CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020592Orig1s040s041

OTHER REVIEW(S)

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 1, 2009
To:	Thomas Laughren, MD, Director
	Division of Psychiatry Products (DPP)
Through:	Claudia Karwoski, PharmD, Director
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Patient Product Information Reviewer, Acting Team Leader
	Division of Risk Management
From:	Sharon R. Mills, BSN,RN, CCRP
	Senior Patient Product Information Reviewer, Acting Team Leader
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide),
Drug Name(s):	Zyprexa (olanzapine) Tablet and Zyprexa Zydis (olanzapine) Tablet, Orally Disintegrating
Application Type/Number:	NDA 20-592
Submission Number:	S-040 and S-041
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2009-1412

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 Zydis (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 Zydis (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 Zydis (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.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON R MILLS
10/01/2009

CLAUDIA B KARWOSKI
10/01/2009
concur

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:	September 3, 2009
To:	M. Dianne Murphy, MD Director, Office of Pediatric Therapeutics (OPT), OIASI Office of the Commissioner CDR Lisa L. Mathis, USPHS, MD Associate Director, Pediatric and Maternal Health Team (PMHS) Office of New Drugs
Thru:	Laura Governale, Pharm.D., MBA Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Hina Mehta, Pharm.D. Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone) Drug Use Review
Drug Name(s):	Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone)
Application Type/Number:	Various
Applicant/sponsor:	Various
OSE RCM #:	2009-1004

EXECUTIVE SUMMARY

This review examines drug utilization patterns for six atypical antipsychotics, Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone), in the pediatric population (age 0-2 years, 3-6 years, 7-12 years, 13-17 years, and 18+ years) from year 2004 through June 2009. Since approximately (b) (4) of the atypical antipsychotics were sold to U.S. outpatient retail settings during year 2008, this review focuses on the outpatient setting.

- All of the antipsychotic agents studied except for (b) (4) had an increase in the number of dispensed prescriptions over the past 5 years.
- Dispensed prescriptions for (b) (4) increased the most by approximately (b) (4)% from year 2004 to year 2008.
- Antipsychotic use among pediatric patients has increased by (b) (4)% over the 5 years. The greatest increase was seen for (b) (4) during this time period.
- (b) (4) had the most prescriptions dispensed (b) (4)%) to pediatric patients (0-17 years) and had a greater amount of use in younger children compared to the other antipsychotics. (b) (4) had the second highest number of dispensed prescriptions (b) (4)%) in the pediatric population.
- In year 2008, (b) (4) unique patients received a prescription for (b) (4) followed by (b) (4) with (b) (4) and (b) (4) with (b) (4).
- For all of the agents studied, the majority of prescriptions dispensed to patients over the entire study period were prescribed by Psychiatrists.
- In children aged 7-12 years old, concomitant use with stimulant medications were most common for those already on (b) (4) Mood stabilizing agents, other antipsychotics and antidepressants were the most common concomitant products for (b) (4) in this age group as well as for older age groups.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone) in the pediatric population as well as in the adult population for years 2004 through 2008 and year-to-date June 2009.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (***see Appendix 2***) were used to determine the setting in which these six atypical antipsychotic products were sold. Sales of these products by number of bottles, packets of pills (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for year 2008 (***data not provided***).[1] During the review period, retail settings (chain stores, independent pharmacies, and food stores) accounted for the majority of atypical antipsychotic product sales (b) (4)% or greater). Distribution towards non-retail pharmacy settings ranged from (b) (4)% during year 2008. The long term care setting within the non-retail channels received the majority of atypical antipsychotic sales. Mail order distribution ranged from (b) (4)% for the six agents analyzed. Thus, we examined outpatient utilization patterns. Mail order and long term care data are not included in this analysis.

[1] IMS Health, IMS Nationals Sales Perspectives™, Years 2004-2008, Data extracted Aug 2009, Source file: 0908apsy.DVR

2.2 DATA SOURCES USED

Outpatient use and patient demographics (stratified by ages 0-2 years, 3-6 years, 7-12 years, 13-17 years, and 18+ years) were measured from SDI Vector One®: National (VONA) and Total Patient Tracker (TPT) (***Appendix 2***). Indications for use were obtained from the SDI's Physician's Drug and Diagnosis Audit (PDDA) (***Appendix 2***). From these data sources, estimates of the number of prescriptions dispensed, the number of patients who received a prescription for Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone), and the number of drug mentions by office-based physicians, were obtained for years 2004-2008 and year-to-date June 2009.

