D-MC-HGIN
F1D-MC-HGIU
F1D-MC-HGMF
F1D-SB-LOAY

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- 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

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

c) 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"):

F1D-MC-HGIN; F1D-MC-HGIU; F1D-MC-HGMF; F1D-SB-LOAY

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
IND # 028705 YES ! NO
! Explain:

Investigation #2
IND # 028705 YES ! NO
! 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
Explain:

!
! NO
! Explain:

Investigation #2

YES
Explain:

!
!
! NO
! 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:

=====

Name of person completing form: Kimberly Updegraff
Title: Project Manager
Date: 12/07/09

Name of Office/Division Director signing form: Thomas Laughren
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

KIMBERLY S UPDEGRAFF
12/11/2009

THOMAS P LAUGHREN
12/11/2009

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-592 [ZYPREXA (olanzapine) Tablets]

Supplement Type (e.g. SE5): SE5-040

Stamp Date: 31 October 2006 PDUFA Goal Date: 30 April 2007

HFD 130 Trade and generic names/dosage form: see above

Applicant: Eli Lilly & Co. Therapeutic Class: Antimanic (Bipolar Disorder)

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

Yes. Please proceed to the next question.

No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact Rosemary Addy or Grace Carmouze.

Indication(s) previously approved: For this dosage form: Schizophrenia, including maintenance in adults; bipolar disorder (acute manic or mixed episodes, monotherapy and adjunctive therapy, in adults; bipolar disorder maintenance monotherapy, in adults)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: Acute manic or mixed episodes associated with bipolar disorder in adolescents

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 13 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: this age range was waived for the original written request

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: .

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: __

Date studies are due (mm/dd/yy): _____.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 13 Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments: As stipulated in the Written Request

This page was completed by:

{See appended electronic signature page}

 Doris J. Bates, Ph.D.
 Regulatory Project Manager
 cc: NDA
 HFD-960/ Grace Carmouze
 (revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Doris Bates

4/30/2007 10:42:03 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-592 [ZYPREXA (olanzapine) Tablets]

Supplement Type (e.g. SE5): SE5-041

Stamp Date: 31 October 2006 PDUFA Goal Date: 30 April 2007

HFD 130 Trade and generic names/dosage form: see above

Applicant: Eli Lilly & Co. Therapeutic Class: Antipsychotic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

Yes. Please proceed to the next question.

No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact Rosemary Addy or Grace Carmouze.

Indication(s) previously approved: For this dosage form: Schizophrenia, including maintenance in adults; bipolar disorder (acute manic or mixed episodes, monotherapy and adjunctive therapy, in adults; bipolar disorder maintenance monotherapy, in adults

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication #1: Schizophrenia in adolescents (monotherapy)

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 13 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: this age range was waived for the original written request

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: .

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: __

Date studies are due (mm/dd/yy): _____.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 13 Tanner Stage _____
 Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments: As stipulated in the Written Request

This page was completed by:

{See appended electronic signature page}

 Doris J. Bates, Ph.D.
 Regulatory Project Manager
 cc: NDA
 HFD-960/ Grace Carmouze
 (revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Doris Bates

4/30/2007 10:45:39 AM



NDA 020592/S-040/S-041
NDA 022173

INFORMATION REQUEST

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

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated October 30, 2006, received October 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg.

We also refer to your new drug application (NDA 022173) dated and received on April 30, 2007, for Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension 210 mg, 300 mg, and 405 mg.

FDA received a recent inquiry from a consumer who raised a general question of whether or not FDA has in its possession all the relevant safety data it needs to make final decisions about pending applications from several manufacturers whose products were involved in certain tort litigation. This consumer referred to pending tort litigation in New Jersey involving three atypical antipsychotic drugs, including Zyprexa. Allegedly a 3-judge panel was appointed to give an opinion on whether the documents involved should be made publically available, and this panel presumably recommended that the documents be released. The consumer has alleged that the documents have remained sealed, however, because of an objection by one of the manufacturers involved in this case. The consumer has raised the question of whether or not FDA has access to any such sealed documents and has had an opportunity to examine them. The consumer has urged FDA to request these documents from the companies involved.

Under 505(k) of the FFDCFA, NDA holders are required to establish and maintain such records, and make such reports, "of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug," as FDA may require, "to determine, or facilitate a determination, whether there is or may be ground for" revoking approval. Additionally, under 21 CFR 314.80 and 314.81, when appropriate, NDA

NDA 020592/S-040/S-041

NDA 022173

Page 2

holders must submit the following reports bearing on drug safety: (1) 15-day expedited reports; (2) periodic reports; (3) field alert reports; and (4) annual reports.

By this letter, we are asking you to ensure that you are in compliance with all applicable statutes and regulations, and we further request that you submit to the agency all data and information regarding any olanzapine products involved in the New Jersey case in question. If there were no documents or other information from your company that were involved in this litigation, we ask that you formally assert that by return letter. We would be happy to discuss these matters if you would find that helpful in preparing a response to this inquiry.

If you have any questions, call Kimberly Updegraff, M.S, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-22173	ORIG-1	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

THOMAS P LAUGHREN
11/24/2009

Updegraff, Kimberly

From: Diaz, Jessica M
Sent: Friday, October 16, 2009 4:15 PM
To: Simon, Sarah
Cc: Dempsey, Mary; Updegraff, Kimberly; Karwoski, Claudia B; Griffiths, LaShawn
Subject: RE: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Importance: High

Hello Sarah,

Good afternoon. Regarding the Zyprexa NDA 020592 REMS Assessment/Modification Submission from Eli Lilly and Company. We, DRISK, have reviewed the submission and the changes are in keeping with our recommendations in the Addendum dated 10-06-2009. The REMS Assessment/Modification Submission submitted by the applicant on 10/13/2009 is acceptable.

Please feel free to contact DRISK with any follow-up questions or concerns.

Best Regards,

Jess

LCDR Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
Division of Risk Management
FDA-CDER-OSE
301-796-4908 (Office)

-----Original Message-----

From: Simon, Sarah
Sent: Friday, October 16, 2009 3:08 PM
To: Updegraff, Kimberly
Cc: Dempsey, Mary; Diaz, Jessica M
Subject: RE: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Hi Kim,

I got notification of this submission the other day and so Mary Dempsey and Jess Diaz are looking into it. They are still determining whether an email acknowledgement of acceptance of the changes will be sufficient or if a new review assignment will be generated. I will certainly pass along Drisk's decision on how they are going to handle it. Thank you for making sure I was aware of the submission!

Enjoy your weekend,
Sarah

-----Original Message-----

From: Updegraff, Kimberly
Sent: Friday, October 16, 2009 2:53 PM
To: Simon, Sarah
Cc: Updegraff, Kimberly
Subject: NDA 020592 Zyprexa REMS Assessment/Modification Submission

Dear Sarah,

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

NIKOO N MANOCHEHRI-KALANTARI
12/22/2009



NDA 20-592 S-040/S-041

REMS Modification Notification

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

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

Dear Dr. Brophy:

We are reviewing your supplemental new drug applications dated and received on September 19, 2008, for Zyprexa (olanzapine) tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg. These supplements provide for the use of Zyprexa (olanzapine) tablets in treating manic or mixed episodes of bipolar I disorder and schizophrenia in adolescents.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENT

The Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa (olanzapine) tablets was approved on March 19, 2009. The REMS consisted of a Medication Guide and a timetable for submission of assessments of the REMS. As these supplemental new drug applications provide for a new indication -- the use of Zyprexa (olanzapine) tablets in the adolescent population-- in accordance with section 505-1(g)(2)(A), you are required to submit an assessment and may propose a modification of the existing REMS. You have proposed modifications to the Medication Guide to extend the current warnings and precautions to include adolescents ages 13 to 17, but you have not yet submitted an assessment of the REMS. Where the REMS consists solely of a Medication Guide, the REMS assessment may consist of a statement that the Medication Guide would be adequate with the proposed modifications to achieve its purpose. Your proposed REMS modification submission should include the REMS document that was approved on March 19, 2009, in addition to your revised Medication Guide. The timetable for submission of assessments of the REMS may remain the same as that approved on March 19, 2009.

We request that you submit your modified REMS and REMS Assessment as described above to these supplements by the close of business on October 16, 2009. The modified REMS, once approved, will create enforceable obligations.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT NDA 20-592 S-040/S-041
PROPOSED REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT NDA 20-592 S-040/S-041
PROPOSED REMS MODIFICATION-AMENDMENT**

If you do not submit electronically, please send 5 copies of your submission.

If you have any questions, please call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301) 796-2201.

Sincerely yours,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

THOMAS P LAUGHREN
10/06/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Office of Biostatistics Safety Group SafetyDivisionCons@fda.hhs.gov Attention: Paul Schuette		FROM: HFD-130/Div. of Psychiatry Products		
DATE September 22, 2009	IND NO. 28705 SDN1553	NDA NO. 20592 SDN414	TYPE OF DOCUMENT SAP	DATE OF DOCUMENT September 18, 2009
NAME OF DRUG Zyprexa (olanzapine)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 60 days	
NAME OF FIRM: Eli Lilly				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input checked="" type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS:				
<p>Eli Lilly has submitted a statistical analysis plan related to a long term study being done utilizing Zyprexa. The Division of Psychiatry Products along with the Office of Biostatistics (Dr. Peiling Yang) are requesting review of this SAP. The submission is located in the edr under the NDA and the IND here \CDSESUB1\EVSPROD\NDA020592\0038 and here \CDSESUB1\EVSPROD\IND028705\1097. Please have the reviewer link their review to both folders when entering into dartrts. Also, as an fyi, there is a clinical review by Dr. Cara Alfaro in dartrts under IND 28705 (3/11/09, N-1085, SDN-1543). Let me know if you have any questions.</p>				
SIGNATURE OF REQUESTER Keith Kiedrow, Pharm.D. Regulatory Project Manager 301-796-1924 keith.kiedrow@fda.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

KEITH J KIEDROW
09/22/2009

THOMAS P LAUGHREN
09/22/2009

REQUEST FOR CONSULTATION

TO (Office/Division):
CDER OSE Consults
Abolade Adeolu
Project Manager, 6-0674

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Psychiatry Products/ HFD-130
From: Kim Updegraff, RPM - DPP HFD-130
Through: Thomas Laughren, Division Director

DATE August 3, 2009	IND NO.	NDA NO. 20-592 S040 & 041	TYPE OF DOCUMENT Medguide Review - minor changes	DATE OF DOCUMENT May 5, 2009
NAME OF DRUG Zyprexa (olanzapine) tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Schizophrenia	DESIRED COMPLETION DATE September 1, 2009

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The sponsor has submitted an updated medguide as part of the proposed labeling to pediatric supplements S040 & S041. The PDUFA date was in March 2009, however, the pediatric applications were presented at a June AC meeting and the Division is currently working toward approval of these applications (in late August/September 2009). There are a few small changes the proposed medguide, please review the medguide and provide comments. This is an electronic submission which can be found in the EDR at:
 \\CDSESUB1\EVSPROD\NDA020592 (5/5/09 submission). Please let me know if you need additional information.
 Thank you.

