CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020592Orig1s040s041

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

REMS MEMO – NEW APPROVAL TEMPLATE
October 21, 2009

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.

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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

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF New Drugs
DIVISION OF Psychiatry Products

NDAs:	21-520 (S-012), 20-592 (S-039, S-040, S-041), 21-086 (S-021)
PRODUCTs:	Symbyax (fluoxetine/olanzapine) capsules Zyprexa (olanzapine) tablets Zyprexa Zydis
SPONSOR:	Eli Lilly
REVIEWER:	Mitchell Mathis, M.D.
DATE:	July 31, 2008

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if the FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)(2)]. Section 505-1(a) 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.

ZYPREXA (olanzapine) is approved for the treatment of schizophrenia as well as bipolar mania (monotherapy or in combination with lithium or valproate) in adults. SYMBYAX (olanzapine and fluoxetine in combination) is approved for the treatment of depressive episodes associated with Bipolar Disorder in adults.

The Division of Psychiatry Products (DPP) became aware of new treatment emergent safety signals of hyperglycemia, hyperlipidemia, and significant weight gain associated with olanzapine treatment. These data were presented in recent supplements for Zyprexa to treat adolescent schizophrenia and manic or mixed episodes of Bipolar I Disorder, and in a supplement for SYMBYAX to treat treatment resistant depression. Lilly provided additional data regarding hyperglycemia, hyperlipidemia, and significant weight gain associated with olanzapine treatment in submissions on September 10, 2007, October 4, 2007, November 1, 2007, December 19, 2007, February 1, 2008, February 5, 2008, May 12, 2008, and June 4, 2008. These data indicate that patients across the age spectrum

taking olanzapine are at increased risk of clinically important hyperglycemia, hyperlipidemia, and weight gain.

These new data have led DPP to conclude that olanzapine should be reserved for second line use in adolescents only after patients have failed to respond to already approved products. In addition, DPP has determined that patients (regardless of age and diagnosis) and their caregivers should be provided with a Medication Guide to help them understand these risks and how to manage them (including monitoring requirements for body weight as well as recommended serum glucose and lipid monitoring). 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 and SYMBYAX outweigh the risks. As part of the REMS, DPP has determined that a Medication Guide should be developed to ensure patients and their caregivers are fully informed about the risks of olanzapine use.

A. The number of patients with Schizophrenia or Bipolar Disorder in the United States is estimated to be about 6 million. Treatment resistant depression is estimated to afflict 4 million Americans.

B. Schizophrenia, Bipolar Disorder, and treatment resistant Major Depressive Disorder represent major psychiatric illnesses which if left untreated result in enormous personal, family, and social disability.

C. Use of ZYPREXA AND SYMBYAX to treat these disorders results in better control of symptoms, decreased hospitalizations, and return to more normal function.

D. The expected duration of therapy with ZYPREXA or SYMBYAX is indefinite and may be lifelong.

E. Known serious risks associated with the use of olanzapine include increased mortality and increased risk of stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinisia, orthostatic hypotension, seizures, impaired cognitive and motor function, and hyperprolactinemia.

F. Olanzapine is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ZYPREXA AND SYMBYAX 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 these products. FDA has determined that ZYPREXA AND SYMBYAX are products that have serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use,

ZYPREXA OR SYMBYAX. In addition, patient labeling could help prevent serious adverse effects related to the use of the product.

The Medication Guide is being requested from sponsor due to the new safety information described above, and is will be considered to be part of a REMS. A timetable for submission of assessments of the REMS is also required, and shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved.

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

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Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of New Drugs

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/s/

Thomas Laughren
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MEDICAL OFFICER

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

Date: April 19, 2007

To: Thomas Laughren, M.D., Director
Division of Psychiatric Products, HFD-130

Through: Ellis Unger, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Risk Management Team

Drug Name: Zyprexa (olanzapine)

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

Sponsor: Eli Lilly

OSE RCM#: 2006-1170

Subject: Review of proposed Risk Management Plan, submitted October 30, 2006

1 INTRODUCTION

This review follows a request from the Division of Psychiatric Products (DPP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Management Plan (RMP) for oral olanzapine for use in adolescent populations with Schizophrenia or Bipolar Disorder.