3 RESULTS

3.1 DISPENSED PRESCRIPTIONS

Figure 1 in Appendix 1 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone). During year 2008, nearly (b) (4) prescriptions were dispensed for these products, an increase of (b) (4)% from approximately (b) (4) dispensed prescriptions in year 2004. Approximately (b) (4) prescriptions were dispensed for (b) (4)% of market) followed by (b) (4)% of market) and (b) (4)% of market) with (b) (4) prescriptions, respectively. All of the agents had an increase in the number of prescriptions dispensed in the past 5 years except for (b) (4) which decreased by abou (b) (4) during the same time period. Dispensed prescriptions for (b) (4) increased by (b) (4)% from year 2004 (b) (4) prescriptions) to year 2008 ((b) (4) prescriptions) followed by (b) (4) with (b) (4)% increase and (b) (4) with (b) (4)% increase.

3.2 DISPENSED PRESCRIPTION BY PEDIATRIC AGE GROUPS

Antipsychotic use in the pediatric population (0-17 years) has increased (b) (4)% in the past 5 years (Figure 2: Appendix 1). The greatest increase was seen for (b) (4)%. In year 2008, of the six agents analyzed, (b) (4) had the most prescriptions dispensed to pediatric patients aged 0-17 years (b) (4)% of all (b) (4) dispensed to pediatric patients versus adults (b) (4) risperidone prescriptions), followed by (b) (4)%; (b) (4) prescriptions), (b) (4) prescriptions), (b) (4) prescriptions), (b) (4) prescriptions), and (b) (4) prescriptions). Analysis of pediatric sub-age groups revealed that the majority of antipsychotic use during year 2008 was among those aged (b) (4) years; (b) (4) . (b) (4), on the other hand, was most commonly dispensed to pediatric patients aged 7-12 years, accounting for (b) (4)% of dispensed prescriptions. Prescriptions dispensed to pediatric patients aged 0-2 years and 3-6 years accounted for less than (b) (4) of the combined total dispensed prescriptions for all six agents with the exception of (b) (4) in which (b) (4) of prescriptions are dispensed to pediatrics aged 3-6 years (Table 1: Appendix 1).

3.3 PATIENT-LEVEL DATA

Trends for patient data were similar to that of prescription data. In year 2008, approximately (b) (4) patients received a prescription for these selected antipsychotic agents in the outpatient retail pharmacy setting, an increase of (b) (4)% from (b) (4) patients in year 2004. Approximately, (b) (4) unique patients received a prescription for (b) (4) respectively. As with dispensed prescription data, analysis of pediatric sub-age groups revealed similar trends in use with patient-level data (Table 2: Appendix 1).

3.4 DIAGNOSES ASSOCIATED WITH USE

We also examined the most common diagnosis associated with the use of Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone) as reported by office-based physician practices in the U.S. (Appendix 1: Tables 3a-3e). Diagnoses among the pediatric age groups 0-2 years and 3-6 years were below the acceptable count allowable to provide a reliable estimate. Among the pediatrics aged 7-12 years "(b) (4) was the most common diagnosis associated with a mention of aripiprazole with approximately (b) (4)% of all mentions for that age group from year 2004 through year to date June 2009 followed by (b) (4) with (b) (4)%. For risperidone, the most common diagnosis among pediatrics aged 7-12 years was "(b) (4) with (b) (4)% followed by "(b) (4) and (b) (4) with (b) (4)%, respectively. For adolescents aged 13-17 years the most common diagnosis associated with a mention for aripiprazole, quetiapine, olanzapine, and ziprasidone was "(b) (4) were the most common diagnosis for risperidone and paliperidone, respectively, for this age group.