SIGNATURE OF REQUESTOR
Kim Updegraff 6-2201

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20592	SUPPL 40		ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA 20592	SUPPL 41		ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

KIMBERLY S UPDEGRAFF
08/07/2009

MITCHELL V Mathis
08/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PEDIATRIC SAFETY CONSULTATION		
TO: Office of Surveillance and Epidemiology/ Division of Epidemiology		FROM: Office of Pediatric Therapeutics (OPT) and Pediatric and Maternal Health Staff (PMHS) NOTE to Safety Reviewers: OPT does not have access to DFS. Please provide a copy of the final DFS'd consult response to Dr. Dianne Murphy, Dr. Judy Cope, and Debbie Avant, R.Ph., 301-827- 1602 Suzanne Malli, 301.827.1675		
DATE May 13, 2009	IND NO.	NDA /INDNO. #	DATE EXCLUSIVITY GRANTED	DATE OF PRODUCT APPROVAL
NAME OF DRUG Risperidal, Zyprexa, Geodon, Abilify, Seroquel, Invega	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Atypical Anti- psychotics	DESIRED COMPLETION DATE August 24, 2009	
NAME OF FIRM:				
REASON FOR REQUEST				
I. GENERAL				
INITIAL BPCA SAFETY REVIEW <input type="checkbox"/> STANDARD (refer BPCA template below) http://eroom.fda.gov/eRoomReq/Files/OC/OC-PAC/0_2ac34/BPCA%20OSE%20Template.doc		SPECIFIC SAFETY ISSUES / PAC Follow/up Request (see comments below) <input type="checkbox"/> SPECIFIC SAFETY ISSUES (see comments below) <input checked="" type="checkbox"/> PAC Follow/up Request (see comments below)		
PEDIATRIC SAFETY ISSUE – INDEPENDENT OF BPCA SAFETY REVIEW <input type="checkbox"/> SCIENTIFIC ISSUES (SPECIFY BELOW): <input type="checkbox"/> LABELING REVISIONS (SPECIFY BELOW): <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input checked="" type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)				
RESOURCE INFORMATION – If applicable, OPT/PMHS will provide the most recent product label, medical and clinical pharmacology executive summary, hyperlinks to previous PAC meeting; as appropriate: Background material are located in the eRoom @ http://eroom.fda.gov/eRoom/OC/OC-PAC				
COMMENTS / SPECIAL INSTRUCTIONS: Background: The November 18, 2008 PAC Committee requested FDA to address the following regarding atypical anti-psychotics: Additional follow-up regarding on-label and off-label product use of this class of drug products with specific attention to age and indication for which the product is being used. The PAC is particularly concerned about the atypical anti-psychotic use in children under 6 years (see below, age bands are grouped accordingly). Please complete a use review for oral products in outpatient settings utilizing the most relevant databases to obtain a better understanding on the use of atypical anti-psychotics in the pediatric population. <ul style="list-style-type: none"> • Drug products including Risperidal, Zyprexa, Abilify, Seroquel, Geodon, Invega • Use data over the last 5 years broken down by year • Breakdown by age groups: 0-2 years, 3-6years, 7-12 years, 13-17 years old and ≥18years • Usage by age and indication and where possible relevant co-morbidities with particular focus on autism, ADHD, behavioral disorder, irritability, and aggression • Usage by type of prescriber: psychiatrist, pediatrician, neurologist, other primary care providers • If possible, please identify concomitant medications and any associated diagnosis 				
Please let us know if you have any questions. Thank you.				
SIGNATURE OF REQUESTOR <i>Dr. Dianne Murphy/Judith Cope/ Debbie Avant/Suzanne Malli</i>		METHOD OF DELIVERY (Check one) DFS ✓ EMAIL		
Additional Staff To Who Consult Response Should Be Sent: NOTE to Safety Reviewers: OPT does not have access to DFS. Please provide a copy of the final DFS'd consult response to Dr. Dianne Murphy , Dr. Judith Cope, Debbie Avant, R.Ph., Suzanne Malli, RN				

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/s/

Debbie Avant

5/21/2009 01:48:16 PM

Updegraff, Kimberly

From: Greeley, George
Sent: Thursday, August 20, 2009 7:19 AM
To: Updegraff, Kimberly
c: Stowe, Ginneh D.
Subject: NDA 20-592 Zypresa

Importance: High

Hi Kimberly,

The Zyprexa (olanzapine) partial waiver/assessment product was reviewed by the PeRC PREA Subcommittee on July 22, 2009. The Division recommended a partial waiver from birth to 12 years of age because too few children with disease/condition to study and completed studies for children 13-17 years of age.

The PeRC informed the Division that an expansion of the patient population is not a PREA trigger. The pediatric page for this supplement should reflect an assessment only.

The PeRC agreed the Division in the review of the assessment for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
0903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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/s/

Renmeet Grewal
10/21/2008 09:06:54 AM
CSO

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Monday, May 11, 2009 7:20 AM
To: 'Christine Ann Phillips'
Cc: Updegraff, Kimberly
Subject: FDA feedback: Draft core slides from Lilly for June PDAC

Dear Christine,

We have briefly reviewed the slides you sent to us on 5/8/09 and have the following comments:

1. We think that outlier data for hyperlipidemia and hyperglycemia should be included in your presentation. It is much more informative to clinicians and to the committee to describe shifts in lipids or glucose from normal to high or borderline to high (as is done in your label), rather than to report small mean changes which have no individual clinical significance. Please add these slides. Addition of Hgb A1C and urine glucose data would also be helpful.
2. We agree that you have demonstrated efficacy, and the reason for second-line status is because of the safety concerns (metabolic and weight changes).
3. Regarding country differences that are not clinically significant: We don't believe this will be a major area of concern for the committee and would not spend too much time in your presentation on this topic. If the issue comes up, you should be prepared to answer questions about it.
4. Regarding the balance question: Once you add the clinically relevant safety slides (shifts from normal or borderline to high in lipids and glucose), the presentation will be balanced.

In response to your request for a telcon, we have Tuesday, May 26, 2009 from 9:00 to 10:00 AM EST available if you would like to discuss your slides and presentation.

Please let me know if you are interested in speaking with us on the 5/26/09.

Sincerely,

Kim Updegraff
Regulatory Project Manager
Division of Psychiatry Products

-----Original Message-----

From: Christine Ann Phillips [mailto:PHILLIPS_CHRISTINE_ANN@LILLY.COM]
Sent: Friday, May 08, 2009 9:20 AM
To: Updegraff, Kimberly; Laughren, Thomas P; Mathis, Mitchell
Cc: PHILLIPS_CHRISTINE_ANN
Subject: Draft core slides from Lilly for June PDAC

Good morning Drs. Updegraff, Laughren and Mathis,

Please find attached our draft slides for the Advisory Committee Meeting being held 9-10 June 2009. We welcome your feedback and suggestions for the slides and presentation itself. We'd like to set up a teleconference with you once you have completed your review to ensure we understand any changes you recommend. We have a couple areas in particular that we would like to focus on, as these have come up in our practice sessions.

First of all, we wish to ensure we appropriately reflect the recommendation for second-line use of olanzapine in adolescents. We believe efficacy has been demonstrated in adolescents without

qualification. The reason for second-line status is because of the safety profile in adolescents, representing a different risk-benefit profile than what is seen in adults. Is this the Division's understanding? Do you have recommendations on the best way to convey this understanding?

Secondly, we would like your guidance on how best to present the subgroup analyses from Study HGIN, the schizophrenia trial, in which non-statistically significant differences between the US and Russian sites were observed.

Finally, is the presentation balanced and does it achieve your objectives for the advisory committee meeting?

We look forward to hearing your comments and I can work with you to schedule an appropriate time for a teleconference.

Thank you,
Christine

(See attached file: Core Slides for FDA Review (8May2009).ppt)

Christine Phillips, PhD, RAC
Eli Lilly and Company
US Regulatory Affairs
317.276.7239 (office)
317.625.6045 (mobile)
phillipsch@lilly.com

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/s/

Kimberly Updegraff
5/27/2009 05:22:10 PM
CSO

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Monday, April 13, 2009 5:34 PM
To: Christine Ann Phillips
Cc: Updegraff, Kimberly
Subject: NDA 20-592 S040/S041

Dear Christine,

Please refer to your submissions dated December 1, 2008 for NDA 20-592 S-040 and S-041 providing for the use of Zyprexa for the treatment of manic or mixed episodes associated with bipolar disorder and schizophrenia in adolescents.

- Please provide a list of investigators for all trials (not just the pivotal trials) for each indication (schizophrenia/bipolar).

Thanks,

Kim

Kimberly Updegraff
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201

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/s/

Kimberly Updegraff
5/22/2009 06:23:27 PM
CSO

REQUEST FOR CONSULTATION

TO (*Division/Office*): CDER OSE Consults
Abolade Adeolu, PM 6-4264 CDER/OSE/RMS
Daniel Brounstein, PM 6-0674 CDER/OSE/RMS

FROM: Division of Psychiatry Products/ HFD-130
Kim Updegraff, Regulatory Project Manager

DATE
09MAR09

IND NO.

NDA NO.
20-639 S045/S046
(b) (4)
20-592 S040/S041

TYPE OF DOCUMENT
Pediatric Efficacy Supplements

DATE OF DOCUMENT
12/22/2008
12/23/2008
12/1/2008

NAME OF DRUG
Seroquel
(b) (4)
Zyprexa

PRIORITY CONSIDERATION
Supplemental NDA review
Info request for PDAC

CLASSIFICATION OF DRUG
Schizophrenia & bipolar disorder

DESIRED COMPLETION
DATE: **April 20, 2009**
PDAC: June 9&10, 2009

NAME OF FIRM: AstraZeneca (b) (4); Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|---|---|
| <input type="checkbox"/> SUPPLEMENTAL NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): Meeting briefing book | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|---|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input checked="" type="checkbox"/> DRUG USE e.g.usage by age/prescriber; adverse rxn | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The Office of Drug Evaluation I / Division of Psychiatry Products has scheduled a PDAC meeting for June 9&10, 2009. The following applications will be discussed: NDA 20-639/S-045 and S-046: Seroquel (quetiapine) for the treatment of schizophrenia in adolescents (13-17 years of age) and in the treatment of bipolar mania in children (10-12 years of age) and adolescents (13-17 years of age); (b) (4); NDA 20-592/S-040: Zyprexa (olanzapine) for the acute second line treatment of manic or mixed episodes associated with bipolar I disorder or schizophrenia in adolescents. The committee will be asked to vote on whether or not these products have been shown to be effective and acceptably safe for the pediatric indications.

We request OSE's assistance in obtaining the following data relating to usage and adverse reactions :

- Usage data over the last 5 years, by year

- Inpatient and outpatient usage
- Breakdown by age groups: 0-6 years, 7-12 years, 13-17 years old.
- Usage by diagnosis
- Usage by type of prescriber: psychiatrist, pediatrician, neurologist, other

Adverse events:

- Over 5 years
- Specific searches for suicide-related AE, other psychiatric AE, metabolic (weight gain, hyperglycemia, diabetes, elevated cholesterol triglycerides) tardive dyskinesia, akathisia, and other movement disorders, agranulocytosis, QT prolongation, torsades, arrhythmia, cardiovascular AE

The Clinical reviewers are Dr. Cara Alfaro/Dr. Mark Ritter and the Team leaders are Dr Ni Khin/Dr Robert Levin. Please let me know if you have any questions or requests.

Thank you!

SIGNATURE OF REQUESTER Kim Updegraff, RPM, WO Bldg 22 Rm 4241, 6-2201	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Thomas Laughren
3/11/2009 03:24:09 PM

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, February 11, 2009 5:01 PM
To: 'Roland W Usher'
Cc: Bates, Doris J; Updegraff, Kimberly; Grewal, Renmeet
Subject: Important Notice: Psychopharmacologic Drugs Advisory Committee Meeting, June 9-10, 2009 [Zyprexa]

Importance: High

{Dear Mr. Usher: Please forward the attached notice to Dr. Phillips and Dr. Brophy as soon as possible; I am forwarding the message via your address for security reasons. Thank you very much!}

Dear Dr. Phillips and Dr. Brophy:

I am forwarding this message to your attention through Mr. Usher, to assure a secure email link for its transmission.

