

1 INTRODUCTION

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Zyprexa (olanzapine) Tablet and Zyprexa Zydys (olanzapine) Tablet, Orally Disintegrating. Please let us know if DPP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS revision is being reviewed by DRISK and will be provided to DPP under separate cover.

2 MATERIAL REVIEWED

- Draft Zyprexa (olanzapine) Tablet and Zyprexa Zydys (olanzapine) Tablet, Orally Disintegrating Prescribing Information (PI) submitted May 5, 2009 and revised by the Review Division throughout the current review cycle, most recent revision dated September 9, 2009.
- Draft Zyprexa (olanzapine) Tablet and Zyprexa Zydys (olanzapine) Tablet, Orally Disintegrating Medication Guide (MG) submitted on May 5, 2009 and revised by the review division throughout the review cycle, most recent version dated September 9, 2009.

3 RESULTS OF REVIEW

Since DRISK previously reviewed the Zyprexa MG in February 2009 and March 2009, we have limited this review to the identified PI revisions, in particular relating to the addition of information about adolescents, and changes to the Indications for Use. In our review of the MG we have:

- simplified wording and clarified concepts where possible
- made minimal reformatting changes to enhance readability
- ensured that the MG is consistent with the PI
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/01/2009

CLAUDIA B KARWOSKI
10/01/2009
concur

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: August 12, 2008
 DRUG/NDA: Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)
 Sponsor: Lilly
 Indications: Schizophrenia

Supplements:

NDA	Supplement	Dated	Action
Zyprexa (olanzapine) tablets (NDA 20-592)			
20-592	SLR-042	12-7-06	AP letter dated 7-6-07
20-592	SLR-049	7-8-08	Open
Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086)			
21-086	SLR-022	12-7-06	AP letter dated 7-6-07
21-086	SLR-028	7-8-08	Open
Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)			
21-253	SLR-026 dated		AP letter dated 7-6-07
21-253	SLR-033 dated	7-8-08	Open

Background:

1. The Agency requested class labeling changes for all of the conventional antipsychotics to treat schizophrenia in a supplement request letter dated 6-16-08. Specifically, the Agency requested that the sponsors add a black box warning pertaining to mortality in elderly patients treated with antipsychotics.

REVIEW

NDA 20-592/SLR-049

NDA 21-086/SLR-028

NDA 21-253/SLR-033

Date: 7-8-08

CBE: No, Prior Approval

Reviewed by Medical Officer: No

These supplemental applications provide for the following changes to product labeling:

Under the **BOXED WARNING** section, the addition of a warning regarding increased mortality in elderly patients with dementia-related psychosis. [This new section will be added to the beginning of the label with bolded font and enclosed in a black box.]

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zyprexa (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

Under **WARNINGS** the language below will be implemented in bolded font in the **WARNINGS** section as the first paragraph in this section.

WARNINGS**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

CONCLUSIONS

1. These supplements only provide for the above labeling changes when compared to the last approved supplements. I have also attached annotated labeling to this review.
2. Additionally, [REDACTED] (b) (4)
3. Given that the sponsor has agreed to our labeling changes, verbatim, I recommend that this review alone be sufficient to take an approval action for the above labeling supplements.

{See appended electronic signature page}

Paul David, R.Ph., DPP CPMS

Attachments: Annotated labeling

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/s/

Paul David
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**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: August 6, 2009

Drug/NDA: Zyprexa (olanzapine): See Table Below for NDAs and Dosage Forms and Strengths

Applicant: Eli Lilly and Company

Labeling Change: Agranulocytosis Class Labeling

Supplements: See Table below

Product Name	NDA / S-#	Date	Recommend
Zyprexa Oral Tablets 2.5, 5, 7.5, 10, 15, 20 mg	20-592 S-051	03AUG09	AP
Zyprexa Zydis Orally Disintegrating Tablet 5, 10, 15, 20 mg	21-086 S-030	03AUG09	AP
Zyprexa IM Injection 10 mg/vial	21-253 S-036	03AUG09	AP

Background, Material Reviewed

Last AP labeling: FDA letter dated March 19, 2009.

FDA requested labeling change: FDA Order Letter dated July 19, 2009.

Firm's proposed labeling: SNDA dated August 3, 2009.

For administrative history of this class labeling request, see FDA letters dated 05APR09, 02JUN09; FDA email dated 09JUN09. The 05APR09 letter was the initial request for class labeling for this product line. Lilly responded 05MAY09 to contest the request and propose alternate language. FDA extended the discussion period by another 30 days on 02JUN09, and provided slightly modified language on 09JUN09 via email. On 17JUN09 and 24JUN09, Lilly responded contesting the language again and proposing further modifications.

On 19JUL09, the Order Letter was issued. The text required in the Order letter follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotics, including Zyprexa. Patients with a history of a clinically significant low white blood count (WBC) or a drug induced leukopenia/neutropenia should their complete blood count (CBC) monitored frequently during the first few months of therapy and

discontinuation of Zyprexa should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

WARNING AND PRECAUTIONS

Leukopenia, Neutropenia and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including Zyprexa. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of Zyprexa should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue Zyprexa and have their WBC followed until recovery.

Lilly complied with the order letter and submitted the required labeling supplement on 03AUG09.

The pertinent excerpt from this labeling is shown below:

from Highlights:

Leukopenia, Neutropenia, and Agranulocytosis: Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.9)

from Warnings And Precautions:

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue ZYPREXA and have their WBC followed until recovery.

Comments:

- Firm's amended changes for the suspension labeling above correspond verbatim to those ordered by FDA on 19JUL09, with the following exceptions:
 - 'a' has been removed from 'or a drug-induced leukopenia'; this is acceptable US usage.
 - the product name has been capitalized.
 - other necessary editorial changes have been made, including addition of heading and renumbering of subsections within Section 5 of the label.
 - internal references to Section 17 subsections have been added and are appropriate.
- Reference in Highlights to changes that are one year old or older are slated for removal, per PLR: acceptable.
- Font changes to emphasize headers in Section 6 are proposed and acceptable.
- Other minor editorial changes ['two' to 2, 'per' to '/', are also acceptable.
- The labeling otherwise corresponds to the last approved labeling.

Important Note Regarding MedGuide:

This label, and the labeling for Symbyax, both include MedGuides. The MedGuides were required to address the issue of suicidality with antidepressant use to support the approved usage in depression and bipolar depression for both drugs [Zyprexa taken in combination with Prozac = Symbyax, for bipolar depression].

Under FDAAA, all MedGuides are now supposed to be used in conjunction with a REMS. A REMS exists for both Zyprexa and Symbyax MedGuides. Also under FDAAA, any revision to a MedGuide, other than the addition of a toll free number for reporting of AEs, requires submission of a REMS assessment and REMS review.

Not all antipsychotic labeling includes MedGuides at this time. None of the prior AP actions for this labeling change included revisions to a MedGuide. If the existing MedGuides for Zyprexa and Symbyax are revised to incorporate this agranulocytosis language, then we should consider

- [a] requiring all other antipsychotics with MedGuides to make similar revisions
- [b] requiring all antipsychotics with such warnings to include a MedGuide
- [c] note that [b] requires a REMS for every affected product.

Rather than make a decision of this scope in connection with this specific action, which is on a 30-day clock under FDAAA and must be completed by September 2 [or 17 if discussions continue to Day 45], I recommend that we approve the labeling text above, without modification of the MedGuide at this time.

Conclusions and Recommendations:

1. The applicant has incorporated our changes as requested into the proposed labeling for the Zyprexa product line.
2. The proposed labeling only provides for those changes noted above when compared to the last approved labeling for Zyprexa, allowing for editorial modifications to eliminate minor typos, correct internal references, and add references to Section 17.
3. The issue of MedGuide revision to incorporate this language points to the possible need for MedGuides, and associated REMSs, for all antipsychotics carrying similar class labeling. I recommend deferral of this decision until we have completed the action on this labeling and on Symbyax.
4. With the provisos noted above, I recommend approval of these supplemental applications.