3.5 PEDIATRIC DISPENSED PRESCRIPTION BY PRESCRIBING SPECIALTY

Table 4a-4f in Appendix 1 shows the total number of prescriptions dispensed for Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone) by patient age and physician specialty. The majority of prescriptions dispensed to patients were prescribed by Psychiatrists over the entire study period for the pediatric as well as adult age groups for all of the agents studied. During year 2008, Nurse Practitioners were the second most common prescriber for aripiprazole, ziprasidone and paliperidone for both adult and pediatric age groups. For risperidone, quetiapine, and olanzapine, GP/FM/DO[2] were the second most common prescribers of these medications to both adult and pediatric age groups.

3.6 CONCOMITANT USE

Tables 5a-5e in Appendix 1 shows the total number of health care physician mentions where one of the select antipsychotics were used concomitantly with another class of products to treat the same diagnosis. Concomitancy for all of the agents among the pediatric age groups 0-2 years and 3-6 years were below the acceptable count allowable to provide a reliable estimate of use. In those aged 7-12 years old, concomitant use with stimulant medications were most common for (b) (4). For (b) (4) mood stabilizing agents such as anticonvulsants, other antipsychotics, and antidepressants were commonly used together to treat the same diagnosis. In those aged 13-17 years, concomitant use with mood stabilizing agents, other antipsychotics and antidepressants were the most common concomitant class of products for all antipsychotic agents studied.

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated Abilify® (aripiprazole), Geodon® (ziprasidone), Seroquel® (quetiapine), Zyprexa® (olanzapine), Risperdal® (risperidone), Invega® (paliperidone) are distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

SDI's Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies,

[2] GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

the small sample size can make these data unstable, particularly if use is not common in the pediatric population. SDI recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