The Office of Drug Evaluation I / Division of Psychiatry Products has scheduled a Psychopharmacologic Drugs Advisory Committee (PDAC) meeting for June 9-10, 2009. The committee will discuss multiple supplemental NDAs, including your submissions:

NDA 21-592/S-040: Zyprexa (olanzapine) for the acute second line treatment of manic or mixed episodes associated with bipolar I disorder or schizophrenia in adolescents.

Arrangements for this PDAC are being managed by Dr. Kimberly Updegraff, Regulatory Health Project Manager, Division of Psychiatry Products. Please contact Dr. Updegraff directly with any specific questions you may have.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates

2/11/2009 05:17:07 PM

CSO

all three companies affected have been notified simultaneously.

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 9:04 AM
To: 'Christine Ann Phillips'
Subject: FW: Zyprexa, Symbyax, Prozac submission in response to AE letter

Please forgive me. A correction to the PDUFA date: March 19, 2009.

Regards,
Rimmy

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 8:58 AM
To: 'Christine Ann Phillips'
Subject: Zyprexa, Symbyax, Prozac submission in response to AE letter

Hi Christine,

Regarding your submission dated and received on September 19, 2008. After an initial review of the submission the agency has decided this is a complete response to the August 1, 2008 approvable letter. This is considered a class 2 submission and the PDUFA date is March 19, 2008, however if the agency completes its review prior to this date we will take an action.

Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
10/21/2008 09:06:54 AM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Tuesday, October 21, 2008 8:58 AM
To: 'Christine Ann Phillips'
Subject: Zyprexa, Symbyax, Prozac submission in response to AE letter

Hi Christine,

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Sincerely,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
10/21/2008 09:02:36 AM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):
OSE/DRISK
Attn: Mary Dempsey

FROM:
OND/ODE1/DPP; HFD-130
From: Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager
Through: Thomas Laughren, M.D., Division Director

DATE 9/25/08	IND NO.	NDA NO. 20-592/s-039/040/041 21-520/012, 21-086/021,18-936/077	TYPE OF DOCUMENT REMS: addition of a Medguide	DATE OF DOCUMENT 9/19/08
-----------------	---------	--	--	-----------------------------

NAME OF DRUG Olanzapine	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE PDUFA: 3-19-09 WANT TO ACT SOONER
----------------------------	------------------------	------------------------	---

NAME OF FIRM: Eli Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE--NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input checked="" type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>): |
|--|--|--|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

Hi Mary,
 This is a response to an approvable letter sent (8-1-08) to the sponsor including a REMS to respond with a MEDGUIDE. The sponsor has responded to our approvable letter. Since this contains a medguide we are coding it a 6 month clock however we would like to act on these supplements sooner. I have attached the links to the sponsor's response.
 The network location for Zyprexa is : \\FDSWA150\NONECTD\N20592\S_040\2008-09-19
 The network location for Symbyax is : \\FDSWA150\NONECTD\N21520\S_012\2008-09-19
 The network location for Prozac is : \\FDSWA150\NONECTD\N18936\S_075\2008-09-19

If you have any further questions please contact me at either renmeet.grewal@fda.hhs.gov or 301-796-1080.

Thanks,
Rimmy

SIGNATURE OF REQUESTER Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Thomas Laughren
9/25/2008 05:47:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592/ (b) (4) /S-039/S-040/S-041 (b) (4)
NDA 21-086/ (b) (4) /S-021 (b) (4)
(b) (4)

Eli Lilly & Company
Attention: Christine A. Phillips, Ph.D., RAC
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Phillips:

Please refer to your supplemental new drug applications dated September 28, 2006 (NDA 20-592/S-039 & NDA 21-086/S-021), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), (b) (4)

We acknowledge receipt of your following amendments submitted to supplemental applications 20-592 (b) (4) S-039 and 20-592/S-019 (b) (4)

September 27, 2007	February 4, 2008	April 1, 2008	May 27, 2008
September 28, 2007	March 4, 2008	May 1, 2008	June 4, 2008
December 7, 2007	March 7, 2008	May 12, 2008	

Your submission of February 4, 2008 constituted a complete response to our September 21, 2007 action letter.

These supplemental new drug applications provide for the addition of the following language to the Indications section of the Zyprexa labeling when fluoxetine and olanzapine are used concomitantly:

- acute treatment of depressive episodes associated with Bipolar Disorder
- acute treatment of treatment resistant depression

Please also refer to your supplemental new drug applications dated October 30, 2006 (NDA 20-592/S-040/S-041), submitted under section 505(b) of the Act for Zyprexa (olanzapine) tablets.

We acknowledge receipt of your submissions dated:

May 8, 2007	September 25, 2007	February 5, 2008	May 14, 2008
June 7, 2007	September 28, 2007	March 4, 2008	June 4, 2008
August 30, 2007	November 1, 2007	May 1, 2008	July 22, 2008
September 10, 2007	December 7, 2007	May 12, 2008	

NDA 20-592 (b) (4) /S-039/S-040/S-041 (b) (4)
NDA 21-086 (b) (4) S-021 (b) (4)

Page 2

Your submission of February 5, 2008 constituted a complete response to our April 30, 2007 action letter.

These supplemental new drug applications provide for the use of Zyprexa (olanzapine) tablets in the acute treatment of Bipolar Disorder (manic or mixed episodes) in adolescent patients (supplement 040) and the acute treatment of Schizophrenia in adolescent patients (supplement 041).

We also acknowledge receipt of the following supplements incorporated into the attached label:

(b) (4)

We completed our review of these applications, and they are approvable. Before these applications may be approved, however, you must address the following deficiencies:

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since Zyprexa was approved in 1996, we have become aware of new safety information from analysis of data related to an increased risk of hyperglycemia, hyperlipidemia and weight gain in adolescents associated with olanzapine use. This information was not available when Zyprexa was granted marketing authorization. Therefore, we consider this information to be “new safety information” as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk that is, weight gain, hyperglycemia, and hyperlipidemia in adolescents treated with Zyprexa.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this known serious risk.

Therefore, based on the new safety information described above, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct postmarketing clinical studies or trial(s) of Zyprexa tablets (NDA 20-592) to assess the known serious risks of weight gain, hyperglycemia, and hyperlipidemia. The specific details of the required postmarketing clinical studies or trial(s) will be described more fully in a future letter.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(2)). This provision took effect on March 25, 2008.

Since Zyprexa was approved in 1996, we have become aware of new safety information from analysis of data related to increase risk of hyperglycemia, hyperlipidemia and weight gain associated with olanzapine use. This information was not available when Zyprexa was granted marketing authorization. Therefore, we consider this information to be “new safety information” as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zyprexa poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of Zyprexa. FDA has determined that Zyprexa is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients’ decisions to use Zyprexa. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zyprexa.

Your proposed REMS must contain a Medication Guide including the metabolic risks of Zyprexa tablets and Zyprexa Zydis and a timetable for submission of assessments of the REMS. The timetable for assessment of the REMS shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved. Your assessment of the REMS should include an evaluation of:

- a. Patients' understanding of the serious risks of Zyprexa
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

In accordance with section 505-1, you are required within 120 days of the date of this letter to amend your supplements with a REMS prior approval supplement containing your proposed REMS.

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

SUPPLEMENT FOR NDAs 20-592/21-086 (b) (4) PROPOSED REMS

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. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. 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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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/s/

Thomas Laughren
8/1/2008 05:46:30 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): OSE/DRISK Attn: Mary Dempsey		FROM: OND/ODE1/DPP HFD-130		
DATE 3/14/08	IND NO.	NDA NO. 20-592/s-40	TYPE OF DOCUMENT Risk MAPP	DATE OF DOCUMENT 8/28/2007
NAME OF DRUG Olanzapine		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Pediatric bipolar	DESIRED COMPLETION DATE 6/16/08
NAME OF FIRM: Eli Lilly				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Hi Mary, This is a RiskMapp the sponsor sent in back in August. They also replied to our approvable letter recently and the PDUFA date is August 1, 2008. Please review the attached RiskMapp and let me know if you have any comments. I can be reached at either renmeet.grewal@fda.hhs.gov or 301-796-1080. Thanks, Rimmy				
SIGNATURE OF REQUESTER Renmeet Grewal, Pharm.D. Regulatory Project Manager 301-796-1080 Renmeet.grewal@fda.hhs.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Thomas Laughren
3/14/2008 03:40:06 PM



NDA 20-592/S-039
NDA 20-592/S-040
NDA 20-592/S-041
NDA 21-520/S-012
NDA 21-086/S-021
NDA 18-936/S-077

Eli Lilly & Company
Attention: Christine A. Phillips, Ph.D., RAC
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Phillips:

We acknowledge receipt on February 1, 2008 of your February 1, 2008 resubmission to your supplemental new drug application S-012 for Symbyax (olanzapine / fluoxetine), NDA 21-520. We acknowledge receipt on February 4, 2008 of your February 4, 2008 resubmissions to your supplemental new drug applications S-039 for Zyprexa (olanzapine) Tablets, NDA 20-592, S-021 for Zyprexa (olanzapine) Zydys, NDA 20-186, and S-077 for Prozac (fluoxetine) Capsules, NDA 18-936. We also acknowledge receipt on February 5, 2008 of your February 5, 2008 resubmissions to your supplemental new drug applications S-040 and S-041 for NDA 20-592.

We consider these submissions to be complete, Class 2 responses to:

- our March 28, 2007 action letter for NDA 21-520 / S-012,
- our April 30, 2007 action letter for NDA 20-592 / S-040 and S-041, and
- our September 21, 2007 action letter for NDA 20-592 / S-039, NDA 21-086 / S-021, and NDA 18-936 / S-077.

Therefore, the user fee goal dates for these submissions will be:

- August 1, 2008 for NDA 21-520 S-012,
- August 4, 2008 for NDA 20-592 / S-039, NDA 21-086 / S-021, and NDA 18-936 / S-077, and
- August 5, 2008 for NDA 20-592 S-040 and S-041.

We do, however, request that you resubmit proposed labeling for all six supplements as soon as possible. We note that the proposed labeling currently provided in the resubmissions incorporates all Changes Being Effected language for the respective products that has been submitted to the Agency later than the March 28, 2007, April 30, 2007, or September 21, 2007 action letters, respectively, but that the labeling text does not highlight these CBE-related changes. We therefore request that you resubmit proposed labeling to these six supplemental applications that highlights all changes to labeling text that are not, at present, approved, for each product in question. Please annotate the

NDA 20-592/S-039
NDA 20-592/S-040
NDA 20-592/S-041
NDA 21-520/S-012
NDA 21-086/S-021
NDA 18-936/S-077

Page 2

marked up labeling to indicate which changes arise from submitted CBE language and which changes are responses to our March 28, 2007, April 30, 2007, or September 21, 2007 action letters.

If you have any questions, call either LCDR Renmeet Grewal, Pharm. D., Regulatory Project Manager, or Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260.

Sincerely,

{See Appended Electronic Signature Page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
2/26/2008 08:22:49 AM

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Friday, September 28, 2007 3:56 PM
To: 'Robin Pitts Wojcieszek'
Cc: Gregory T Brophy; 'Catherine Melfi'; Bates, Doris J
Subject: Dear Health Care Provider Letter

Dear Robin,

The division met regarding the Dear Health Care Provider letter you submitted September 25, 2007. As you are aware, we will of course have to review the supporting data before we can make a final determination about the acceptability of the proposed labeling changes. Nevertheless, we don't have any objections to what has been proposed, either for the letter or labeling. However, we do think the labeling would be improved by the addition of language regarding hyperglycemia and potential weight gain in the Information for Patients section of the labeling.