Olanzapine (Zyprexa) is an atypical antipsychotic available as oral tablets, oral disintegrating tablets (Zyprexa Zydis), and as an intramuscular injection. It was originally approved on 9/30/1996 for the treatment of schizophrenia in adults. Olanzapine oral tablets are currently approved for the following indications in adults: treatment of schizophrenia, treatment of acute mixed or manic episodes associated with bipolar I disorder, maintenance monotherapy for bipolar I disorder, and combination therapy (with lithium or valproate) for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder.

Two efficacy supplements were submitted in the pediatric adolescent population (ages 13-17 years old). The Sponsor proposes the following indications, "Schizophrenia in adolescents" and "Acute mixed or manic episodes associated with bipolar I disorder in adolescents." The current proposed indications are based on two pivotal studies (HGIN for adolescent schizophrenia and HGIU for adolescent bipolar disorder) and a pharmacokinetic study in the adolescent population.

2 MATERIALS REVIEWED

- Risk Management Plan For Zyprexa for oral Olanzapine for Use in Adolescent Populations with Schizophrenia or Bipolar Disorder, Manic or Mixed Episodes, submitted by Eli Lilly
- Alfaro C. Medical Officer's Clinical Review of Zyprexa (olanzapine) NDA 20-592/SE5-040: Treatment of Bipolar I Disorder in Adolescents; review completion date 4/6/07.
- Alfaro C., Medical Officer's Clinical Review of Zyprexa (olanzapine) NDA 20-592/SE5-041: Treatment of Schizophrenia in Adolescents; review completion date 4/6/07.
- Proposed Zyprexa Physician Labeling, submitted October 30, 2006.
- Guidance documents:
    - Development and Use of Risk Minimization Action Plans http://www.fda.gov/cder/guidance/6358fnl.pdf
    - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment http://www.fda.gov/cder/guidance/6359OCC.pdf

3 RESULTS OF REVIEW

3.1 Safety Risks

3.1.1 Sponsor's Safety Concerns

The Sponsor specifically identified weight gain, sedation, and hyperprolactenemia as risks associated with olanzapine occurring at a higher frequency in the adolescent clinical trial database in comparison to the adult clinical trial database. Hepatic changes were also identified as an identified risk by the Sponsor. Because of the different reference ranges used for hepatic laboratory analyses in adolescent and adult patients, no analyses were performed to compare hepatic results between adolescent and adult patients. Other safety issues including glucose dysregulation and dyslipidemia occurred at lower frequencies in adolescents in comparison to adults. The potential drug interactions with olanzapine adolescents are thought to be similar as in adults.

Information provided in the Sponsor's safety specification regarding the identified safety issues are summarized in the table below.

Safety Risk	Clinical Trials	Postmarketing
weight gain	• Significantly higher increases in weight gain for olanzapine	341/1450 case reports in adolescents had at least one

Safety Risk	Clinical Trials	Postmarketing
	compared to placebo at every visit • Greater incidence of treatment emergent weight gain ≥ 7% (Placebo controlled trials: 43.5% OLA vs 6.8% PLA). In the entire adolescent database 65% of OLA treated adolescents had weight gain ≥ 7% • Higher incidences of weight gain ≥ 7% in adolescents than adults (65% adolescents versus ~36% adults)	MedDRA term related to weight gain.
sedation	• Overall 158 of 454 (38%) of olanzapine treated patients reported at least 1 sedation event. • Adolescents reported sedation 1.9x and somnolence 1.7x more frequently than adults	227/1450 case reports in adolescents had at least one MedDRA term related to sedation
hyperprolactinemia	• 55% of all olanzapine exposed patients had abnormally high prolactin levels, one dc'd txt • Higher incidence of high prolactin levels in adolescents (23% vs -4% in adults)	116/1450 case reports in adolescents had at least one MedDRA term related to hyperprolactinemia
hepatic changes	• No Hy's rule cases • Significantly higher incidence of abnormal elevations in AST, ALT in olanzapine vs placebo treated patients. • No analyses comparing adolescents to adults	• One fatal case – adolescent male found dead; autopsy revealed hepatic steatosis • 92/1450 case reports in adolescents had at least one hepatic-related MedDRA term • 39% of these had clinically significant elevations (met definition of Hy's rule ALT/AST 3x ULN and TB 1.5 x ULN)
glucose dysregulation	parameters higher in adults in clinical trials	total of 95 postmarketing cases with AEs related to glucose dysregulation; 6 were fatal – the cause of death were reported in 3 diabetic ketoacidosis (2), necrotizing pancreatitis (1)
dyslipidemia	Clinical trials - Triglycerides higher in adolescents, LDL higher in adults	34 lipid related postmarketing reports