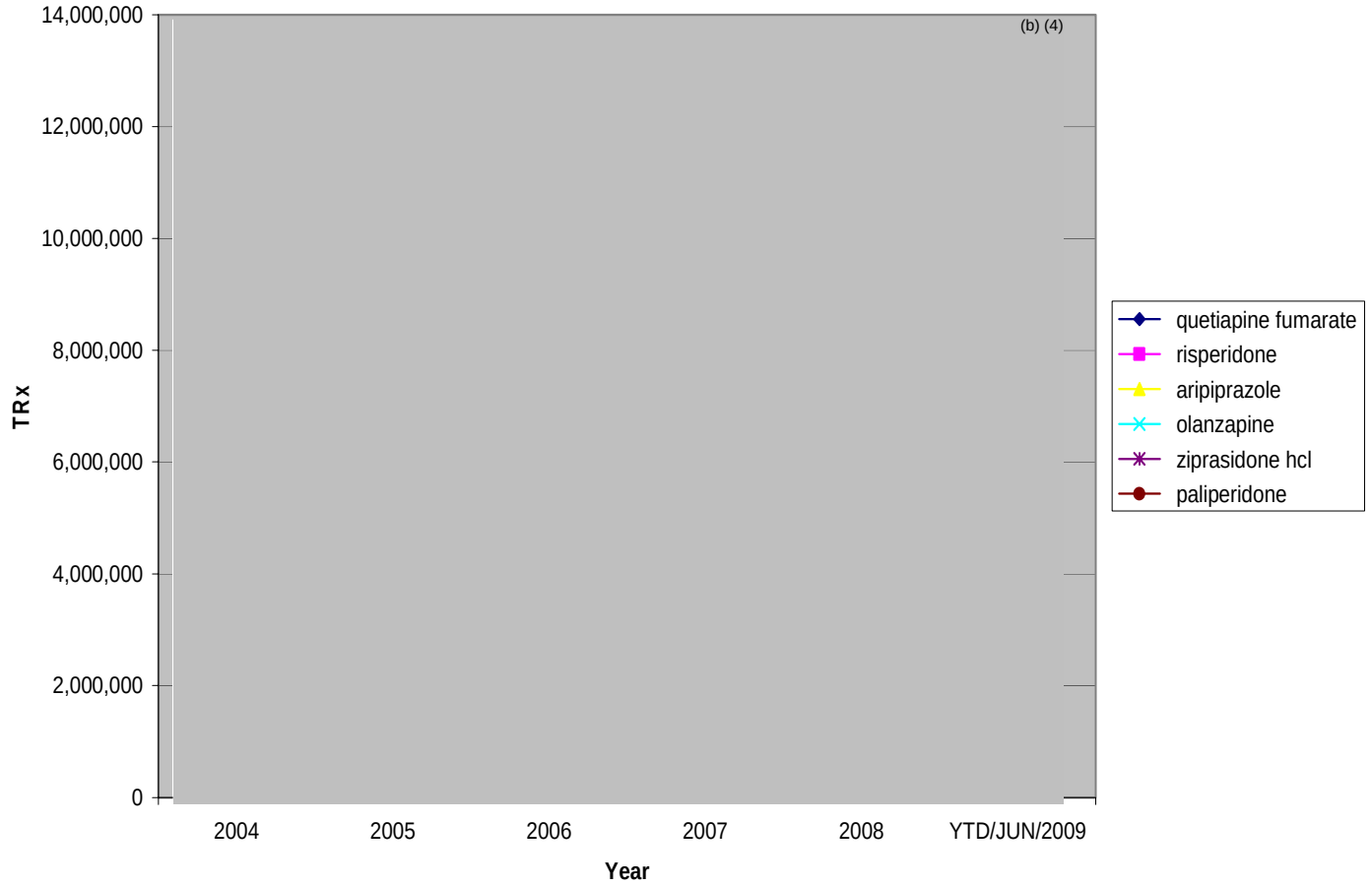
5 CONCLUSIONS

All of the antipsychotic agents studied except for [redacted] had an increase in the number of dispensed prescriptions over the past 5 years. Dispensed prescription for [redacted]) increased the greatest amount [redacted]%). Antipsychotic use among pediatric patients aged 0-17 years have increased [redacted]% over the past 5 years. Use among pediatrics aged 0-2 years and 3-6 years accounted for less than [redacted] of the total for each of the antipsychotic agents studied. [redacted] was the most commonly dispensed atypical antipsychotic agent among pediatrics, especially those aged 7-12 years. [redacted] pediatric prescriptions are most commonly dispensed to adolescents aged 13-17 years. Trends for patient data were similar to that of prescription data. Psychiatrists prescribe the majority of antipsychotic prescriptions dispensed. In younger children (7-12 years old), concomitant use with stimulant medications were most common for [redacted]. Mood stabilizing agents, other antipsychotics and antidepressants were the most common concomitant class of products used with [redacted] in this age group as well as for older age groups.