Thank you,
Rimmy

*Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838*

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/s/

Renmeet Grewal
9/28/2007 04:11:14 PM
CSO



NDA 20-592 / S-040
NDA 20-592 / S-041
NDA 21-520 / S-012

Eli Lilly & Company
Attention: Catherine A. Melfi, Ph.D.
Scientific Director, U.S. Regulatory Affairs
Attention: Robin Pitts Wojcieszek, R. Ph.
Senior Associate Director, U. S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi and Ms. Wojcieszek:

We acknowledge receipt on August 31, 2007 of your August 30, 2007 resubmissions to your supplemental new drug applications for Zyprexa (olanzapine) Tablets and Symbyax (olanzapine /fluoxetine combination) Capsules.

We do not consider these submissions to be complete responses to our March 28, 2007 and April 30, 2007 action letters. Therefore, we will not start the review clocks until we receive a complete response. The following deficiencies from our action letters still need to be addressed:

As we noted in our action letters, a primary concern with these applications is that we lack important safety information related to hyperglycemia, hyperlipidemia, and weight gain, in order to adequately update the labeling with all relevant risk information. As we stated in the letters, we need you to address these concerns, including the provision of pertinent data and analyses, before we will be able to take a final action on these applications. We referenced then, and again refer to, our letter dated January 12, 2007 regarding New York Times coverage of these issues.

We note that your resubmissions include only the requested information that relates to placebo controlled fasting/nonfasting adult and adolescent analyses. You have indicated that other information related to these issues remains outstanding and is slated for submission in September/October 2007 [Comparator-controlled fasting/nonfasting adult and adolescent analyses], December 2007 [long-term integrated database information for adult and adolescent use of olanzapine], and February 2008 [first episode/antipsychotic naive patient analyses, analyses for patients suffering from Alzheimer's and Parkinson's Disease, and single study analyses for the published longitudinal data studies HGJU and HGGF].

As was discussed in our meeting of May 24, 2007 related to NDA 21-520 S-012, a rolling timetable of submissions is acceptable, and we will consider after each such submission whether or not it can be considered to represent a complete response. However, upon receipt of the first portion of data, we

have determined that review of certain of the analyses targeted for later completion will in fact be necessary before adequate labeling pertaining to metabolic effects can be drafted. In particular, we will need to receive the data slated for submission in December, 2007, i.e., the long-term integrated database information for adult and adolescent use of olanzapine. It is not possible for us to adequately assess the safety of olanzapine with respect to the three metabolic issues noted above, until we have received this additional information requested in our March 28, 2007 and April 30, 2007 action letters. Although the first portion of data in the current submission does contain some long-term data, most of the metabolic data related to long-term exposure to olanzapine will be available in the long-term integrated database. Data pertaining to the metabolic effects of olanzapine over the longer term are necessary to fully and adequately characterize its metabolic effects. Therefore, your submissions will not be considered complete until we have received this outstanding information.

You must make separate submissions to NDA 21-520 / S-012 and NDA 20-592 / S-040 and S-041 when responding to this letter.

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 these supplemental applications for Zyprexa tablets are pediatric submissions in fulfillment of the requirement. Please refer to our April 30, 2007 action letter for further details.

If you have any questions, call Doris Bates, Regulatory Project Manager, at (301) 796-1040, or contact her via secure electronic mail at doris.bates@fda.hhs.gov, with respect to NDA 20-592 S-040 and S-041; for any questions relevant to NDA 21-520 S-012, contact LCDR Renmeet Grewal, Regulatory Project Manager, at (301) 796-1080, or contact her via secure electronic mail at renmeet.grewal@fda.hhs.gov.

Sincerely,

{See Appended Electronic Signature Page}

Thomas P. Laughren, M.D.
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
9/13/2007 04:06:18 PM

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 20592	BLA STN# NDA Supplement # 040 AND 041	If NDA, Efficacy Supplement Type SE5 [both supplements]
Proprietary Name: Zyprexa Established Name: (olanzapine) Dosage Form: Tablets		Applicant: Eli Lilly & Co.
RPM: Bates	Division: 130	Phone # 6-2260
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>	
❖ User Fee Goal Date ❖ Action Goal Date (if different)		April 30, 2007
❖ Actions		
<ul style="list-style-type: none"> Proposed action Approvable action for both supplements 		<input type="checkbox"/> AP <input type="checkbox"/> TA <input checked="" type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed		<input type="checkbox"/> To be requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p>NDAs, BLAs and Supplements:</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2</p> <p><input type="checkbox"/> Orphan drug designation</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>NDAs and NDA Supplements: <input type="checkbox"/> OTC drug</p> <p>Other:</p> <p>Other comments:</p>	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only) PRESS OFFICE DECISION.	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other PRESS OFFICE DECISION

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires: <input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner’s receipt of the applicant’s 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If “No,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If “Yes,” a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director)	see package
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM)	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	See AE letter
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	see package
❖ Patient Package Insert <i>NOT APPLICABLE</i>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide <i>NOT APPLICABLE</i>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels) <i>NOT APPLICABLE</i>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
❖ Labeling reviews and minutes of any labeling meetings	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA)	✓
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	NOT APPLICABLE
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	✓ Included for both supplements
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	✓ Verified, statement is acceptable for both supplements
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	<input type="checkbox"/> None see letter.
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	✓
❖ Internal memoranda, telecons, email, etc.	NOT APPLICABLE
❖ Minutes of Meetings <ul style="list-style-type: none"> • Pre-Approval Safety Conference • Pre-NDA/BLA meeting • EOP2 meeting • Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg <input type="checkbox"/> No mtg
❖ Advisory Committee Meeting <ul style="list-style-type: none"> • Date of Meeting • 48-hour alert or minutes, if available 	NOT APPLICABLE
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s)	✓
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> • <input type="checkbox"/> Categorical Exclusion (<i>all original applications and all efficacy supplements that could increase the patient population</i>) • <input type="checkbox"/> Review & FONSI • <input type="checkbox"/> Review & Environmental Impact Statement) 	✓
❖ NDAs: Microbiology reviews (sterility & apyrogenicity)	<input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection <ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) 	<input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review • Compliance Status Check (approvals only, both original and supplemental applications) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews	NOT APPLICABLE
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s)	✓
❖ Financial Disclosure reviews(s) or location if addressed in another review	✓
❖ Clinical consult reviews from other review disciplines/divisions/Centers	✓ None
❖ Microbiology (efficacy) reviews(s)	✓ Not needed
❖ Safety Update review(s)	not applicable
❖ Risk Management Plan review(s) (including those by OSE)	✓
❖ Controlled Substance Staff review(s) and recommendation for scheduling	✓ Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	✓
• Clinical Studies	✓
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s)	✓
❖ Clinical Pharmacology review(s)	✓

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/s/

Doris Bates

4/30/2007 10:34:35 AM

AE actions for two pediatric exclusivity supplements submitted concurrently
under one Written Request.

Bates, Doris J

From: Bates, Doris J
Sent: Monday, March 19, 2007 4:06 PM
To: 'Catherine Melfi'
Cc: Alfaro, Cara; Khin, Ni Aye; Bates, Doris J
Subject: NDA 20-592 S-040 and S-041: Clinical Review Questions
Importance: High

Dear Dr. Melfi:

I am forwarding the following questions from our clinical review team. As previously, I am including the clinical review team members as CC recipients on this message. Please 'reply to all' in your response if you send an initial reply by e-mail; the official submission will need to be amended as well, for recordkeeping purposes.

1. For the Acute Placebo Controlled Combined Database, please provide a subgroup analysis for age (< 15, >= 15) for the variable "weight in kg" similar to Table 2.7.4.70 in the summary-clin-safety document.
 2. Please provide a subgroup analysis for age (< 15 and >=15) and gender for the variable "PCS weight change (> 7%)" for the Acute Placebo Controlled Combined Database.
 3. It appears that the study report for HGIN includes all vital signs analyses for all subgroups (e.g. Table HGIN.14.47) while these analyses are only included in the study report for HGIU if the treatment by subgroups analysis was significant (e.g. HGIU.12.45). Please provide the subgroup analyses for HGIU similar to that provided in Table HGIN.14.47.
 4. In section 2.7.4.7.5 of the summary-clin-safe-app document, analyses are provided for suicide-related adverse events. In reviewing Table APP.2.7.4.7.5.9 (patients with possible suicidal behavior or ideation - combined database), there appear to be 3 cases that do not have narratives listed in this document or in the Table of Significant and Notable Patients document. Please provide case narratives for the following cases: HGMF-008-0805, LOAY-401-4012 and LOAY-407-4077.
 5. In the summary-clin-safe-app document, section 2.7.4.7.1.3.2.6 presents correlation coefficients between weight and a number of factors for the Overall Olanzapine Exposure Combined Database. Please provide these data for the Acute Placebo Controlled Database.
 6. In the summary-clin-safe-app document, section 2.7.4.7.1.3.3 compares data between the adolescent and adult populations. For these population comparisons, the Overall Olanzapine Exposure Combined Database is used. Is a comparison of these populations including only the acute, double-blind trial data available?
 7. In proposed labeling, some adverse events have been removed from the sections "other adverse events observed during the clinical trial evaluation of oral olanzapine" and "other adverse events observed during the clinical trial evaluation of intramuscular olanzapine for injection". In the former section, it appears that all of the frequently occurring AEs ("frequent") have been removed. In both sections, many adverse events that were included in the infrequent and rare categories have been removed. Please provide a justification for removal of these adverse events from proposed product labeling.
-

Please feel free to contact me if you have any questions about this message.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates

3/19/2007 04:11:13 PM

CSO

See email for time of transmission to firm

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, March 08, 2007 4:55 PM
To: 'Catherine Melfi'
Cc: Alfaro, Cara; Kong, Fanhui; Bates, Doris J
Subject: RE: NDA 20-592 S-040, S-041: Additional Questions
Importance: High

Dear Dr. Melfi:

We have additional questions from our clinical reviewer for these supplements, which I am forwarding below:

These questions pertain to the Acute Placebo-Controlled Combined Database:

1. It is unclear whether there was greater weight gain in patients with lower BMI at baseline (and visa versa). Please provide an analysis of weight gain based on the patient's baseline BMI to address this question.
2. Please provide the numbers of patients in both the placebo and olanzapine treatment groups who were obese (BMI > 30) at baseline and at end of study. Was there a statistical difference?
3. Please provide a subgroup analysis for laboratory data (similar to the summary in Table 2.7.4.33 in summary-clin-safety). Include all olanzapine patients who gained greater than 3.9 kg (mean weight gain from baseline) compared to all placebo patients.

As with prior questions, I am including the clinical and statistical reviewers as CC recipients; please feel free to reply via email prior to amending the supplements with a formal response.

Please feel free to contact me if you have any questions concerning this message,

Sincerely,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

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/s/

Doris Bates
3/8/2007 04:58:50 PM
CSO

Message copied and pasted to WORD and carriage returns inserted, because a software glitch has apparently eliminated automatic line breaks in the email text editor, resulting in text cutoff when the message is converted to .pdf format for DFS.

From: Bates, Doris J
Sent: Thursday, March 08, 2007 1:33 PM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Kong, Fanhui; Alfaro, Cara
Subject: NDA 20-592: S-040, S-041: Additional URGENT Question from statistical review team
Importance: High

Dear Dr. Melfi:

Regarding the two efficacy supplements referenced above, we have another urgent question with respect to the statistical review. Please again feel free to reply via email initially, then amend the supplements accordingly.

It is claimed in the Clinical Study Report, that of the 161 randomized patients, 159 were analyzed for the primary efficacy measure. Two of the patients randomized to receive olanzapine did not have a post baseline observation that could be used for the primary efficacy analysis.