3.1.2 DPP Safety Concerns

The DPP medical officer, Cara Alfaro, reiterates the above concerns in her clinical reviews of the supplemental applications. According to the medical officer's review, the most common adverse events (> 5%, olanzapine > placebo) occurring in the pivotal trials were weight increased (30%), somnolence (25%), increased appetite (24%), sedation (19%), headache (17%), fatigue (10%), dizziness (7%), dry mouth (6%) and pain in extremity (5%). The adverse event profiles were similar between the two studies.

She considered weight gain, liver function test abnormalities, hyperprolactinemia, hypertriglyceridemia, and hypercholesterolemia to be significant safety signals.

3.2 Sponsor's Proposed Risk Management Plan

3.2.1 Pharmacovigilance Activities

Eli Lilly proposes the following pharmacovigilance activities:

- Routine pharmacovigilance of spontaneously reported cases will be conducted for oral olanzapine in adolescents. The Sponsor will target specific adverse events for targeted follow-up. These terms are the same as FDA's DME list as well as additional AE terms specific for olanzapine (adverse pregnancy outcomes, bradycardia with serious outcome, convulsions, eosinophila with a serious outcome, hematological effects, hepatic effects, hyperglycemia/diabetes mellitus/ketoacidosis, hypotension, hypertriglyceridemia/hyperlipidemia, hypotension, overdose, pancreatitis, QT interval prolonged, respiratory depression, sinus pause, sudden death, thromboembolic events, and withdrawal symptoms). It does not appear that the company plans enhanced surveillance of spontaneously reported adverse events involving pediatric or adolescents patients.
- Long term Safety Study – The Sponsor proposes a longterm safety study in adolescent patients with schizophrenia or bipolar disorder to estimate the incidence and prevalence of identified and potential risks of olanzapine in adolescents. The study is still in the planning phase and plans to provide an update of this planned study in the May 2007 PSUR.
- Pharmacoepidemiology Study – The Sponsor proposes a retrospective cohort analysis of a large US health claims database to estimate the incidence and prevalence of diabetes mellitus and dyslipidemia among adolescent patients with schizophrenia or bipoloar disorder compared with the general adolescent population. The Sponsor is currently developing a protocol for this study.

3.2.2 Risk Minimization Activities

Eli Lilly intends to utilize product labeling and customary prescriber education as the risk minimization tools to address all risks in adolescents specified in their submission. They did not propose a Risk Minimization Action Plan (RiskMAP) to address any of the identified risks.

4 DISCUSSION AND CONCLUSION

The Sponsor's goals and overall proposal are consistent with an enhanced pharmacovigilance and routine risk minimization activities. The proposal places particular emphasis on identifying the incidence and prevalence of identified risks and potential risks in adolescents in the postmarketing setting. At present, Zyprexa is marketed with an education-based risk management plan to address the potential medication errors with Zyrtec. There is no risk management plan or RiskMAP to address the safety issues identified in the Sponsor's submission or in the clinical review.

Based on the clinical review and email correspondence with the project manager, DPP plans to take a non-approval action for the schizophrenia indication in adolescents because the efficacy results were only statistically significant in patients enrolled in sites from Russia driven primarily by a low placebo response. DPP is also planning an approvable action for the bipolar indication because a number of requests for safety information and other analyses are required for approval.

Because additional data will be required to assess the primary safety issues described above, OSE will defer comment on the sponsor's submitted risk management plan at this time. A final discussion on the appropriateness of a RMP or Risk MAP will be undertaken after the sponsor submits a complete response to the action taken decided by the FDA.

OSE Risk Management Team
Claudia Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO
Mary Dempsey, Risk Management Program Coordinator, OSE-IO

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/s/

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DRUG SAFETY OFFICE REVIEWER

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