APPENDICES

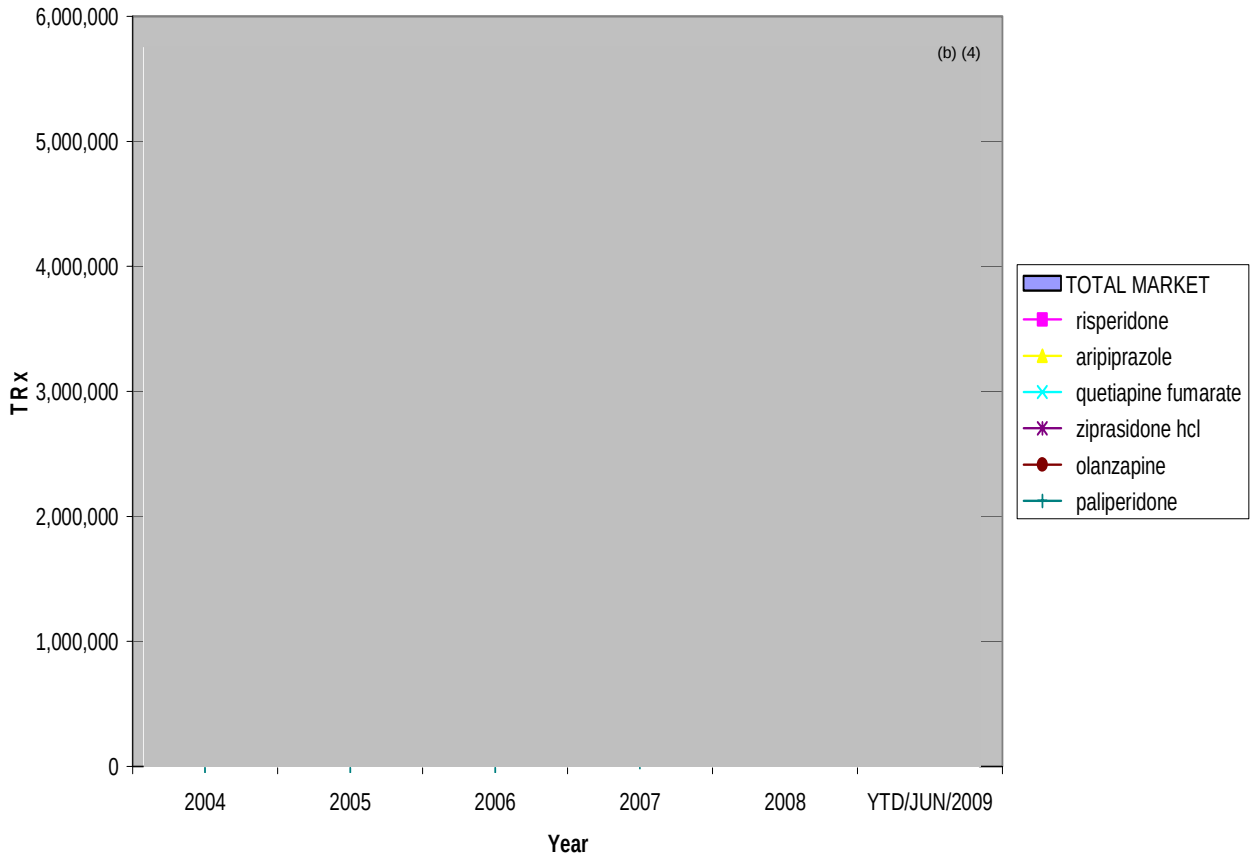
APPENDIX 1: Figures and Tables

Figure 1: Total Number of Dispensed Prescriptions for 6 Atypical Antipsychotic Agents Through U.S. Outpatient Retail Pharmacies, Years 2004-2008 and YTD Jun 2009



Source: SDI: Vector One®: National. Data Extracted 8-4-09. File: VONA 2009-1004 TRx 8-4-09.qry

Figure 2: Total Number of Prescriptions Dispensed for 6 Atypical Antipsychotics Among Pediatrics 0-17 Years Through U.S. Outpatient Retail Pharmacies, 2004-2008 and YTD Jun 2009



Source: SDI: Vector One: National. Data Extracted 9-1-09. File: VONA 2009-1004 TRx by Ages 0-17 only 9-1-09.qry

Table 1: Total Number of Prescriptions Dispensed for Atypical Antipsychotics Through U.S. Outpatient Retail Pharmacies, Years 2004-2008 and YTD 2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	(b) (4)											(b) (4)
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
Age UNSPEC.												

Source: SDI: Vector One®: National. Data Extracted 8-4-09. File: VONA 2009-1004 TRx by Age 8-4-09.qry

Table 2. Total Number of Unique Patients Receiving a Prescription for Atypical Antipsychotics Through U.S. Outpatient Retail Pharmacies, 2004-2008 and YTD 2009

	2004		2005		2006		2007		2008		YTD/Jun/2009	
	N	%	N	%	N	%	N	%	N	%	N	%
Total Market	(b) (4)											(b) (4)
Age 0 - 2												
Age 3 - 6												
Age 7 - 12												
Age 13 - 17												
Age 18+												
Age Unknown												

Source: SDI: Total Patient Tracker. Data Extracted 8-5-09 and 8-6-09. Files: TPT 2009-1004 Abilify Patient Count by Age 8-5-09.xls, TPT 2009-1004 Abilify Patient Count by Age YTD 2009 8-5-09.xls, TPT 2009-1004 Geodon Patient Count by Age 8-5-09.xls, TPT 2009-1004 Geodon Patient Count by Age YTD 2009 8-5-09.xls, TPT 2009-1004 Invega Patient Count by Age 8-5-09.xls, TPT 2009-1004 Invega Patient Count by Age YTD 2009 8-5-09.xls, TPT 2009-1004 Risperdal Patient Count by Age 8-5-09.xls, TPT 2009-1004 Risperdal Patient Count by Age YTD 2009 8-5-09.xls, TPT 2009-1004 Seroquel Patient Count by Age 8--5-09.xls, TPT 2009-1004 Seroquel Patient Count by Age YTD 2009 8-5-09.xls, TPT 2009-1004 Total Patient Count 8-6-09.xls, TPT 2009-1004 Total Patient Count YTD 2009 8-6-09.xls, TPT 2009-1004 Zyprexa Patient Count by Age 8-5-09.xls, TPT 2009-1004 Zyprexa Patient Count by Age YTD 2009 8-5-09.xls