In addition, the primary analysis, LOCF mean change from baseline to Endpoint of the YMRS total score, was conducted without data from patients in Site 021.

Appendix 16.1.9 gives a list of patients who were excluded from efficacy analyses.

However, the primary efficacy results in the Study Report were based on the whole set of 161 patients. The YMRS total score data set provided to the Agency contained all 161 patients, with none excluded due to lack of baseline efficacy measure or post baseline efficacy measure.

Please clarify which set[s] of data, and how many patients in the respective dataset[s], were included in the performance of which specific analyses. If you could provide the patient numbers and site numbers, per dataset, for those patients excluded from the respective datasets/analyses, this would be very helpful.

Please feel free to contact me if you have any questions. I have again included both clinical and statistical reviewers in the CC line, along with myself, to speed any reply sent via email.

Thank you, and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates

3/8/2007 01:53:10 PM

CSO

This is not an exact duplicate of the email
sent to Lilly. A failure of the email
text editor caused loss of text on direct
conversion to .pdf format. Carriage returns have been
inserted to prevent dropped text. See note, top
of first page.

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, February 21, 2007 3:06 PM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Kong, Fanhui; Alfaro, Cara; 'Robin Pitts Wojcieszek'
Subject: NDA 20-592 S-040 and S-041: URGENT Statistics Questions
Importance: High

Dear Dr. Melfi:

I have received the following urgent questions from our statistical review team. Please provide an initial response via return email, to facilitate our review, if possible; we will need amendments submitted to the supplements for the record.

I have included the clinical and statistical reviewers as CC recipients to minimize routing delays on your response, and I have copied Ms. Wojcieszek to facilitate routing for you at Lilly.

For Study HGIN: please provide

- (a) the IND numbers and the **serial numbers** and their **submission dates** for the study **protocol and its amendments A, B, C**, along with **those for the SAP**;
- (b) please indicate whether an interim analysis was performed, and, if so, please indicate when this was done and provide results;
- (c) please provide any available correspondence, etc. to demonstrate that the full SAP was submitted to the Division, and reviewed, prior to data unblinding. [If the SAP was modified in any way based on Division feedback, this should also be indicated]

For Study HGIU: please provide

- (a) the IND numbers and the **serial numbers** and their **submission dates** for the study **protocol and its amendments A**, along with **those for the SAP**;
- (b) any available correspondence, etc. to demonstrate that the full SAP was submitted to the Division, and reviewed, prior to data unblinding. [If the SAP was modified in any way based on Division feedback, this should also be indicated].

Please feel free to contact me if you have any questions about this message.

With best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
2/21/2007 03:20:09 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Monday, January 29, 2007 11:07 AM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Alfaro, Cara
Subject: N 20-592 S-040, S-014: Questions from Clinical Reviewer

Good morning Dr. Melfi:

Per our teleconference this morning, I am sending you the questions received from our clinical reviewer below: if you have any questions please feel free to contact me, and as always, we welcome 'e-desk' copies of any reply if it is convenient for you to do so. I have included Dr. Alfaro on the CC list here to facilitate her receipt of any reply via email.

Please provide patient baseline severity of illness and statistical analysis for US vs. Russia sites (similar to HGIN.11.2 but comparing US vs. Russia). Include the following variables: age of onset of illness, # of previous schizophrenia episodes, total hospitalization, length of current episode, days since last hospitalization, psychiatric hospitalization, CGI-S, BPRS-C subscales, BPRS-C total score, PANSS subscales, and PANSS total score

Do study reports for HGIN and HGIU include information regarding the adverse events associated with patient drop-outs? Please indicate where this information may be found.

In table HGIN.11.2, it is noted that the minimum value for age for Age of Illness Onset was 5 years old for each treatment group. Please provide the study numbers for all patients with an age of illness onset < 10 years old and CRFs for these patients.

In table HGIN.11.2, it is noted that the minimum value for the Length of Current Episode is "0" - please clarify.

For Psychiatric Hospitalization in table HGIN.11.2, please clarify whether this is past or current hospitalization.

Please provide # of prior psychiatric hospitalizations for both treatment groups with statistical analysis for this variable.

Thank you, and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

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/s/

Doris Bates
1/29/2007 11:19:40 AM
CSO



NDA 20-592 / S-040
NDA 20-592 / S-041

**FILING COMMUNICATION
ISSUES IDENTIFIED**

Eli Lilly & Co., Inc.
Attention: Catherine Melfi, Ph.D.
Scientific Director
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Melfi:

Please refer to your October 30, 2006 supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg.

We also refer to your submissions to both sNDAs dated and received November 15, 2006.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, as you were informed on December 15, 2006 in a voice mail from Dr. Doris Bates, Regulatory Project Manager for this Division, these applications have been filed as of that date, under section 505(b) of the Act, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following clinical review issues, and we request that you amend your supplements to respond to these issues. We anticipate that any response submitted in a timely manner will be reviewed during this review cycle, but review decisions will be made on a case-by-case basis at the time we receive the submission.

1. In protocols HGIU and HGIN, height was obtained using "a measuring device supplied by the sponsor" that required calibration. Please provide a description of this measuring device.
2. The primary efficacy analysis in study HGIN excluded data from site 021 due to GCP issues at that site (it is noted that results are similar with and without this site). Please provide details regarding the GCP issues at this site or specify where this information may be found in the study report.
3. In protocol HGIN, it is noted that "The scoring of the anchored version of the BPRS-C is determined by interviews with both the patient and the parent/legal guardian at all visits. The reference score (as recorded in the CRFs) should be the higher of the two scores". Viewing the

CRF, it does not appear that there is an area where the recorder could state the source of the ratings. Are both ratings, patient and parent/legal guardian, available for subjects in this study? If so, please provide these ratings and indicate the primary source for the ratings.

We are providing these comments at this time in order to give you prompt notice of these issues. Our filing review is only a preliminary evaluation of the application and is therefore not indicative of all deficiencies that may be identified during our ongoing review. Issues may be added, deleted, expanded upon or modified as we continue our substantive review of your applications.

If you have any questions, please call Dr. Bates, at (301) 796-2260.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
1/4/2007 09:58:13 PM

Bates, Doris J

From: Bates, Doris J
Sent: Thursday, December 21, 2006 5:53 PM
To: 'Catherine Melfi'
Cc: 'Robin Pitts Wojcieszek'; Bates, Doris J; 'Gregory T Brophy'
Subject: RE: NDA 20-592/S-040 and S-041: No AC Meeting Planned.

Good afternoon Dr. Melfi:

This e-mail message formally confirms that the Division does not plan to hold an Advisory Committee Meeting for the two supplemental NDAs referenced above.

For rapid dissemination, I have also copied Ms. Wojcieszek and Dr. Brophy.

If you have any questions about this message, please feel free to follow up with me.

Sincerely,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

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/s/

Doris Bates
12/21/2006 05:57:20 PM
CSO

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, December 06, 2006 4:38 PM
To: 'Catherine Melfi'
Subject: RE: URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on FDA Forms 3542a

Please send two - one for each - I'd rather not take chances at this stage. Sorry I didn't see this sooner, Cathy. Thanks for the quick turnaround.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Wednesday, December 06, 2006 3:38 PM
To: Bates, Doris J
Subject: Re: URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on FDA Forms 3542a

Doris: I have contacted our patent attorney to get me the 3542a. I'm not sure how it was left out of the submission, but you're right -- it was left out. Do you need me to send 2 copies (one for each indication), or should I send just one? It would be the exact same document, and in the original submission we only submitted one copy of the information that pertained to both applications. Thanks, and I hope to get something to you very shortly!

Cathy

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile 317-777-1309
email: melfi@lilly.com

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"Bates, Doris J" <doris.bates@fda.hhs.gov>

12/06/2006 02:42 PM

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>
cc
Subject URGENT: NDA 20-592: S-040 and S-041: Requesting Patent Information on F
Forms 3542a

Hi Cathy

I am going through the submission prior to our filing meeting and realized that I could not locate the patent information forms, FDA 3542a. I found a written statement regarding the patent, but we need these actual forms, signed and submitted for each indication. Can you get these to me by the start of next week? You can .pdf them to me when they're sent in to the official file.

I've attached the template in WORD format for your convenience... thanks!

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Friday, December 01, 2006 2:30 PM
To: Bates, Doris J
Cc: Alfaro, Cara; Bates, Doris J; Kong, Fanhui; Malek, Khairy W
Subject: Re: URGENT: NDA 20-592: S-040 and S-041: Requesting a Comprehensive List of Study Sites / Investigators / Patients Randomized / Patients Completing at each site

Hi Doris. I have attached the information you requested. While all of the information is in the supplements, it is not all there in a single document. The attached files include information on sites, investigators, addresses, and number of patients randomized and completed for studies HGIU (S-040, bipolar) and HGIN (S-041, schizophrenia). Please note that we have 2 columns for completed patients -- one column shows the number of patients who completed the acute phase of the study and the other column shows the number of patients who completed the open-label phase. Please let me know if you have any questions or require additional information.

Cathy Melfi

Catherine A. Melfi, Ph.D
 U.S. Regulatory Affairs
 Phone 317-277-2905 Fax 317-276-1652
 Mobile 317-777-1309
 email: melfi@lilly.com

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"Bates, Doris J"
 <doris.bates@fda.hhs.gov>

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

cc "Bates, Doris J" <doris.bates@fda.hhs.gov>, "Malek, Khairy W" <khairy.malek@fda.hhs.gov>, "A
 Cara" <cara.alfaro@fda.hhs.gov>, "Kong, Fanhui" <fanhui.kong@fda.hhs.gov>

Subject URGENT: NDA 20-592: S-040 and S-041: Requesting a Comprehensive List of Study Sites /

11/29/2006 03:10 PM

Hi Cathy

As we conduct our filing reviews for these supplements, our reviewers have had difficulty locating a single comprehensive list of sites with investigators, addresses, and patients randomized / completed.

Could you send me this information for both of the pediatric supplements, via reply email, using the Reply to All function so that my colleagues on the CC list receive it as well? This will save us time since our need is urgent.

If the information is already in these submissions, if you could indicate where we can find it, that would also be very helpful.

Again, this is urgent - we need the information, if at all possible, by the end of the day this Friday.

Thanks in advance,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

Bates, Doris J

From: Catherine Melfi [MELFI_CATHERINE@LILLY.COM]
Sent: Tuesday, December 19, 2006 8:07 AM
To: Jackson, Andre J
Cc: Bates, Doris J
Subject: Assays for NDA 20-592/S-040 and S-041
Attachments: Note to reviewer for methods final dec 18th.doc; F1D-MC-HGCS.pdf; F1D-MC-HGGC.pdf; F1D-MC-HGMF.pdf; emfinfo.txt

Dr. Jackson:

I have obtained supporting documentation regarding the bioanalytical methods for the study reports included in NDA 20-592/S-040 and S-041. The attached Note to the Reviewers provides details on the supporting documentation for each of the four studies. Because we are not able to send zip files over e-mail, I am sending you the information in 3 separate e-mail messages. I will also be submitting the information as an amendment to NDA 20-592/S-040 and S-041. Information to be included in this, plus 2 subsequent e-mail messages is described below.

Included in this e-mail message is:

- The Note to the Reviewers
- 3 bioanalytical methods study reports, one for each of the studies:
 - 1.F1D-MC-HGGC
 - 2.F1D-MC-HGCS
 - 3.F1D-MC-HGMF

In a subsequent e-mail message, I will send the following 2 documents that provide detailed bioanalytical methods information:

- 820-0457: Automated Extraction of Olanzapine (LY170053) in Heparinized Human Plasma. [This report is relevant to all studies]
- 820-0192: The Measurement of Olanzapine in Heparinized Human Plasma [This report is relevant to study HGMF]

In the third e-mail message, I will send the four manuscripts (described in the Note to the Reviewers) that support the bioanalytical methods for study LOAY.