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Safety Project Manager

Attachments:

- 1) Annotated labeling from firm.

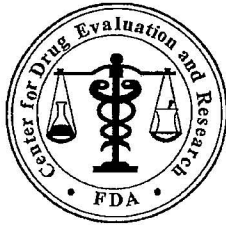
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/s/

DORIS J BATES
08/31/2009

VICTOR D CRENTSIL
08/31/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 12, 2009

To: Thomas Laughren, M.D., Division Director
Division of Psychiatry Products (DPP)

Through: Claudia Karwoski, PharmD, Director (Acting)
Division of Risk Management
Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide), and
Proposed Risk Evaluation and Mitigation Strategy
(REMS), Review #2

Drug Name(s):

- Zyprexa (olanzapine) Tablets; NDA 20-592/S039, 040, 041
- Zyprexa Zydys (olanzapine) Tablets, Orally Disintegrating;
NDA 21-086/S-021

Applicant/sponsor: Eli Lilly & Company

OSE RCM #: 2008-1547

1 INTRODUCTION

This review is written in response to a request from the Division of Psychiatry Products (DPP) for the Division of Risk Management to review the sponsor's proposed amended Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that Zyprexa (olanzapine) 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 (olanzapine). FDA has determined that Zyprexa (olanzapine) meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Zyprexa (olanzapine) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use; Zyprexa (olanzapine) is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Proposed Zyprexa (olanzapine) Risk Evaluation and Mitigation Strategy (REMS), submitted on December 1, 2008, and the Amendment to the Proposed REMS submitted on February 27, 2009.
- Draft Zyprexa (olanzapine) Medication Guide, revised and submitted on March 4, 2009

3 BACKGROUND

DRISK previously reviewed the sponsor's proposed Medication Guide and Risk Evaluation and Mitigation Strategy (REMS) for Zyprexa (olanzapine), on February 24, 2009. Prior to completion of the consult, DRISK provided preliminary email comments to DPP in advance in order to facilitate negotiations with the sponsor. These comments were also conveyed in the memo for the review of the MG and REMS.

The sponsor submitted an original proposed REMS as part of a Complete Response to the August 1, 2008 Approvable Letter for multiple outstanding supplements for Zyprexa (olanzapine) on September 19, 2008. Based on feedback from OSE regarding the Proposed REMS, and questions from the sponsor about the REMS and MG, the sponsor submitted a REMS Amendment, on February 27, 2009 using the provided REMS template.

4 DISCUSSION

4.1 MEDICATION GUIDE

Since DRISK previously provided a line-by-line review of the sponsor's proposed MG previously, this review focuses on the proposed changes submitted by the sponsor.

The revised draft MG submitted by the sponsor has a Flesch Kincaid grade level of 8.7, and a Flesch Reading Ease score of 58.3%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

In our review of the MG, we have:

- ensured that the sponsor's proposed MG changes are consistent with the PI
- provided rationale for adding back certain information that was recommended in DRISK's prior review of the MG
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division with a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

a. Goal

The sponsor has proposed the following revised REMS goal, as requested:

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of hyperglycemia, hyperlipidemia, and weight gain.

b. REMS elements

- Medication Guide: The proposed REMS states that the Medication Guide will be made available for distribution.
- The Timetable for Submission of Assessments is as follows:
 - 1st assessment: September 2010, 18 months after approval
 - 2nd assessment: March 2012, 3 years after approval
 - 3rd assessment: March 2016, 7 years from approval unless it is determined that serious risks have been adequately identified and assessed and are being adequately managed.

The sponsor will submit the assessments within 60 days of the close of the intervals as noted above.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the sponsor's Amended proposed REMS for Zyprexa (olanzapine) generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. Below we have additional recommendations on the proposed REMS and Medication Guide. If the revisions are not acceptable to DPP, DRISK would like to review this material again prior to approval.

Recommendations to be conveyed to Sponsor

1. See the appended Zyprexa (olanzapine) REMS proposal (Appendix A) for additional track changes corresponding to comments in this review.
2. We remind the sponsor of their requirement to comply with 21 CFR 208.24
 - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
 - “Dispense the enclosed Medication Guide to each patient.” or
 - “Dispense the accompanying Medication Guide to each patient.”
 - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:
 - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.
3. The timetable for submission of assessment will be at minimum at 18 months, 3 years and within the 7th year following the approval of the REMS.
 - The REMS assessments should include information needed to assess the effectiveness of the REMS including:
 - Patients' understanding of the serious risks of Symbyax (olanzapine and fluoxetine hydrochloride)
 - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
 - If the sponsor feels the REMS assessment at 7 years of the patient's understanding of the Medication Guide is not needed because they have determined that serious risks have been adequately identified and assessed, the

sponsor should submit an amendment to the REMS following the REMS 3 year assessment. The agency will then determine if additional assessments of the patient's understanding of the Medication Guide are necessary.

4. We recommend the Sponsor submit a complete description of methodology and the instruments used to measure patient's understanding of the risks and safe use of Symbayx to FDA 60 days prior to conducting the survey. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Zyprexa (olanzapine). This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Recommendation for DPP

5. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of:
 - Patients' understanding of the serious risks of Zyprexa (olanzapine)
 - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

We have the following comments on the sponsor's proposed MG revisions:

6. We deleted all of the sponsor's shaded text boxes.
7. In the section "What is the most important information I should know about Zyprexa?":
 - We revised the first sentence of the section. DRISK stands by the language in our previous formal review. This is the standard language that we currently use at the beginning of this section of the MG, and is consistent with other MGs. To

enhance patient comprehension in a wide range of audiences, including those with lower levels of literacy, we recommend that the MG not include phrases such as “(b) (4).” Use patient-friendly language. Additionally, these are not just risks; rather they are actual side effects that happen. Hyperglycemia, elevated cholesterol and triglycerides, and weight gain, are the serious and significant public health concerns that require the distribution of a MG for Zyprexa and should be clearly conveyed to patients and caregivers.

- In the bullet for “high blood sugar (hyperglycemia):” DPP should confer with DDMAC to determine if it is acceptable to include mitigating language such as proposed by the sponsor. If this is acceptable, we recommend more patient friendly language, such as “Rarely” instead of “In rare cases.”
 - In the bullet for “high cholesterol and triglyceride levels in the blood (fat in the blood)”: We recommend not using language such as “(b) (4),” in patient directed materials. We recommend telling patients that certain things may or can happen with TRADENAME. DRISK does not feel that the additional language proposed by the sponsor is needed because we already state that Zyprexa can cause serious side effects, and it is discussed here.
 - In the bullet “Increase in weight (weight gain)”: In general, DRISK recommends using active voice in patient directed materials. We agree with the sponsor that it is ok to remove the word “(b) (4)” here because it is stated above. However, we have changed the language to active voice and patient-friendly terminology.
8. In the section “What is Zyprexa?”
- We agree with the sponsor’s proposed change to the first statement so that it reads: “Zyprexa is a prescription medicine used (b) (4), and is followed by four bullets. All of the labeled indications include “in adults” or “in adult patients.”
 - The sponsor added back information about the onset of feeling better and improvement of symptoms. DRISK deleted this in our prior MG review. We recommend consulting with DDMAC for their input regarding the appropriateness of including this information in the MG. Additionally, if based on consultation with DDMAC this language is to remain in the MG, we recommend against using “(b) (4)” statements.
9. In the section “What should I tell my doctor before taking Zyprexa?”
- We agree with the sponsor’s suggestion to add a bullet for “heart problems.”
 - We concur with the sponsor’s suggestion to delete the information about (b) (4) from this section.
 - Under “Tell your doctor about all the medicines you take...” we agree with taking out the list of medicines.
10. In the section “What are the possible side effects of Zyprexa?”
- We added back the statement “(b) (4).” This is currently our standard statement at the beginning of this section, and is consistent with the first sentence in the section “What is the most important information I should know about Zyprexa?”