Table 3a. Most Common Indications by Age Associated with the Use of Atypical Antipsychotics in Office-Based Practice Settings, 2004-2008 and YTD 2009

	Uses (000)	*Share (%)*
TOTAL MARKET	(b) (4)	
quetiapine fumarate		
(b) (4)		

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 8-4-09. File: PDDA 2009-1004 Dx4 by Age 8-4-09.qry

Table 3b. Most Common Indications by Age Associated with the Use of Atypical Antipsychotics in Office-Based Practice Settings, 2004-2008 and YTD 2009

	Uses (000)	Share (%)
aripiprazole	(b) (4)	
		(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 8-4-09 File: PDDA 2009-1004 Dx4 by Age 8-4-09 qry

Table 3c. Most Common Indications by Age Associated with the Use of Atypical Antipsychotics in Office-Based Practice Settings, 2004-2008 and YTD 2009

	Uses (000)	Share (%)
risperidone	(b) (4)	
		(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 8-4-09 File: PDDA 2009-1004 Dx4 by Age 8-4-09 qry

Table 3d. Most Common Indications by Age Associated with the Use of Atypical Antipsychotics in Office-Based Practice Settings, 2004-2008 and YTD 2009

	Uses (000)			Share (%)		
olanzapine	(b) (4)					
						(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 8-4-09. File: PDDA 2009-1004 Dx4 by Age 8-4-09.qry

Table 3e. Most Common Indications by Age Associated with the Use of Atypical Antipsychotics in Office-Based Practice Settings, 2004-2008 and YTD 2009

	Uses (000)	Share (%)
ziprasidone hcl	(b) (4)	
		(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 8-4-09 File: PDDA 2009-1004 Dx4 by Age 8-4-09 qry

Table 4a. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET												(b) (4)
Abilify (aripiprazole)												
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
PED												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run. File: Copy of VONA Custom_Spec by Age_HMehta081309.xls

Table 4b. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %
Geodon (ziprasidone)												(b) (4)
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
PA												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run. File: Copy of VONA Custom_Spec by Age_HMehta081309.xls

Table 4c. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
Invega (paliperidone)												(b) (4)
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
PA												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run. File: Copy of VONA Custom_Spec by Age_HMehta081309.xls

Table 4d. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
Risperdal (risperidone)												(b) (4)
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
PED												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run. File: Copy of VONA Custom_Spec by Age_HMehta081309.xls and VONA Custom_Spec by Age_HMehta081709_v2.xls

Table 4e. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %
Seroquel (quetiapine)												(b) (4)
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NEURO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run. File: Copy of VONA Custom_Spec by Age_HMehta081309.xls

Table 4f. Estimated Number of Prescriptions Dispensed for Atypical Antipsychotics by Patient Age and Top 5 Physician Specialty, Years 2004 -2008 and YTD/Jun/2009

	2004		2005		2006		2007		2008		YTD/JUN/2009	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%
Zyprexa (olanzapine)	(b) (4)											
PSYCH												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
GP/FM/DO												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
IM												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
NP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
UNSPEC												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
HOSP												
Age 0-2												
Age 3-6												
Age 7-12												
Age 13-17												
Age 18+												
All Others												

Source: SDI: Vector One®: National. Custom Run: File: Copy of VONA Custom_Spec by Age_HMehta081309.xls

Table 5a. Total Number of Mentions for Atypical Antipsychotics used Concomitantly with Another Class of Products to Treat the Same Diagnosis Through U.S. Outpatient Retail Pharmacies, Jan 2004 - June 2009

	Occur (000)	*Share %*
TOTAL MARKET	(b) (4)	
quetiapine fumarate		
	(b) (4)	

Source: SDI: Physician Drug and Diagnosis Audit. File: PDDA 2009-1004 Concomitant Class 8-28-09.qry