Please let me know if you have further questions or need additional information. I will be out of the office until January 3, but I will be checking e-mail and voicemail while I'm out in case there are any urgent matters.

Cathy Melfi

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile 317-777-1309
email: melfi@lilly.com

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1/18/2007

"Jackson, Andre J" <andre.jackson@fda.hhs.gov>

To melfi@lilly.com

cc

Subject Assays

12/14/2006 09:57 AM

The NDA 20-592 has four studies:

- 1.F1D-MC-HGGC
- 2.F1D-MC-HGCS
- 3.F1D-MC-HGMF
- 4.F1D-SB-LOAY

I have taken a quick look and I did not see any detailed analytical information.

Please look at these submissions and let me know if the analytical data is present and if so where at.

If the data is not at the FDA or not in the project # 1000-0457 report which I called you about, please see that it gets added to the submission.

Please be certain that study dates and assay dates are given so that total storage time can be compared with reported stability data.

Thanks

Andre Jackson
CDER/DCP1
301-796-1545

Please note new E-mail Address:
Andre.Jackson@fda.hhs.gov

1/18/2007

Bates, Doris J

From: Catherine Melfi [MELFI_CATHERINE@LILLY.COM]
Sent: Monday, December 18, 2006 10:50 AM
To: Alfaro, Cara
Cc: Bates, Doris J
Subject: Re: HGIU and HGIN Protocol Submissions
Attachments: emfinfo.txt

Cara:

Thanks for your question. This one is easy. Protocols HGIN and HGIU were submitted to IND 28,705 in a submission dated October 31, 2002; serial number 876.

Our statisticians are validating the programming used to respond to your recent request about exposure numbers. As soon as I get confirmation of the validation, I will send you the response by e-mail. I am not anticipating any problems getting this to you before 1:00 today.

Doris: Should I also submit our response as an amendment to the applications? Our submissions group will have to burn the CDs, etc, so we'd probably submit it later this week. We're also working on sending some site information to DSI as well as working on Dr Jackson's request for the bioanalytical information.

Cathy

Catherine A. Melfi, Ph.D
 U.S. Regulatory Affairs
 Phone 317-277-2905 Fax 317-276-1652
 Mobile 317-777-1309
 email: melfi@lilly.com

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"Alfaro, Cara" <cara.alfaro@fda.hhs.gov>

To Catherine Melfi <MELFI_CATHERINE@LILLY.COM>

12/18/2006 10:35 AM

CC "Bates, Doris J" <doris.bates@fda.hhs.gov>

Subject HGIU and HGIN Protocol Submissions

Cathy,

There is no hurry on this request. Can you tell me to what IND numbers these protocols were submitted, the dates of the submissions and the serial no. of the submissions? Thank you.
 (Yes, I do realize that the protocols are included as addenda to the study reports that I have).

Do you have any questions about our earlier request re: exposure data? Our apologies about needing the information so quickly - as Doris said, we are feeling time pressure as well.

1/18/2007

Thank you.

Cara

Cara Alfaro, Pharm.D., BCPP

Clinical Reviewer

Food and Drug Administration

CDER/Division of Psychiatry Products

10903 New Hampshire Avenue, Building 22, Room 4219

Silver Spring, MD 20993-0002

cara.alfaro@fda.hhs.gov

Bates, Doris J

From: Bates, Doris J
Sent: Monday, February 12, 2007 4:54 PM
To: 'Catherine Melfi'
Cc: 'Robin Pitts Wojcieszek'; Bates, Doris J
Subject: RE: Follow-up; NDA 20-592; S-040 and S-041
Attachments: PLR POSSIBLE CONTENT FORMAT DEFICIENCIES.pdf

Hi Dr. Melfi:

Thanks for your very timely inquiry. I will not be here tomorrow; am going to be home riding out the predicted ice storm and, unfortunately, not available online. I plan to be working, but it will involve reading and scheduled teleconferences only. Under the circumstances I wanted to contact you before leaving today:

(b) (4)

2. Regarding your question on coding, PMs have not been trained to address coding issues; we don't code SLR and we don't code PLR. I would therefore recommend having your coding experts take any coding related questions directly to the Labeling Review Team committee. I can get you contact information later this week, if you aren't able to locate them on the CDER web page [you would search on SEALD, they are the Study Endpoint And Labeling Development group, I believe, and I think they have an externally accessible site. I am also attaching a link to the labeling guidance information below, from which it may be possible to work back to their main page.] I do understand the basic issue, but I don't have the detailed knowledge to provide any solutions -- nor does anyone else in the Division, for which I apologize.

3. Regarding general labeling issues, we now have in hand a list of the most commonly identified labeling deficiencies, which I am attaching to this email. The standard language meant to accompany our transmission of this list to applicants is provided below.

Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to verify that none of these deficiencies are in your PLR labeling submitted on October 30, 2006. If you find, at the conclusion of your PLR review, that there are deficiencies in your submitted PLR labeling, please amend your application to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address:

<http://www.fda.gov/cder/regulatory/physLabel/default.htm>

3/5/2007

We request that you complete this review and respond to this e-mail within 30 days of receipt of this message.

4. I plan to follow up with you later this week, weather permitting. We will be starting our substantive review of labeling earlier than usual in the review cycle, because of the format change; this does not imply any conclusions regarding efficacy, but is due solely to the format change.

Best regards and I hope you all avoid the ice storm in IN; on a side note, you may want to share the PLR deficiencies list with Robin and the SYMBYAX TRD team, since it is also pertinent there.

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

From: Catherine Melfi [mailto:MELFI_CATHERINE@LILLY.COM]
Sent: Monday, February 12, 2007 4:15 PM
To: Robin Pitts Wojcieszek; Bates, Doris J
Subject: Follow-up; NDA 20-592; S-040 and S-041

Hi Doris:

I just wanted to follow up on our teleconference on January 29 where we discussed the review of the pending supplements for the pediatric indications for Zyprexa. On the teleconference, you had mentioned that you use a template to go over the submitted labeling in PLR format, and I was hoping that it might be possible for you to send us a copy of that template so that we can be sure our PLR submissions follow appropriate formatting for greater ease of review.

Also, my team is working through the coding for the Highlights section of the Zyprexa label in PLR format. I am wondering if you can provide any insight as to how and when coding of the Highlights section needs to be finalized. We're finding that in some cases, there is no appropriate coding available in the current dictionaries, and we also need guidance on how class labeling is to be coded. Do you know if Divisions are requiring labels to have all of the Highlights coding mapped prior to approval, or is the final coding something that can be worked out after approval?

As we work through this together, let me know what I can do to make things easier for you, and any insights you can provide regarding status of the review and details regarding working through PLR would be greatly appreciated.

Thanks!

Cathy

PS (Big winter storm warning for Indianapolis through Tuesday, so there may not be many people in the office tomorrow. I will have access to e-mail whether I'm in the office or at home, so should be available regardless.)

Catherine A. Melfi, Ph.D
U.S. Regulatory Affairs
Phone 317-277-2905 Fax 317-276-1652
Mobile 317-777-1309

3/5/2007

email: melfi@lilly.com

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Bates, Doris J

From: Bates, Doris J
Sent: Monday, March 05, 2007 11:36 AM
To: 'Catherine Melfi'
Cc: Bates, Doris J; Alfaro, Cara
Subject: NDA 20-592 S-040 / S-041: Additional Clinical Questions
Importance: High

Good morning Dr. Melfi:

I have the following questions from our clinical reviewer regarding the above referenced pediatric supplements.

1. In the brief summary for study HGCS, it is noted that 2 patients experienced the adverse event "intentional injury". Please provide brief summaries for these two events.

2. For study HGGC, were there any serious adverse events? The synopsis states that no patients experienced serious adverse events associated with cardiac abnormalities or weight gain - but there is no mention of other SAEs that may have occurred in this trial.

3. For the adult studies HGDH and HGGF that included adolescent patients, please submit narratives for the serious adverse events (per Table 2.7.4.4 in the summary-clin-safety document).

For the adult studies HGGF and HGKL, please submit narratives for the discontinuations due to adverse event cases.

4. For patient HGIU-028-2804, the narrative indicates that she experienced bilateral galactorrhea while hospitalized for a recurrence of bipolar symptoms. Please provide the prolactin concentrations that were obtained by the hospital (pending at time patient was discharged).

5. Patient HGMF-003-0304 had the SAE "exacerbation of bipolar illness with positive suicidal ideation". However, it appears that this was coded to the preferred term "bipolar disorder". Why weren't both verbatim terms coded to preferred terms - i.e. bipolar disorder and suicidal ideation?

6. For the discontinuations due to the adverse event "weight gain" in the acute and combined databases, please provide weight data for the post-study follow-up visits. Some of the narratives have this information, but the majority indicate that the adverse event had resolved without providing weight data.

I am also including a comment from our reviewer, verbatim as I received it: please feel free to share this comment with all to whom it might apply...

I also wanted to thank the Sponsor for the narratives provided in this submission. These are among the best narratives I have seen from Sponsors and I truly appreciate the effort that was obviously put into the organization of them.

Please feel free to contact us if you have any questions regarding this message. If you wish to reply by email, please reply to all, as I have included the clinical reviewer as a CC recipient on this message to facilitate that process. Please amend the supplemental NDAs with any information provided by email, as we need the official documents to reflect all additions to the file.

Thank you, and best regards,

*Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center*

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/s/

Doris Bates

3/5/2007 12:22:47 PM

CSO

Questions sent 06DEC, 18DEC, 19DEC, 12FEB, 05MAR 2007. Clin,
biopharm, and administrative.

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/s/

Doris Bates
12/6/2006 05:56:06 PM
Please link consult to both SE5 040 and SE5
041 in DFS - thank you!