- DRISK disagrees and has revised this section. The most serious side effects are placed first; however, all side effects from the Warnings and Precautions section are listed. Generally this is done in the order that they appear in the PI, and descriptions are provided of what is important for the patient to know. DPP should consider the placement of NMS in the MG because it appears before the metabolic issues and implies that this adverse reaction is of greater importance.
- Regarding the bullet for elderly patients with dementia-related psychosis: The sponsor's proposed change makes the bullet too complex. Additionally, "incidence" is not a patient-friendly term. In a Memo to File, from OSE to DPP dated January 2009¹, OSE stated that a MG is not appropriate for the conventional and atypical antipsychotics to address the issue of increased mortality in elderly patients with dementia related psychosis. However, since Zyprexa now requires a MG due to the risk of metabolic side effects, we must address this with patients. We do not usually put language in patient directed materials stating that 'TRADENAME is not approved for...' Rather we state what the labeled indications are. The product is not contraindicated in this patient population. DRISK believes that the review division should consider whether to add a statement to the PI indicating that use of Zyprexa is not recommended in this patient population. If such language is added to the PI, a statement such as "Elderly patients who have psychosis related to dementia should not take Zyprexa" could be added to the MG. The MG must be consistent with the PI.
- In the bullet "Neuroleptic malignant syndrome (NMS)" we concur with the sponsor (b) (4). However, because of the seriousness of this condition, DRISK does not believe that patients should be told to simply call their doctor right away if they have any of these symptoms. It is important to get treated in a hospital and we are concerned about delay in treatment if patients can not reach their doctor in a timely manner, such as on the weekend or a holiday.
- In the bullet "Decreased blood pressure when you change positions," we disagree with the sponsor's proposed changes to this bullet. The sponsor's changes (b) (4). We have changed this bullet in accordance with the recommendation in our prior review. DPP should review this bullet and determine if DRISK's description is accurate. We recommend adding an instruction to PI section 17.7 regarding how to avoid orthostatic hypotension and what to do if it happens. We have added back that patients should tell their doctor if they have dizziness, fast heartbeat, or fainting. Section 5.8 indicates that more gradual titration of Zyprexa may be needed. We have added slow heart beat because bradycardia is also listed in section 5.8.
- In the bullet "(b) (4)," the sponsor's change removes information about the possibility of aspiration into the lungs that can happen in people who take

¹ OSE Memo to File re: Issue of a Medication Guide for Conventional and Atypical Antipsychotic Drugs; January 2009: RCM #: 2008-1200

antipsychotic medicines, including Zyprexa.” We added the language from our prior review and further revised it to clarify that these problems are a common cause of sickness and death in people with advanced Alzheimer’s disease, and can happen in people who take antipsychotic medicines, such as Zyprexa.

- In the bullet “Problems with control of body temperature” the sponsor’s language does not appear to be consistent with PI section 5.13 which states “Disruption of the body’s ability to reduce core body temperature...” Zyprexa has anticholinergic-like effects; with some other medicines that have anticholinergic activity, the concern is about heat prostration due to decreased ability to sweat. The sponsor states that there is “excessive sweating”. This should be clarified. Also, the word “excessive” is not patient-friendly; use another word or phrase, such as “too much.” In the meeting between the DRISK Patient Labeling Reviewer, Paul David, and Dr. Mathis on February 18, 2009, it was discussed and agreed that it is a good idea to tell patients to drink plenty of fluids to prevent dehydration. This addresses the issue of dehydration in PI section 5.13. There is currently no instruction in the PI to address this. An instruction should be added to section 17 to instruct healthcare providers to educate patients about avoiding dehydration while taking Zyprexa.
- DRISK disagrees with the sponsor’s proposal to (b) (4) (b) (4). Although Zyprexa is not currently indicated in adolescents, the review division has decided to add the safety information to the labeling at this time; therefore, the common side effects that pertain to adolescents should be added to the MG to be consistent with the labeling that is currently being negotiated. The MG was determined to be necessary because data indicates that patients across the age spectrum are at risk for the metabolic side effects highlighted in the section “What is the most important information I should know about ZYPREXA?” Therefore, DRISK believes that it is appropriate to include common side effects in adolescents in the MG.
- We revised the side effect statement as follows:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides in accordance with 21 CFR 208.20 (b) (7) (iii). The sponsor may not change the statement.

Please let us know if you have any questions.

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/s/

Sharon Mills
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DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
3/12/2009 02:57:32 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/12/2009 03:33:34 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 23, 2009

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products (DPP)

Through: Jodi Duckhorn, M.A., Team Leader
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
**Patient Labeling and Education Team
Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide) and
Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s):

- Zyprexa (olanzapine) Tablets; NDA 20-592/ S039, 040, 041
- Zyprexa Zydis (olanzapine) Tablets, Orally Disintegrating; NDA 21-086/S-021

Applicant/sponsor: Eli Lilly & Company

OSE RCM #: 2008-1547

1 INTRODUCTION

This review is written in response to a request from the Division of Psychiatry Products (DPP) for the Division of Risk Management's Patient Labeling and Education Team to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

FDA has determined that Zyprexa (olanzapine) 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 (olanzapine). FDA has determined that Zyprexa (olanzapine) meets two of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Zyprexa (olanzapine) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use; Zyprexa (olanzapine) is a product for which patient labeling could help prevent serious adverse events.

2 MATERIAL REVIEWED

- Draft Zyprexa (olanzapine) Prescribing Information (PI) submitted September 19, 2008 and revised by the Review Division on February 9, 2009.
- Draft Zyprexa (olanzapine) Medication Guide (MG) submitted on September 19, 2008.
- Proposed Zyprexa (olanzapine) Risk Evaluation and Mitigation Strategy (REMS), submitted on September 19, 2008.

3 BACKGROUND

Eli Lilly & Company submitted New Drug Applications, NDA 20-592 for Zyprexa (olanzapine) Tablets on September 30, 1996, and NDA 21-086 for Zyprexa Zydis (olanzapine) Table, Orally Disintegrating, on April 6, 2000. Zyprexa is indicated as follows:

Bipolar I Disorder (Manic or Mixed Episodes)

- **Monotherapy:** Oral Zyprexa is indicated for acute treatment of manic or mixed episodes associated with Bipolar I Disorder (monotherapy and in combination with lithium or valproate) and maintenance treatment of Bipolar I Disorder (monotherapy) in adults.
- **Combination Therapy:** The combination of oral Zyprexa with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults.

Zyprexa and Fluoxetine in combination: Depressive Episodes Associated with Bipolar I Disorder

- Oral Zyprexa and fluoxetine in combination is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adult Patients.
- Zyprexa monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.

Zyprexa and Fluoxetine in Combination: Treatment Resistant Depression

- Oral Zyprexa and fluoxetine in combination is indicated for the acute treatment of treatment resistant depression (Major Depressive Disorder in adult patients who do not

respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

- Zyprexa monotherapy is not indicated for treatment of treatment resistant depression.

Since Zyprexa was approved in 1996, DPP has 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 treatment. This information was not available when Zyprexa was granted approval.

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 provide FDA with new authorities to require sponsors of approved drugs to develop and comply with REMS section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

DPP informed the sponsor in an Approvable Letter for multiple outstanding supplements, dated August 1, 2008, that a REMS is necessary for Zyprexa (olanzapine). The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

The sponsor submitted a proposed REMS as part of a Complete Response to the August 1, 2008 Approvable Letter for multiple outstanding supplements for Zyprexa (olanzapine) on September 19, 2008.