Table 5b. Total Number of Mentions for Atypical Antipsychotics used Concomitantly with Another Class of Products to Treat the Same Diagnosis Through U.S. Outpatient Retail Pharmacies, Jan 2004 - June 2009

	Occur (000)	*Share %*
risperidone	(b) (4)	(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit. File: PDDA 2009-1004 Concomitant Class 8-28-09.qry

Table 5c. Total Number of Mentions for Atypical Antipsychotics used Concomitantly with Another Class of Products to Treat the Same Diagnosis Through U.S. Outpatient Retail Pharmacies, Jan 2004 - June 2009

	Occur (000)		*Share %*	
aripiprazole	(b) (4)			(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit. File: PDDA 2009-1004 Concomitant Class 8-28-09.qry

Table 5d. Total Number of Mentions for Atypical Antipsychotics used Concomitantly with Another Class of Products to Treat the Same Diagnosis Through U.S. Outpatient Retail Pharmacies, Jan 2004 - June 2009

	Occur (000)	*Share %*
olanzapine	(b) (4)	(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit. File: PDDA 2009-1004 Concomitant Class 8-28-09.qry

Table 5e. Total Number of Mentions for Atypical Antipsychotics used Concomitantly with Another Class of Products to Treat the Same Diagnosis Through U.S. Outpatient Retail Pharmacies, Jan 2004 - June 2009

	Occur (000)		*Share %*	
ziprasidone hcl	(b) (4)			(b) (4)

Source: SDI: Physician Drug and Diagnosis Audit. File: PDDA 2009-1004 Concomitant Class 8-28-09.qry

Appendix 2: Database Descriptions

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

SDI uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

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/s/

HINA S MEHTA
09/10/2009

LAURA A GOVERNALE
09/10/2009
Cleared by data vendors for PAC background package.

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:	April 17, 2009
To:	Mark Ritter, Medical Officer Division of Psychiatry Products Office of New Drugs
Through:	Laura Governale, PharmD, MBA Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Hina Mehta, PharmD Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Total number of prescriptions and patients for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone)
Drug Name(s):	Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone)
Application Type/Number:	Various
Applicant/sponsor:	Various
OSE RCM #:	2009-439

1 INTRODUCTION

The Division of Psychiatry Products (DPP) is preparing for a presentation at the PDAC meeting. The committee will be asked to vote on whether or not Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) have been shown to be effective and acceptably safe for pediatric indications. In support of that presentation , the Division of Epidemiology (DEPI) has been requested to provide prescription and patient utilization data in the pediatric population for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone), for years 2004 through 2008.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

The IMS Health, IMS National Sales Perspectives™ (see Appendix 1 for database descriptions) was used to determine the various retail and non-retail channels of distribution for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone).[i] The examination of wholesale sales data by eaches (packets, bottles, etc.) in year 2008 indicate that the majority of distribution for most of these products is toward outpatient pharmacy settings ((b) (4)% or greater). Outpatient pharmacy settings include chain, independent, and food stores with pharmacies. Distribution towards non-retail pharmacy settings ranged from (b) (4)% during year 2008. The long term care setting within the non-retail channels received the majority of (b) (4) sales. Mail order distribution ranged from (b) (4)% for the three agents analyzed. Thus, we examined outpatient utilization patterns. Mail order and long term care data are not included in this analysis.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions by product using SDI, Vector One®: National (VONA) (see Appendix 1 for full description) for calendar years 2004 through 2008. We also examined the number of patients who received a prescription for quetiapine, olanzapine, or ziprasidone products using SDI, Vector One®: Total Patient Tracker (TPT) for calendar years 2004 through 2008. Diagnosis associated with the use of these products, as reported by office-based physicians, were determined using SDI's Physician Drug and Diagnosis Audit (PDDA) for calendar years 2002 through 2008.

3 DATA

3.1 OUTPATIENT DISPENSED PRESCRIPTIONS

Table 1 in Appendix 2 shows the total number of prescriptions dispensed in the outpatient retail setting (mail order excluded) for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone). During year 2008, approximately (b) (4) prescriptions were dispensed for (b) (4) followed by (b) (4) prescriptions, respectively. Both (b) (4) products realized an increase in the number of

[i] IMS Health, IMS Nationals Sales Perspectives™, Years 2004-2008. Data extracted 4-1-09. File: 0904psyc.dvr

dispensed prescriptions in the past 5 years except for [redacted] which decreased by about [redacted] during the time period. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than [redacted] of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately [redacted] of dispensed prescriptions of [redacted] followed by [redacted] respectively.