Thomas Laughren
12/6/2006 05:58:40 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR SEALD CONSULTATION		
TO (Division/Office): Study Endpoints and Label Development Team (SEALD) CDER/OND-IO White Oak Bldg 22, Mail Drop 6411		FROM (Division/Office): Doris J. Bates, Ph.D. - Regulatory Project Manager, HFD-130 WO 22 Room 4102		
DATE of REQUEST 15 NOV 2006	NDA/BLA/IND NO. 20-592 SE5-040 20-592 SE5-041	SERIAL NO/SUPPL. NO SE5-040, SE5-041	TYPE OF DOCUMENT PEDIATRIC EXCLUSIVITY / EFFICACY SUPPLEMENT	DATE OF DOCUMENT 30 OCT 2006 for both -- Waiver request submitted 15NOV2006
NAME OF DRUG Olanzapine	MEETING DATES FOR SUBMISSION 15 December 2006 - filing meeting. Waiver Request Decision Due: 12 January 2007 [60 days after Nov. 15]	CLASSIFICATION OF DRUG adolescent bipolar S040 adolescent schizophrenia S041	REQUESTED COMPLETION DATE January 10, 2007: January 12 is also our 74-day letter date, and we would like to include the SEALD decision in the 74-day letter.	
NAME OF SPONSOR or INVESTIGATOR (for investigator Initiated INDs): LILLY				
DRUG DEVELOPMENT PHASE & MILESTONE				
<input type="checkbox"/> pre-IND/pre-BBIND <input type="checkbox"/> PHASE II <input type="checkbox"/> PHASE III <input type="checkbox"/> PRE-NDA/BLA MEETING		<input checked="" type="checkbox"/> NDA/BLA/sNDA/SBLA REVIEW <input type="checkbox"/> NDA/BLA SAFETY/EFFICACY UPDATE <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> NDA/BLA/sNDA/SBLA RESUBMISSION REVIEW <input type="checkbox"/> ADVISORY COMMITTEE MEETINGS <input type="checkbox"/> LABELING (INITIAL OR REVISION) <input type="checkbox"/> ADVERTISING REVIEW		<input type="checkbox"/> OTHER (Specify)
STUDY ENDPOINT OR LABELING To BE REVIEWED				
STUDY ENDPOINT REVIEW			LABELING REVIEW	
<input type="checkbox"/> TYPE A MEETING PACKAGE <input type="checkbox"/> CLINICAL HOLD/DISPUTE RESOLUTION <input type="checkbox"/> SPA RESPONSE <input type="checkbox"/> TYPE B MEETING PACKAGE <input type="checkbox"/> PRE-IND MEETING <input type="checkbox"/> END OF PHASE II/Pre-PHASE III <input type="checkbox"/> PRE-NDA/BLA <input type="checkbox"/> TYPE C MEETING PACKAGE		<input type="checkbox"/> SPECIAL PROTOCOL ASSESSMENT REVIEW <input type="checkbox"/> STANDARD PROTOCOL REVIEW <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> STATISTICAL ANALYSIS PLAN REVIEW <input type="checkbox"/> ENDPOINT DEVELOPMENT/VALIDATION DOSSIER <input type="checkbox"/> NDA / BLA REVIEW <input type="checkbox"/> AC MEETING		<input type="checkbox"/> PROPOSED LABELING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input checked="" type="checkbox"/> OTHER (SPECIFY): APPLICANT HAS REQUESTED A PLR WAIVER FOR A HIGHLIGHTS SECTION LONGER THAN PLR SPECIFIED LENGTH.
CONSULT REVIEW REQUESTED				
<p>Please see attached copy of proposed labeling in PLR format, and waiver request. Applicant is requesting a waiver of the length limitation on the Highlights section.</p> <p>Note that, because of the submission date for the waiver request , the 60-day waiver request decision date falls on the issue date for our 74-day filing letters for these supplements. We would like to include the SEALD decision in our 74-day letter if possible, and are therefore requesting feedback by January 10 to allow us to issue the letter with the decision included, by January 12, 2007.</p> <p>Please link any consult review or feedback to both SE5 040 (PM) and SE5 041 (PM) in DFS. There is currently only one EDR link for both submissions, as below, but both supplement numbers exist in COMIS and DFS: \\CDSESUB1\N20592\S_040\2006-10-30</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> INTEROFFICE MAIL <input type="checkbox"/> E-MAIL <input type="checkbox"/> HAND -CARRIED <input type="checkbox"/>		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Doris Bates

11/15/2006 04:49:05 PM

Please contact Dr. Bates at doris.bates@fda.hhs.gov or at 301-796-1040
if there are questions or additional information is
needed regarding this consult.

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-710, Dr. Yang, Dr. Kong

FROM: HFD-130, Dr. Bates

DATE 11-8-06

IND NO.
28705

NDA NO.
20-592 SE5-040
20-592 SE5-041

TYPE OF DOCUMENT
Pediatric Exclusivity
Supplements [TWO]

DATE OF DOCUMENT
30OCT2006

NAME OF DRUG
Olanzapine

PRIORITY CONSIDERATION
Pediatric Exclusivity
PRIORITY 6 month clock

CLASSIFICATION OF DRUG
S-040 pediatric bipolar disorder
S-041 pediatric schizophrenia

DESIRED COMPLETION DATE:
filing meeting Dec. 15, 2006
PDUFA goal date April 30, 2007

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY

- PRE--NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT

- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Information for both indications is currently available in the EDR only under S-040. Link: [\CDSESUB1\N20592\S_040\2006-10-30](#)

Submission is electronic only, no hard copy is provided.

Please link reviews in DFS to SE5-040 or SE5-041: Both are available in COMIS. If one review is written to address both supplements please link to both supplements in DFS for ease of retrieval.

Please include Dr. Bates and Mr. Berman in the CC lists for the reviews, Dr. Bates is not the PM listed in COMIS for this NDA.

SIGNATURE OF REQUESTER see DFS signature page

METHOD OF DELIVERY (Check one)

EMAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doris Bates

11/9/2006 05:56:35 PM

Please link review to both uncoded and PM coded
submissions for SE5 040 and SE5 041 in
DFS.

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-860, Dr. Baweja, Dr. Jackson

FROM: HFD-130, Dr. Bates

DATE 11-8-06

IND NO.
28705

NDA NO.
20-592 SE5-040
20-592 SE5-041

TYPE OF DOCUMENT
Pediatric Exclusivity
Supplements [TWO]

DATE OF DOCUMENT
30OCT2006

NAME OF DRUG
Olanzapine

PRIORITY CONSIDERATION
Pediatric Exclusivity
PRIORITY 6 month clock

CLASSIFICATION OF DRUG
S-040 pediatric bipolar disorder
S-041 pediatric schizophrenia

DESIRED COMPLETION DATE:
filing meeting Dec. 15, 2006
PDUFA goal date April 30, 2007

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):.

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Information for both indications is currently available in the EDR only under S-040. Link: [\CDSESUB1N20592\S_040\2006-10-30](#)

Submission is electronic only, no hard copy is provided.

Please link reviews in DFS to SE5-040 or SE5-041: Both are available in COMIS. If one review is written to address both supplements please link to both supplements in DFS for ease of retrieval.

Please note these submissions will be discussed at the January 10, 2007 Pediatric Exclusivity Board. A standard format summary of the pharmacokinetic and pharmacodynamic studies/analyses will be needed for this meeting in order for the PEB to determine if the terms of the Written Request were met. Dr. Bates and /or Dr. Alfaro will work with Dr. Jackson on this summary.

Please include Dr. Bates and Mr. Berman in the CC lists for the reviews, Dr. Bates is not the PM listed in COMIS for this NDA.

SIGNATURE OF REQUESTER see DFS signature page

METHOD OF DELIVERY (Check one)

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/s/

Doris Bates

11/9/2006 05:48:54 PM

Corrected drug name on consult sheet. Please send reviews
to Mr. Berman and Dr. Bates in DFS.

Please link to PM and uncoded documents for
both S040 and S041.

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-860, Dr. Baweja, Dr. Jackson

FROM: HFD-130, Dr. Bates

DATE 11-8-06

IND NO.
28705

NDA NO.
20-592 SE5-040
20-592 SE5-041

TYPE OF DOCUMENT
Pediatric Exclusivity
Supplements [TWO]

DATE OF DOCUMENT
30OCT2006

NAME OF DRUG
Risperidone

PRIORITY CONSIDERATION
Pediatric Exclusivity
PRIORITY 6 month clock

CLASSIFICATION OF DRUG
S-040 pediatric bipolar disorder
S-041 pediatric schizophrenia

DESIRED COMPLETION DATE:
filing meeting Dec. 15, 2006
PDUFA goal date April 30, 2007

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):.

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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SIGNATURE OF REQUESTER see DFS signature page

METHOD OF DELIVERY (Check one)

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/s/

Doris Bates

11/9/2006 05:36:53 PM

Please link review to both the uncoded and the
PM coded submissions in DFS.

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-710, Dr. Yang, Dr. Kong

FROM: HFD-120, Dr. Bates

DATE 11-8-06

IND NO.
28705

NDA NO.
20-592 SE5-040
20-592 SE5-041

TYPE OF DOCUMENT
Pediatric Exclusivity
Supplements [TWO]

DATE OF DOCUMENT
30OCT2006

NAME OF DRUG
Risperidone

PRIORITY CONSIDERATION
Pediatric Exclusivity
PRIORITY 6 month clock

CLASSIFICATION OF DRUG
S-040 pediatric bipolar disorder
S-041 pediatric schizophrenia

DESIRED COMPLETION DATE:
filing meeting Dec. 15, 2006
PDUFA goal date April 30, 2007

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
- END OF PHASE II MEETING
- CONTROLLED STUDIES
- PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):.

- CHEMISTRY REVIEW
- PHARMACOLOGY
- BIOPHARMACEUTICS
- OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Information for both indications is currently available in the EDR only under S-040. Link: [\ICDSESUB1\N20592\S_040\2006-10-30](#)

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Please include Dr. Bates and Mr. Berman in the CC lists for the reviews, Dr. Bates is not the PM listed in COMIS for this NDA.

SIGNATURE OF REQUESTER see DFS signature page

METHOD OF DELIVERY (Check one)

EMAIL

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/s/

Doris Bates

11/9/2006 05:31:59 PM

Please link review to both the uncoded and PM
coded submissions in DFS.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-592

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

Dear Dr. Brophy:

Please refer to your correspondence dated May 21, 2002, requesting changes to FDA's November 30, 2001, Written Request for pediatric studies for Zyprexa (olanzapine).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 30, 2001, and amended on April 9, 2002, remain the same.

- **Under ADOLESCENT SCHIZOPHRENIA; General Advice for Developing a Drug for Adolescent-Onset Schizophrenia; Specific Study Requirements for Development Program in Adolescent Schizophrenia; Study Design; Pediatric Efficacy and Safety Study**

We have amended the clinical design for either inpatient or outpatient status as follows:

"For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 6 to 8 weeks."

We note your plans to include patients that meet the diagnostic criteria for schizophrenia, schizophreniform disorder and schizoaffective disorder. Our evaluation will focus on the schizophrenia patients.

- **Under ADOLESCENT BIPOLAR DISORDER; General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder; Specific Study Requirements for Development Program in Adolescent Mania in Association with Bipolar Disorder; Study Design; Pediatric Efficacy and Safety Study**

We have amended the clinical design for either inpatient or outpatient status as follows:

"For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient or outpatient trial, with a recommended duration of at least 3 weeks."

JUL 05 2002

- **Under Format of Reports to be Submitted**

We have amended the "Format of reports to be submitted" section of your Written Request, which states the specific information on racial and ethnic minorities to be included in the final study report in accordance with Section 18 of the BPCA. Please note that we are changing the word "must" to "should" twice.

"In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino."

All other terms stated in our original Written Request or any subsequent amendments remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2001, as amended by our letter of April 9, 2002, and by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

COPY

NDA 20-592

Page 3

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

COPY

JUL 05 2005

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/s/

Robert Temple
6/29/05 02:20:26 PM

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JUL 05 2005



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Lilly Research Laboratories
Attn: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research, as well as the amendment issued in July 2002, from the Office of Counter-Terrorism and Pediatric Drug Development.

BPCA § 18: Minority Children and Pediatric Exclusivity Program

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

Format of reports to be submitted:

In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request issued or re-issued under BPCA and filed by FDA, regardless of the following circumstances:

- (1) the type of response to the Written Request (complete or partial);
- (2) the status of the supplement (withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e. approval, approvable, not approvable); or
- (4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at [<http://www.fda.gov/cder/pediatric/Summaryreview.htm>] and publish in the Federal Register a notification of availability.

MAY 18 2004

G. Brophy

Page 2

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug
Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
5/7/04 02:05:24 PM

Food and Drug Administration
Rockville, MD 20857CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to the Written Request, originally issued on November 30, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using olanzapine. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

*{See appended electronic signature page}*M. Dianne Murphy, M.D.
Director
Office of Counterterrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

RECEIVED JUL 17 2002

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/s/

Dianne Murphy
7/3/02 12:55:24 PM

RECEIVED JUL 17 2002



NDA 20-592

Eli Lilly and Company
Attention: H. John Roth, Ph.D.
Sr. Reg. Res. Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Roth:

Please refer to your correspondence dated January 28, 2002, requesting changes to FDA's November 30, 2002, Written Request for pediatric studies for Zyprexa (olanzapine).