4 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 9.6. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level. Our revised MG has a Flesch Kinkaid grade level of 8.5.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information as necessary to be consistent with the MG format as specified in 21 CFR 208.20
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

5 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments on the proposed REMS:

1. We are aware that the sponsor was not provided with a REMS template prior to submission of the REMS as part of their Complete Response. As a result, the sponsor's proposed REMS does not follow the recommended format.
2. We recommend that the review division provide the sponsor with the attached REMS template (Appendix A) and request that the sponsor revise and submit their proposed REMS according to the REMS template.
3. We recommend the REMS goal be revised as follows:
The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of hyperglycemia, hyperlipidemia, and weight gain.
4. To date, the sponsor has not submitted revised carton and containers. The sponsor must comply with 21 CFR 208.24(d), which requires a statement alerting pharmacists to dispense the MG with the product is on the carton and container on all strengths and formulations. DMEPA will review the carton and containers under separate cover, once they are submitted.
5. The sponsor's proposed timetable for assessments annually after approval of the REMS is acceptable; however, the assessments must be submitted separately and not as part of a Periodic Safety Update Report (PSUR). The sponsor should submit for review a detailed plan to evaluate patients' understanding about the safe use of *Zyprexa (olanzapine)* at least 2 months before they plan to conduct the evaluation. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of *Zyprexa (olanzapine)*. This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias

- Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.
- 6. We recommend including in the approval letter a reminder of the sponsor's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including an evaluation of:
 - Patients' understanding of the serious risks of
 - A report *Zyprexa (olanzapine)* on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
 - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

We have the following comments on the sponsor's Questions Regarding REMS:

The following comments were sent to DPP on February 20, 2009 to share with the sponsor prior to completion of a full review of the MG and REMS for Zyprexa:

7. The sponsor included within their Complete Response Document a *Discussion of Approvable Letters Received 1 August 2008* for Zyprexa, (olanzapine), Symbyax (olanzapine/fluoxetine combination), and Prozac (fluoxetine hydrochloride), beginning on page 19. Section 3 poses questions regarding the REMS on pages 22 and 23 of the Complete Response Document.

3.1 Clarify the Scope of the Medication Guides for Zyprexa and Symbyax

Question 1: Does the Division agree with the scope of the draft Medication Guides provided for Zyprexa and Symbyax?

DRISK Response: The MG for Zyprexa is under review. We will provide subsequent comments about the scope of the MG in the future. The Symbyax MG review is being addressed by DRISK under separate cover.

Question 2: Does the Division agree that the Medication Guide for Zyprexa only applies to the tablet and Zydis formulations?

DRISK Response: We defer to the review division to respond to this question.

3.2 Clarify the Wording of the Suicidality Medication Guides for Symbyax and Prozac

Question 3: Does the Division agree that we should use the 2007 template for the suicidality Medication Guide for Symbyax and Prozac?

DRISK Response: We note that this question does not pertain to Zyprexa or the Zyprexa REMS; however, it is included in the sponsor's Complete Response for Zyprexa. We defer to the review division to address this with the sponsor.

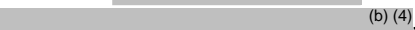
3.3 Clarify Expectations for Assessments and Timetable for Evaluation of the REMS for Zyprexa and Symbyax.

Question 4: Does the Division agree with the REMS proposal for Zyprexa and Symbyax?

DRISK Response is as follows:

- We are aware that the Lilly was not provided with a REMS template prior to submission of the REMS as part of your Complete Response. As a result, the proposed REMS does not follow the recommended format.
- We recommend that the Lilly revise and resubmit the proposed REMS to follow the template that the review division provides.
- We recommend the REMS goal be revised as follows:
The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine), including the risks of hyperglycemia, hyperlipidemia, and weight gain.
- The sponsor's proposed timetable for assessments annually after approval of the REMS is acceptable; however, the assessments must be submitted separately and not as part of a Periodic Safety Update Report (PSUR). The sponsor should submit for review a detailed plan to evaluate patients' understanding about the safe use of Zyprexa (olanzapine) at least 2 months before they plan to conduct the evaluation. The submission should include:
 - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Zyprexa (olanzapine). This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

We have the following comments on the proposed Medication Guide:

8. In the section “What is the most important information I should know about Zyprexa?”
- We moved “Increase in weight” so that it follows “high cholesterol and triglyceride levels in the blood” to be consistent with the ordering of metabolic events in PI section 5 *Warnings and Precautions*.
 - Under “High blood sugar (hyperglycemia), we added the following language:
If you have diabetes, follow your doctor’s instructions about how often to check your blood sugar while taking Zyprexa.
This instruction should be added to section 17.4 of the PI.
9. In the section “What is Zyprexa?”
- Information about the onset of feeling better and instruction to call your doctor if you do not think you are getting better does not belong in the section “What is Zyprexa?” This section should reflect the labeled indications for the product. We deleted the first two sentences entirely and moved the last statement to the section “How should I take Zyprexa?”
 - The following statement is not consistent with the current draft labeling:
Zyprexa is not approved in children under the age of 13 years.
 (b) (4)
10. In the section “What should I tell my doctor before taking Zyprexa?”
- In the first paragraph, we deleted “ (b) (4).” The patient’s medical conditions are relevant,  (b) (4).
 - A bullet was added for “bowel obstruction” to convey the “paralytic ileus.”
 - The two statements at the end of the section relate to the indication and have been moved to the section “What is Zyprexa?” and have been modified to be consistent with the PI.
11. In the section “How should I take Zyprexa?”
- The instruction to “ (b) (4),” is not in the PI. If the sponsor wishes to include this language, then it should be added to the PI. The language in the MG must be consistent with the language in the PI.
 - Add an instruction to section 17 if the PI telling patients to contact their doctor if they do not think that they are getting better or have any concerns about their condition while taking Zyprexa. The language in the MG must be consistent with the language in the PI.
12. In the section “What should I avoid while taking Zyprexa?” the review division should clarify if using the term “react quickly” accurately addresses the issue of “motor skills” as proposed by the sponsor.”
13. In the section “What are the possible side effects of Zyprexa?”
- All serious side effects should be listed first and should be consistent with the Warnings and Precautions section of the PI, followed by a list of the common side effects of Zyprexa.

- We added the bullet “Decreased blood pressure when you change positions” to address the issue of orthostatic hypotension. Add the reportable signs and symptoms of orthostatic hypotension to section 17 of the PI and an instruction for patients to change positions carefully to help prevent this from happening.
- The review division should review and revise the list of common side effects below in the MG and make it consistent with the PI section 6 Adverse Reactions. Give further consideration as to whether there are distinctions between teens and adults. If so, include a separate list. If there is no distinction, combine into one list. Use a consistent percentage cutoff for the common side effects.
- We have revised the side effect statement at the end of the section, “What are the possible side effects of Zyprexa?” to state:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides.¹

Please let us know if you have any questions.

¹ 21 CFR 208.20 (b)(7)(iii)

APPENDIX A- REMS TEMPLATE

<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

APPEARS THIS WAY ON ORIGINAL

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

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/s/

Sharon Mills
2/23/2009 04:54:57 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
2/24/2009 08:55:28 AM
DRUG SAFETY OFFICE REVIEWER

**REGULATORY PROJECT MANAGER
LABELING REVIEW**

Date: August 12, 2008
 DRUG/NDA: Zyprexa (olanzapine) tablets (NDA 20-592), Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086), and Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)
 Sponsor: Lilly
 Indications: Schizophrenia

Supplements:

NDA	Supplement	Dated	Action
Zyprexa (olanzapine) tablets (NDA 20-592)			
20-592	SLR-042	12-7-06	AP letter dated 7-6-07
20-592	SLR-049	7-8-08	Open
Zyprexa Zydis (olanzapine) orally disintegrating tablets (NDA 21-086)			
21-086	SLR-022	12-7-06	AP letter dated 7-6-07
21-086	SLR-028	7-8-08	Open
Zyprexa IntraMuscular (olanzapine) injection (NDA 21-253)			
21-253	SLR-026 dated		AP letter dated 7-6-07
21-253	SLR-033 dated	7-8-08	Open

Background:

1. The Agency requested class labeling changes for all of the conventional antipsychotics to treat schizophrenia in a supplement request letter dated 6-16-08. Specifically, the Agency requested that the sponsors add a black box warning pertaining to mortality in elderly patients treated with antipsychotics.

REVIEW

NDA 20-592/SLR-049

NDA 21-086/SLR-028

NDA 21-253/SLR-033

Date: 7-8-08

CBE: No, Prior Approval

Reviewed by Medical Officer: No

These supplemental applications provide for the following changes to product labeling:

Under the **BOXED WARNING** section, the addition of a warning regarding increased mortality in elderly patients with dementia-related psychosis. [This new section will be added to the beginning of the label with bolded font and enclosed in a black box.]

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Zyprexa (olanzapine) is not approved for the treatment of patients with dementia-related psychosis (*see* **WARNINGS**).

Under **WARNINGS** the language below will be implemented in bolded font in the **WARNINGS** section as the first paragraph in this section.

WARNINGS**Increased Mortality in Elderly Patients with Dementia-Related Psychosis** —

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Zyprexa is not approved for the treatment of patients with dementia-related psychosis (*see* **BOXED WARNING**).

CONCLUSIONS

1. These supplements only provide for the above labeling changes when compared to the last approved supplements. I have also attached annotated labeling to this review.
2. Additionally, [REDACTED] (b) (4)
3. Given that the sponsor has agreed to our labeling changes, verbatim, I recommend that this review alone be sufficient to take an approval action for the above labeling supplements.

{See appended electronic signature page}

Paul David, R.Ph., DPP CPMS

Attachments: Annotated labeling

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this page is the manifestation of the electronic signature.**

/s/

Paul David
8/13/2008 07:22:22 AM
CSO

DRUGS: ZYPREXA, PROZAC

PRIMARY REVIEWER: Andre Jackson

ZYPREXA

NDA 20-592 (b) (4)
NDA 21-086 (b) (4)

Submission dates : (b) (4)
Submission dates : (b) (4)

NDA 20-592/SE8-039
NDA 21-086/SE8-021

Submission date : 2-4-08
Submission date : 2-4-08

NDA 20-592/SE5-040
NDA 20-592/SE5-041

Submission date : 2-5-08
Submission date : 2-5-08

NDA 21-253 (b) (4)
NDA 21-086 (b) (4)

Submission date : (b) (4)
Submission date : (b) (4)

SYMBYAX (Zyprexa/Prozac)

NDA 21-520/SE1-012
NDA 21-520 (b) (4)

Submission date : 2-1-08
Submission dates : (b) (4)

PROZAC

NDA 18-936/SE8-077
NDA 18-936/SLR-075

Submission date : 2-4-08
Submission date : 3-21-07

Applicant : Eli Lilly

FORMULATIONS: Zyprexa (Tablet, Intramuscular, ODT), Fluoxetine (Capsules), Zyprexa/Prozac) Capsules

Review of a CBE Labeling Supplement

Background:

The firm has submitted a detailed list of outstanding Label revisions for Zyprexa NDA 20-592, Zyprexa Zydis NDA 21086 and Zyprexa Intramuscular NDA 21-253 and Prozac NDA 18-936, Symbyax NDA 21520.

Only those supplement items with relevant concerns for OCP will be listed.

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A. Supplements for Zyprexa tablets NDA 20-592

- o S- (b) (4) (_____ (b) (4) _____)
- o S-039 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)
- o S-040 (PAS: adolescent use in bipolar disorder [acute manic or mixed episodes])
- o S-041 (PAS: adolescent use in schizophrenia)

FIRM'S PROPOSED LABEL FOR ZYPREXA

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FDA LABEL CHANGES FOR ZYPREXA

2.3 Bipolar Disorder (Depressive Episodes)

Dosing in Special Populations— The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP]When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.15), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

2.4 Treatment Resistant Depression

Dosing in Special Populations— The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP]When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.15), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

B. Supplements for Zyprexa Zydis NDA 21-086

o S- (b) (4) ((b) (4))

o S-021 (PAS for use of Zyprexa and Prozac in combination to treat treatment-resistant depression)

o S- (b) (4) ((b) (4))

FDA RESPONSE for Zyprexa Zydys NDA 21-086
Wording only: No issues for OCP

C. Supplements for Zyprexa IntraMuscular (21-253)

o S- [REDACTED] (b) (4)

FDA RESPONSE FOR ZYPREXA INTRAMUSCULAR
Wording only: No issues for OCP

D. Supplements For NDA 18-936 S075 PROZAC

NDA 18-936/S075, S077, and S [REDACTED] (b) (4)

• 26 June 2006: Provided revised label language consistent with that provided in Symbyax NDA 21-520/S010 (submitted 22 June 2006 to add a lower starting dose); revised language in the DESCRIPTION, DOSAGE AND ADMINISTRATION, Special Populations and HOW SUPPLIED sections.

FIRM'S PROPOSED LABEL FOR PROZAC

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FDA LABEL CHANGES FOR PROZAC

2.3 Bipolar Disorder (Depressive Episodes)

Dosing in Special Populations — The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP] When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.10), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

2.4 Treatment Resistant Depression

Dosing in Special Populations — The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. [Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism.-Relocated to this position by OCP] When indicated, dose escalation should be performed with caution in these patients. Olanzapine and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.10), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

7. DRUG INTERACTIONS

7.3 CNS acting drugs

The risk of using PROZAC in combination with other CNS active drugs, [except olanzapine,-The sponsor should explain the origin of this data to the FDA] has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of PROZAC and such drugs is required.

7.12 Tryptophan

Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress. [The concomitant use with tryptophan is not recommended.-This statement was added by the sponsor and should be noted by the Medical Officer since it was not in the original label]

7.13 Monoamine oxidase inhibitors

[There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, PROZAC should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see *Clinical Pharmacology (12.3)*] should be allowed after stopping PROZAC before starting an MAOI.-This statement has been moved from Contraindications and placed in this position by the sponsor and should be noted by the Medical Officer]

FIRM'S PROPOSED LABEL FOR SYMBYAX

9 pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

FDA LABEL CHANGES FOR SYMBYAX

2.3 Special Populations

The starting dose of SYMBYAX 3 mg/25 mg - 6 mg/25 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of SYMBYAX (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. Relocated to this position by OCP] When indicated, dose escalation should be performed with caution in these patients. SYMBYAX has not been systematically studied in patients over 65 years of age or in patients <18 years of age [see *Warnings and Precautions (5.20), Use in Specific Populations (8.4 and 8.5), and Clinical Pharmacology (12.3)*].

5.23 Long Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment [see *Clinical Pharmacology (12.3)*]. [This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine. Relocated to this position by OCP]

7 DRUG INTERACTIONS

7.7 CNS Acting Drugs

(b) (4)

7.13 Monoamine oxidase inhibitors

[SYMBYAX should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. There have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with an MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see *Clinical Pharmacology (12.3)*] should be allowed after stopping SYMBYAX before starting an MAOI. [See *Contraindications (4)*].-This section has been moved from Contraindications by the sponsor to the Drug Interaction section and should be noted by the Medical Officer]

7.18 Thioridazine

[Thioridazine should not be administered with SYMBYAX or administered within a minimum of 5 weeks after discontinuation of SYMBYAX.

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs that inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine [see *Contraindications (4)*].