We reviewed your proposed changes and are amending the following section of the Written Request:

- **Under GENERAL REQUIREMENTS AND COMMENTS; Timeframe for Submitting Reports of the Study(ies)**

We have amended the timeframe for submitting the reports of the studies from 3 years to 5 years (i.e., on or before November 30, 2006) as follows:

"Reports of the above studies must be submitted to the Agency within 5 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request."

Your requests to 1) omit the requirement to conduct a relapse prevention trial in adolescent schizophrenia, 2) revise the adolescent bipolar mania study to allow for a flexible dose design, and 3) allow the use of behavioral and/or dietary interventions for patients who gain weight during the trials will be dealt with in a separate letter. All other terms stated in our Written Request remain the same.

Reports of the studies that meet the terms of the Written Request dated November 30, 2002, as amended by this letter must be submitted to the Agency on or before November 30, 2006, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

RECEIVED APR 12 2006

ZY 8264 692

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ZY 8264 693

RECEIVED APR 12 2002

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/s/

Robert Temple
4/9/02 06:42:02 PM

RECEIVED APR 12 2002

ZY 8264 694



NDA 20-592

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

Dear Dr. Brophy:

Reference is made to your Proposed Pediatric Study Request submitted on June 11, 1999, to your New Drug Application for Zyprexa (olanzapine) tablets (NDA 20-592).

We have completed our review of your submission and conclude that your proposed pediatric study request is incomplete.

To obtain needed pediatric information on olanzapine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from trials in pediatric patients with (1) schizophrenia, and with (2) acute mania, as part of bipolar I disorder, as described below.

ADOLESCENT SCHIZOPHRENIA

General Advice for Developing a Drug for Adolescent-Onset Schizophrenia

Schizophrenia is a chronic and debilitating illness that has an estimated lifetime adult prevalence of 0.5 to 1%. According to the DSM IV, the diagnostic criteria for schizophrenia are the same for the pediatric and adult populations, but the symptomatology and prevalence of schizophrenia in these two populations have been recognized to be somewhat different. Within the pediatric age group, a diagnosis of schizophrenia is most commonly made in adolescents, and the symptoms in this age group are generally similar to those in adults (APA Practice Parameters, 1997). Schizophrenia has also been described in children, but it is thought to be uncommon (AACAP Practice Parameters, 2001). Although there are not adequate epidemiological data, one author suggests that 0.1 to 1 % of schizophrenic psychoses will present prior to age 10 (Remschmidt, 1996). In addition, the symptoms in childhood schizophrenia differ from those typically seen in adult schizophrenia and the diagnosis is more difficult to establish in this younger population (Volkmar, 1996).

Given the finding that childhood onset schizophrenia may present with symptoms quite different from those of adult onset schizophrenia, it would be important to systematically study the efficacy of treatment within this pediatric population. The very low incidence of schizophrenia diagnosed prior to the age 13, however, makes it unlikely that it would be possible to conduct a sufficiently large study of this age group within a reasonable time. For this reason, and because there is still controversy about the validity of this diagnosis in children, this written request will be limited to the study of schizophrenia in adolescents aged 13 to 17 years.

RECEIVED DEC 10 2001

ZY 8264 558

In issuing this request, we would like to stress the importance and challenge of accurately diagnosing schizophrenia in the pediatric population. The differential diagnosis may include bipolar disorder, mood disorder with psychosis, personality disorders, other psychotic disorders with organic etiologies, in addition to many disorders that classically present in childhood, such as the pervasive developmental disorders and developmental language disorders (AACAP Practice parameters, 2001). An indication of the difficulty of diagnosis is an NIMH study reporting that 7 of 31 (23%) children originally diagnosed with treatment-resistant childhood-onset schizophrenia were re-assessed after a 4 week medication free wash-out period and found not to have that disease; revised diagnoses included posttraumatic stress disorder, atypical psychosis, and personality disorder (Kumra, 1999).

Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. Although we are aware of only two published placebo controlled studies supporting the efficacy of neuroleptics (haloperidol & loxitane) in the treatment of pediatric schizophrenia (Spencer et al., 1992 & Pool et al., 1976), we believe that a sufficiently strong case has been made for continuity between adult and adolescent schizophrenia to permit a pediatric claim for a drug already approved in adults to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia. In addition, a pediatric schizophrenia program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric schizophrenia, we consider the relevant age group to include adolescents aged 13-17 years.

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Specific Study Requirements for Development Program in Adolescent Schizophrenia

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent schizophrenia, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Study

- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, with a recommended duration of at least 6 to 8 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. A relapse prevention trial should follow the acute treatment trial, in which responders to acute treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial.

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

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- Safety data must be collected in the controlled efficacy trial. In addition, longer-term safety data, for a minimum duration of 6 months exposure to the drug, must be collected. The longer-term safety data could come from open studies, e.g., a longer-term open extension of the controlled efficacy trial populations, from separate longer-term open safety studies, or from controlled

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studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement.

Age Group in Which Study(ies) will be Performed –All Studies

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution within this sample.

Number of Patients to be Studied

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult schizophrenia have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with schizophrenia.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

- A sufficient number of pediatric patients to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with schizophrenia. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Study

- A scale specific to schizophrenia and sensitive to the effects of drug treatment of schizophrenia in the target population should be used. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trial; ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trial.

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Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max} , t_{max} , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate efficacy in schizophrenia.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels ($\alpha=0.05$, 2-tailed) of statistical significance.

Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

ADOLESCENT BIPOLAR DISORDER

General Advice for Developing a Drug for Mania in Adolescent Bipolar Disorder

According to the DSM IV, the diagnostic criteria for mania are the same for the pediatric and adult population. However, the lower end of the age range for bipolar disorder is not clear. Bipolar disorder below the age of 13 years is considered both uncommon and difficult to diagnose. On the other hand, bipolar disorder in the adolescent population is thought to be relatively common and phenomenologically similar to bipolar disorder seen in adults. Thus, the study of bipolar disorder in adolescents should be feasible and should yield useful information.

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Under FDAMA (1997), adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is explicitly considered in the guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires that the adult data be considered reasonably relevant to the course of the disease and the effects of the drug in the pediatric populations. We believe that a sufficiently strong case has been made for continuity between adult and adolescent bipolar disorder to permit a pediatric claim for a drug already approved in adults for mania to be supported by a single, independent, adequate and well-controlled clinical trial in adolescent mania in association with bipolar disorder. In addition, a pediatric mania program would need to include pharmacokinetic information and safety information in the relevant pediatric age group. For pediatric mania, we consider the relevant age group to include adolescents aged 13-17 years.

Bibliography

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Specific Study Requirements for Development Program in Adolescent Mania in Association with Bipolar Disorder

Types of Studies

Pediatric Efficacy and Safety Study

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale

The overall goal of the development program would be to establish the safety and efficacy of the study drug in the treatment of adolescent mania in association with bipolar disorder, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design

Pediatric Efficacy and Safety Study

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- For the controlled efficacy study, you must conduct a randomized, double-blind, parallel group, placebo-controlled acute inpatient trial, with a recommended duration of at least 3 weeks. The trial must allow for early rescue, i.e., treatment with active medication, for patients whose symptoms are not adequately controlled to a specific extent at some point on assigned treatment or who worsen. At least 50% of patients assigned to active drug must complete to the nominal endpoint of this trial in order for it to be considered a completed trial. We strongly recommend that the trial be a fixed dose study including at least two fixed doses of the study drug. Given the lack of a robust evidence base for the use of lithium in adolescent mania, there is uncertainty about the optimal therapeutic approach in this population. Thus, this could be a monotherapy trial, or an add-on trial, e.g., adding study drug or placebo to patients already taking lithium. In addition, you may consider a relapse prevention trial to follow from the acute treatment trial, in which responders to acute

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treatment would be randomized to study drug or placebo, with follow-up observation for relapse for a period of 6 months or more with assessment of time to relapse and treatment of relapsed patients. Both the acute and the relapse prevention trials should be limited to patients capable of giving assent to participate in the trial.

Pediatric Pharmacokinetic Study

- You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to the controlled efficacy trial or to other safety trials. Adequate pharmacokinetic data from studies in a single indication would be sufficient to meet this requirement. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

- Safety data must be collected in the controlled efficacy trial. You may consider collecting longer-term safety data. The longer-term safety data could come from open studies, e.g., a longer-term open extension from the controlled efficacy trial and/or in separate longer-term open safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data from studies in a single indication would be sufficient to meet this requirement.

Age Group in Which Study(ies) will be Performed --All Studies

Adolescents (ages 13 to 17 years) must be included in the sample, and there must be a reasonable gender and age distribution.

Number of Patients to be Studied

Pediatric Efficacy and Safety Study

- The study must have a sufficient number of patients to provide reasonable statistical power to show a difference between drug and placebo. While it is difficult to specify the sample size needed to accomplish this, it should be noted that positive trials in adult mania have generally utilized samples of at least 60 patients per treatment arm. It will probably be necessary to conduct a multicentered study to ensure a sufficient population accurately diagnosed with mania.

Pediatric Pharmacokinetic Study

- A sufficient number of patients to adequately characterize the pharmacokinetics of the study drug in the above age group.

Pediatric Safety Study

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- A sufficient number of pediatric patients in the above age group to adequately characterize the safety of the study drug at clinically relevant doses for a sufficient duration. At least 100 patients exposed to drug for at least 6 months would be a minimum requirement for long-term safety.

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Entry Criteria

The protocols must include a valid and reliable diagnostic method for recruiting and enrolling adolescents with mania. Given the difficulty in making the diagnosis for screening purposes, it is recommended that a clinical interview of children and their parents or caregivers be conducted by an adequately trained clinician (e.g. child psychiatrist) to assure accurate diagnosis. It is also recommended that the diagnosis be confirmed using a reliable and valid semi-structured interview.

Patient Evaluations and Study Endpoints

Pediatric Efficacy and Safety Study

- A scale specific to mania and sensitive to the effects of drug treatment of mania in the target population should be used. It may also be useful to add a global measure, e.g., the Clinical Global Impression (CGI). It is essential to identify a primary outcome (or outcomes if more than one is considered important) for the controlled efficacy trials, and ordinarily this would be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.

Pediatric Pharmacokinetic Study

- Pharmacokinetic assessments must be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite measured, the data collected should provide estimates of important pharmacokinetic parameters, e.g., AUC, half-life, C_{max} , t_{max} , and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

Pediatric Safety Study

- Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, hematology, and urinalysis), ECGs, and monitoring for adverse events (including extrapyramidal symptoms and dyskinesias). Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and you may consider longer-term studies of a year or more to address this question, if the acute studies and any longer-term efficacy studies that you may conduct demonstrate efficacy in bipolar disorder.

Statistical Information

Pediatric Efficacy and Safety Study

- This trial must have a detailed statistical plan. The trial should be designed with at least 80% statistical power to detect a reasonable treatment effect (probably best based on typical effects in adults) at conventional levels ($\alpha=0.05$, 2-tailed) of statistical significance.

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Pediatric Pharmacokinetic Study

- Descriptive analysis of the pharmacokinetic parameters.

Pediatric Safety Study

- Descriptive analysis of the safety data.

GENERAL REQUIREMENTS AND COMMENTS

Drug Information

Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of adolescents (ages 13 to 17), your marketed solid dosage formulation should be adequate for these studies.

Drug Concerns

No specific concerns related to administration to schizophrenic or manic pediatric patients were identified while studying olanzapine in adults, nor have specific concerns been identified during the postmarketing experience.

Labeling That May Result from the Studies

The pediatric schizophrenia and mania efficacy, safety, and pharmacokinetic studies described in this request could result in the addition to labeling of information pertinent to these studies.

Format of Reports to be Submitted

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

Timeframe for Submitting Reports of the Study(ies)

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

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Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely yours,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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