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism [see *Contraindications (4)*].-This section has been moved from Contraindications by the sponsor to the Drug Interaction section and should be noted by the Medical Officer]

12.3 Pharmacokinetics

Absorption and Bioavailability

Distribution

Metabolism and Elimination-These 3 subheadings under pharmacokinetics were bolded in the approved label but are not in the proposed version from the firm, they need to be bolded for easier reading.

SIGNATURES

Andre Jackson _____
Reviewer, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Raman Baweja , Ph.D. _____
Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

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

/s/

Andre Jackson
7/15/2008 10:50:49 AM
BIOPHARMACEUTICS

Raman Baweja
7/15/2008 03:25:37 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

020592 / S-035, 039, 040, 041, 049,053, 055

021086 / S-21, 031, 032, 034

021253 / S-037, 039, 043

**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

NDA# 021086

Zyprexa Zydis (olanzapine) orally disintegrating tablets

NDA# 021253

Zyprexa IM (olanzapine) injection

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS 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/

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

/s/

KIMBERLY S UPDEGRAFF
12/11/2009

THOMAS P LAUGHREN
12/11/2009

EXCLUSIVITY SUMMARY

NDA # 20-592 & 21-086

SUPPL # 039 & 021

HFD # 130

Trade Name Zyprexa

Generic Name olanzapine tablets (20-592) & oral disintegrating tablets (21-086)

Applicant Name Lilly

Approval Date, If Known 3-19-09

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

SE8

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:

Both the Prozac (18-936/SE8-077) and Zyprexa (20-592/SE8-039 & 21-086/SE8-021) efficacy supplements are labeling supplements in which clinical data are referenced to the Symbyax efficacy supplement 21-520/SE1-012. Symbyax, a combination of fluoxetine and olanzapine, is approved for depressive episodes associated with bipolar disorder

(approval date 12-24-03) and treatment resistant depression (approval date 3-19-09). The applicant has received approval to place these 2 indications into the individual product's labeling stating the indications when used concomitantly with the other individual product.

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, for the TRD claim

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?

No

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# 20-592 Zyprexa (olanzapine)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS 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:

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"):

One positive study (HDAO-2) and 2 supportive studies (Studies HGFR & HGIE)

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 # 28705 YES ! NO
! Explain:

Investigation #2 !
!
IND # 28705 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 NO
! Explain: ! Explain:

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

DPP believes that exclusivity should extend to the treatment resistant indication (approved on 3-19-09). However, exclusivity should not extend to the depressive episodes associated with bipolar disorder indication (approval date 12-24-03) since this indication was approved more than 5 years ago. Regardless, if the decision is to allow generic sponsors to place either or both of these indications in the individual fluoxetine or olanzapine labelings, all of the safety information, pertaining to concomitant use of both products, should also be placed into labeling.

Name of person completing form: Paul David
Title: CPMS
Date: 3-30-09

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

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

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

/s/

Thomas Laughren
3/30/2009 11:39:03 AM

MEMORANDUM

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

DATE: 3 December 2009

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 20-592 S-040, S-041

SUBJECT: Approval Recommendation for Zyprexa [olanzapine] Tablets for the Treatment of Schizophrenia and the Acute Treatment of Manic or Mixed Episodes Associated with Bipolar Disorder in Adolescents (ages 13-17)

BACKGROUND AND REGULATORY HISTORY

Zyprexa is an atypical antipsychotic approved (as an oral formulation) in adults for the treatment of schizophrenia, and the acute treatment of manic or mixed episodes associated with bipolar I disorder (monotherapy or adjunctive therapy to lithium or valproic acid). The sponsor submitted one positive short-term trial in adolescents with schizophrenia (ages 13-17) and in one trial of adolescents with manic or mixed episodes associated with bipolar I disorder (ages 13-17), as well as pharmacokinetic data to support dosing in this population, and longer-term (6 months) safety data.

The Division was prepared to approve these applications after reviewing the data (see team member reviews, this NDA), but decided to first take this application (along with two others pending for similar indications) to the Psychopharmacologic Drugs Advisory Committee (PDAC) for a public discussion among experts in the fields of child psychiatry, general psychiatry, drug safety, cardiology, and endocrinology. We were specifically interested in expert opinion about expanding the indications of atypical antipsychotics into broader populations, especially given the adverse metabolic profile and yet unquantified risk of tardive dyskinesia with this class of medications.

Zyprexa (and others in the atypical antipsychotic class) has an adverse impact on glucose, lipids, and weight gain. In fact, although there are limited comparative safety data, it is our impression from having evaluated the controlled trial data for each of the atypicals that Zyprexa poses a greater risk of metabolic changes than do the others in the class (except for perhaps clozapine). Since schizophrenia and bipolar I disorder are life-long illnesses, our concern was that pediatric patients with these disorders would be treated earlier in life and for an extended period of time compared to adults, therefore increasing exposure-related risks of adverse reactions associated with drugs in this class. Zyprexa appears to have a greater adverse metabolic impact than the other drugs being evaluated in children/adolescents, and we felt like a public discussion of how to differentially label this drug would be in order.

Our safety review revealed that younger patients experienced qualitatively similar adverse reactions as adults, but there were some quantitative differences related to adverse changes in metabolic

parameters, as well as other adverse events. Our belief has been that pediatric patients represent a more treatment-naïve population, and so effects on glucose, lipids and weight are more apparent in this population, but we wanted to hear from experts and discuss these issues in public before taking a final action.

PEDIATRIC ADVISORY COMMITTEE MEETING (PDAC)

The PDAC met on June 9-10, 2009. The members agreed with us that efficacy had been established in the studied populations for both indications. We then discussed the safety issues of concern with the committee. From a discussion of the facts and from the experience of treating physicians, it was obvious that schizophrenia and bipolar I disorder affect the pediatric population (in fact these diseases often onset during the pediatric years) and that the availability of multiple treatment options is important to the clinical management of these routinely devastating disorders. It was noted that the American Academy of Child and Adolescent Psychiatry (AACAP) recommends in its practice guidelines that antipsychotics be used in both disorders, and it was routinely accepted as fact that children and adolescents were already being treated with atypical antipsychotics, including Zyprexa, because their safety profiles are considered by many clinicians to be superior to the typical antipsychotics which have a known exposure-related risk of tardive dyskinesia. The Sponsor presented their data, and also indicated their acceptance of the Division's proposed labeling language which states that the increased potential in adolescents compared to adults for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first.

The votes of the PDAC were as follows:

- Schizophrenia
 - Effective? 11 yes; 5 no, 2 abstain
 - Safe? 10 yes; 4 no; 4 abstain
- Bipolar mania/mixed episodes
 - Effective? 17 yes; 0 no; 1 abstain
 - Safe? 11 yes; 4 no; 2 abstain

LABELING/MEDICATION GUIDE

The labeling and Medication Guide were updated to include the pediatric indications, and pediatric safety data (which had already been included in labeling prior to our evaluation of these supplements). We also included a new section in labeling entitled *Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder*, which states that (b) (4)

[REDACTED] . *Dosing and Administration* describes what we learned from the trials about dosing younger patients, and is presented in an easy to read tabular form in Highlights. The Medication Guide was updated to include a comprehensive description of what can be expected when using the drug, and when the patient/parent should call the prescriber. The Office of Safety and Epidemiology were consulted to evaluate the Medication Guide and the safety review team reviewed the final REMS documents.

CONCLUSIONS

The safety and efficacy of Zyprexa has been established in pediatric patients with schizophrenia and manic or mixed episodes associated with bipolar I disorder. My recommendation to the Director is to approve these indications, with the expanded labeling and Medication Guide. This action will provide clinicians treating these patients with the proper information about dosing, a complete description of the risks of treating pediatric patients with Zyprexa (including our labeling stating that other drugs should be tried first in adolescent patients secondary to adverse metabolic effects), and a comprehensive Medication Guide to provide to patients with their prescription. These approvals would provide another treatment option for clinicians treating pediatric patients suffering from these debilitating diseases.

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/

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

/s/

MITCHELL V Mathis
12/04/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 020592 BLA #	NDA Supplement # 040 & 041 BLA STN #	If NDA, Efficacy Supplement Type: SE5
Proprietary Name: Zyprexa Established/Proper Name: olanzapine Dosage Form: tablets		Applicant: Lilly Agent for Applicant (if applicable):
RPM: Kimberly Updegraff		Division: HFD-130
NDA's: NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (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.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>03/19/2009</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☐ None AE 04/30/2007 AE 08/01/2008

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ²	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☒ Submitted in response to a Pediatric Written Request Comments:	
BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? 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.	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
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.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[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).	☐ No paragraph III certification Date patent will expire _____
[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). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	☐ N/A (no paragraph IV certification) ☐ Verified

- [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 notice of certification?

Yes No

(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 the rest of the patent questions.

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? (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 within the 45-day period). <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> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist³	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 12/04/2009 AE 08/01/2008 AE 04/30/2007
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11/10/2009
• Original applicant-proposed labeling	09/19/2008
• Example of class labeling, if applicable	NA

³ Fill in blanks with dates of reviews, letters, etc.
 Version: 12/4/09

Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11/10/2009
Original applicant-proposed labeling	09/19/2008
Example of class labeling, if applicable	NA
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	NA
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) - Review(s) (<i>indicate date(s)</i>)	NA
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☐ DMEDP ☒ DRISK 10/01/2009 03/12/2009 ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	Filing Review & Filing Meeting Minutes: 1/04/2007
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant in on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) - Date reviewed by PeRC 06/22/2009 If PeRC review not necessary, explain: _____ - Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ 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
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	6/09/2009 & 6/10/2009
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 12/4/2009 4/29/2007
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 4/19/2007
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁵	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	4/12/2007
• Clinical review(s) (<i>indicate date for each review</i>)	7/18/2008 5/21/2007 4/18/2007 4/18/2007
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical review dated 4/18/2007
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	10/13/2009 11/29/2009 ☐ None 10/6/2009 & 10/16/2009 email 04/19/2007
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	☒ None
Statistical Review(s) <i>(indicate date for each review)</i>	☐ None 4/27/2007 4/6/2007
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ None 4/2/2007
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None 3/27/2007
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☐ None
• Supervisory Review(s) <i>(indicate date for each review)</i>	☐ None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☐ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 1/17/2007
❖ Microbiology Reviews	☒ Not needed
☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	
☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	1/17/2007
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

SUPPLEMENT NDA 20-592 S-040/S-041
REMS ASSESSMENT TO SUPPORT PROPOSED REMS MODIFICATION

Per FDCA 505-1(g), Eli Lilly and Company, Inc. (Lilly) has assessed the REMS for Zyprexa tablets (approved 19 March 2009) and determined that a modification to the Medication Guide is necessary to extend the population for the indications of schizophrenia and mixed or manic episodes associated with bipolar I disorder to include adolescents (13-17 years). The goal of the REMS remains unchanged. Lilly believes the Medication Guide included in this submission is adequate to achieve its purpose. Lilly will continue to assess the REMS per the timetable approved on 19 March 2009.

NDA 20-592, ZYPREXA (olanzapine) Tablet for Oral Use
NDA 21-086, ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating
for Oral Use

Deleting contact information as not required per FDA communication on 20 March 2009

(b) (4)

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. Goals(s)

The goal of the REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine) Tablet for Oral Use and Tablet, Orally Disintegrating for Oral Use, including the risks of hyperglycemia, hyperlipidemia, and weight gain.

II. REMS Elements

A. Medication Guide

The Medication Guide will be dispensed with each Zyprexa prescription in accordance with 21 CFR 208.24.

B. Communication Plan

This REMS for Zyprexa does not include a Communication Plan.

C. Elements to Assure Safe Use

This REMS for Zyprexa does not include elements to assure safe use.

D. Implementation System

Because this REMS for Zyprexa does not include elements to assure safe use, an implementation system is not required.

Revised timetable as requested by FDA on 7 October 2009. Deleted text shown as strike-through, new text shown in red.

E. Timetable for Submission of Assessments

The Timetable for Assessments is as follows:

(b) (4)

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010)
- The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012)
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016)

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Psychiatry Products

NDA/BLA #s: 020592/S040/S041
Products: ZYPREXA (olanzapine) oral tablets
ZYPREXA ZYDIS (olanzapine) orally disintegrating tablets
APPLICANT: Eli Lilly and Company
FROM: Thomas Laughren, MD, Director, Division of Psychiatry Products
DATE: November 13, 2009

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of ZYPREXA outweigh the risks of weight gain, hyperglycemia and hyperlipidemia associated with all forms of ZYPREXA (olanzapine). In reaching this determination, we considered the following:

- A. Schizophrenia affects about 1% of the population (DSM-IV-TR, APA 2000). The estimated number of patients in the United States with schizophrenia is about 2.4 million (Regier et. al., 1993).

The estimated prevalence of bipolar disorder is about 0.4 to 1.6% (DSM-IV-TR, APA 2000). The estimated number of patients in the United States with bipolar disorder is about 5.7 million (Kessler et. al., 2005).

- B. Schizophrenia is a serious mental illness that includes disorder of thinking, disorganized behavior, deficits in cognition, affect, and social functioning. It is a chronic and debilitating illness that affects many aspects of a patient's life and has

been associated with reduced life expectancy (AACAP 2001, APA 2000a, APA 2004). Adolescents with schizophrenia, like affected adults, have significant impairment, including similar thought disorder, deficits in cognition, affect, and social functioning. Childhood onset schizophrenia is a clinically severe form of schizophrenia in which the disruption in cognitive, linguistic, and social development can occur before the appearance of psychotic symptoms (Jacobsen and Rapoport 1998).

Bipolar disorder is a lifelong psychiatric illness that is characterized by significant morbidity and mortality and is often progressive (Lish et al 1994). Children and adolescents with mania, like affected adults, have significant social impairment leading to conflict within the family, repeated hospitalization, and increased economic burden on the family (Findling et al 2003, Papolos and Papolos 1999). Adolescents with bipolar disorder have an increased risk of substance-abuse disorders (Wilens et al 1999).

- C. Prior to approval of this set of NDA supplements for adolescents with schizophrenia and bipolar disorder, there were there were limited therapeutic options approved for adolescent patients with schizophrenia and bipolar mania. ZYPREXA (olanzapine) demonstrated efficacy as compared to placebo in two clinical trials (one in adolescents with schizophrenia 13 to 17 years of age and one in adolescents with bipolar). ZYPREXA (olanzapine) has been shown to reduce the psychotic signs and symptoms in adolescent patients with schizophrenia and to reduce manic symptoms in adolescent patients with bipolar mania when compared to placebo in clinical trials. ZYPREXA (olanzapine) is approved in the US for the treatment of adult patients with schizophrenia and mania.
- D. The expected duration of therapy with ZYPREXA (olanzapine) in patients who obtain a clinical response will minimally be 6 months to a year, and may be for many years; schizophrenia and bipolar disorder are considered life-long diseases, although the severity of symptoms may vary over time.
- E. Several safety concerns have been identified in the adult clinical trials programs for olanzapine. Known potential safety signals include weight gain, hyperlipidemia, and hyperglycemia. Based on the DPP review of safety data included in the pending pediatric efficacy supplements for schizophrenia and bipolar disorder under NDA-20592/S-040 and 041, the submissions revealed consistent findings with the previously observed safety profile of ZYPREXA (olanzapine) in adult clinical trials.

The current ZYPREXA(olanzapine) label contains Warning language describing an association with hyperglycemia, diabetes mellitus, weight gain, and lipid elevations. The label also contains the standard Boxed Warning regarding increased risk of mortality in elderly patients with dementia related psychosis. This risk has been addressed in the revised Medication Guide for ZYPREXA (olanzapine).

F. ZYPREXA (olanzapine) is not a new molecular entity (NME).

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for ZYPREXA (olanzapine). FDA has determined that ZYPREXA (olanzapine) 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 (olanzapine). FDA has determined that ZYPREXA (olanzapine) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use ZYPREXA (olanzapine).

The elements of the REMS will be a revised Medication Guide and a new timetable for submission of assessments of the REMS.

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

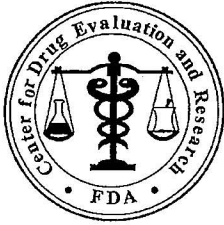
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

KIMBERLY S UPDEGRAFF
11/28/2009

THOMAS P LAUGHREN
11/29/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 6, 2009

To: Thomas Laughren, M.D., Director
Division of Psychiatry Products (DPP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management

From: Jessica M. Diaz, RN, BSN
Patient Product Information Reviewer
Division of Risk Management

Subject: Review of ZYPREXA REMS (originally approved March 19, 2009), submitted with S040 and S041

Drug Name(s): ZYPREXA (olanzapine) tablets

Application Type/Number: NDA 20-592 S040 & 041

Applicant/sponsor: Eli Lilly and Company

OSE RCM #: 2009-1412

This memorandum serves as a review of the ZYPREXA (olanzapine) tablets Risk Evaluation and Mitigation Strategy (REMS) approved March 19, 2009. Eli Lilly and Company submitted the REMS and an updated Medication Guide as part of the proposed labeling to pediatric supplements S040 and S041. DRISK completed a review of the Medication Guide on October 1, 2009. In addition, to the changes to the Medication Guide there are some minor modifications that are needed, specifically to the Timetable for Submission of Assessments for the already approved REMS to ensure clarity around the REMS Assessments due date. The language in the REMS should be revised as follows:

Timetable for Submission of Assessments

- The first assessment is due 18 months from the original approval date of the REMS (September 19, 2010)
- The second assessment is due 3 years from the original approval date of the REMS (March 19, 2012)
- The third assessment is due 7 years from the original approval date of the REMS (March 19, 2016)

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Eli Lilly and Company will submit each assessment so it will be received by the FDA on or before the due dates listed above.

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/s/

JESSICA M DIAZ
10/06/2009

CLAUDIA B KARWOSKI
10/06/2009
concur



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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:

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

Page 2

**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

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

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

DATE: 19 March 2009

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: NDA 21-520/S-012 Symbyax (fluoxetine/olanzapine) Capsules, NDA20-592/S-039 Zyprexa (olanzapine) tablets, NDA 21-086/S-021 Zyprexa (olanzapine) Zydis, 18-936/S-077 Prozac (fluoxetine) tablets

SUBJECT: Medication Guides for Symbyax, Zyprexa, and Prozac

The Division is in the process of evaluating Symbyax (olanzapine and fluoxetine in combination) for the treatment of Treatment Resistant Depression (TRD). Symbyax is a marketed product approved for the acute treatment of depressive episodes of Bipolar I Disorder. At the same time, Zyprexa (olanzapine) and Prozac (fluoxetine) are being evaluated to be used in combination to treat TRD and the acute treatment of depressive episodes of Bipolar I Disorder. The Division determined that modifications to the existing Medication Guide would be necessary for Symbyax secondary to the metabolic changes seen with olanzapine (hyperglycemia, hyperlipidemia, and weight gain) so that patients will be able, in light of these metabolic changes, to make an informed decision about the risks and benefits of the drug.

Having made a decision to include this information in a Medication Guide, and given that Zyprexa and Prozac also have supplements pending to be used together to treat TRD and the acute episodes of Bipolar I Disorder, it became clear that the Division would have to include the information from the updated Symbyax Medication Guide in the Medication Guides for both Zyprexa and Prozac.

For Zyprexa, the Medication Guide is new and was derived from those portions of the Symbyax Medication Guide pertinent to olanzapine. For Prozac, the already existing class Medication Guide for suicidality had to be modified to include the other particular serious and significant concerns for fluoxetine.

In sum, the Division decided to make changes to the Zyprexa and Prozac Medications Guides to ensure that when a patient is treated with both drugs for TRD or depressive episodes of Bipolar I Disorder, they receive the same information from the combination of the two individual product Medication Guides that is presented in the single combination product Medication Guide for Symbyax.

We requested draft Medication Guides for all three products from the sponsor in our August 1, 2008 complete response letter. The sponsor submitted a response to the Agency letter on September 19, 2008 and the review division consulted the Division of Risk Management (DRISK) in the Office of

Surveillance and Epidemiology (OSE) to assist us with editing these prior to negotiation with the sponsor. Although DRISK was consulted early in the process (September 25, 2008), they were unable to provide draft edits to our Medication Guides until much later (February 20, 2009). We had two meetings (February 19, 2009 and March 10, 2009) with DRISK to understand their draft edits to the Medication Guides.

The advice we received from DRISK was useful in helping us to formulate our final documents, and we incorporated many of their suggested changes. However, we did not agree with some of their proposed changes because we felt they significantly detracted from the overall message we intended to send to the patients receiving these products. Specifically, the recommendations from DRISK included adding information from every bullet within the Warnings and Precautions section of labeling in an effort to provide a comprehensive picture of the risk of these drugs. While this seemed reasonable on face, it practically meant that the Medication Guides would be nearly eight pages long, which in our opinion made it a much less likely document to be distributed by pharmacists and read by the patients. In addition, 21CFR 208.20 states that Medication Guides should be written to convey, "the particular serious and significant public health concern that has created the need for a Medication Guide..." and we did not believe that including every warning and precaution, particularly if there was no direct way to communicate risk to the patient, would be consistent with our interpretation of this regulation.

Therefore, we included only the particular serious and significant public health concerns in our versions of the Medication Guides sent to the sponsor for negotiation, and we will include these Medication Guides in any future approval letters for these products.

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/s/

Mitchell Mathis
3/19/2009 12:20:43 PM
MEDICAL OFFICER

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Monday, March 16, 2009 3:30 PM
To: 'Christine Ann Phillips'
Cc: Grewal, Renmeet
Subject: REMS proposal templates for Zyprexa, Symbyax & Prozac

Attachments: Appendix A.pdf

Hi Christine,

Regarding the REMS template we have the following comments from our DRISK team. Please respond by COB, Tuesday, March 17th with an updated template for Symbyax, Zyprexa and Prozac. We have also provided you (in appendix A) the appended Symbyax REMS proposal with track changes and comments below to help you understand the minor track changes.

1. We remind you of your requirement to comply with 21 CFR 208.24

- A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

“Dispense the enclosed Medication Guide to each patient.” or “Dispense the accompanying Medication Guide to each patient.”

- Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.

- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

3. The timetable for submission of assessments will be at minimum at 18 months, 3 years and within the 7th year following the approval of the REMS.

- The REMS assessments should include information needed to assess the effectiveness of the REMS including:

- Patients’ understanding of the serious risks of Symbyax (olanzapine and fluoxetine hydrochloride)

- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

- If you feel the REMS assessment at 7 years of the patient’s understanding of the Medication Guide is not needed because you have determined that serious risks have been adequately identified and assessed, submit a modification to the REMS following the REMS 3 year assessment. The agency will then determine if additional assessments of the patient’s understanding of the Medication Guide are necessary.

4. We recommend submitting a complete description of methodology and the instruments used to measure patient’s understanding of the risks and safe use of Symbyax to FDA 60 days prior to conducting the survey. The submission should include:

- All methodology and instruments that will be used to evaluate the patients’ understanding about the safe use of Symbyax (olanzapine and fluoxetine hydrochloride). This should include, but not be limited to:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients to be surveyed