3.2 PATIENT COUNT

Trends for patient data were similar to that of prescription data (Appendix 2: Table 2). During year 2008, approximately [redacted] patients received a prescription for [redacted] while [redacted] patients received a prescription for [redacted] and [redacted] received [redacted] Pediatric patients aged 0-12 years accounted for less than [redacted] of patients receiving a prescription for each of the agents studied. Adolescents aged 13-17 years accounted for approximately [redacted] of patients receiving a prescription for [redacted] with [redacted] respectively.

3.3 DIAGNOSIS ASSOCIATED WITH USE

We also examined the most common diagnosis associated with the use of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) as reported by office-based physician practices in the U.S. (Appendix 2: Tables 3a, 3b, and 3c). [redacted] was the most common diagnosis associated with the use of quetiapine with approximately [redacted] of all uses in year 2008 followed by "[redacted] with [redacted] For olanzapine and ziprasidone the most common diagnosis was "[redacted], respectively, followed by [redacted]%, respectively.

3.4 PRESCRIBER SPECIALTY

Table 4 in Appendix 2 shows the total number of prescriptions dispensed for Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) by physician specialty. The majority of prescriptions dispensed for all three were prescribed by Psychiatrists [redacted] for quetiapine, [redacted] for olanzapine, and [redacted] for ziprasidone) over the entire study period. Unspecified physicians prescribed approximately [redacted]% of prescriptions dispensed for all three agents during year 2008. Approximately [redacted] of prescriptions dispensed were prescribed by General Practice/Family Medicine/Doctor of Osteopathy for both quetiapine and olanzapine and [redacted] for ziprasidone during year 2008.

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for

the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

5 CONCLUSIONS

The majority of sales of Seroquel® (quetiapine), Zyprexa® (olanzapine), and Geodon® (ziprasidone) were to outpatient retail pharmacy settings. During year 2008, approximately (b) (4) prescriptions were dispensed for (b) (4) followed by (b) (4) prescriptions, respectively. Prescriptions dispensed to pediatric patients aged 0-12 years accounted for less than (b) (4) of the total dispensed prescriptions for all three agents. Adolescents aged 13-17 years accounted for approximately (b) (4) of dispensed prescriptions of (b) (4) followed by (b) (4), respectively. The trends for patient data were similar to prescription data. The most common diagnosis associated with the use of the three agents is (b) (4) Psychiatrists were the most common prescribers for all three of the agents studied.

APPENDIX 1: DATABASE DESCRIPTIONS

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

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Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

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SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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6 APPENDIX 2: TABLES AND FIGURES

Table 1. Total Number of Dispensed Prescriptions for Selected Antipsychotic Agents by Patient Age Through U.S. Outpatient Retail Phamacies, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	(b) (4)									(b) (4)

Source: SDI. Vector One®: National. Extracted 4-1-09. File: VONA 2009-439 TRx by Age 4-1-09.qry

Table 2. Total Number of Unique Patients Receiving a Prescription for Selected Antipsychotic Agents by Patient Age Through U.S. Outpatient Retail Phamacies, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***	**TRxs**	***Share***
	N	***%***	**N**	***%***	**N**	***%***	**N**	***%***	**N**	***%***
[redacted]										(b) (4)

Source: SDI. Vector One®: Total Patient Tracker. Extracted 4-1-09. File: TPT 2009-439 Geodon Patient Count 4-1-09.xls, TPT 2009-439 Seroquel Patient Count 4-1-09.xls and TPT 2009-439 Zyprexa Patient Count 4-1-09.xls

Table 3a. Most Common Indications by Age Associated With the Use of Quetiapine in Office-Based Practice Settings, 2004-2008

	2004		2005		2006		2007		2008	
	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %	Uses (000)	*Share* %
(b) (4)										

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 3b. Most Common Indications by Age Associated With the Use of Olanzapine in Office-Based Practice Settings, 2004-2008

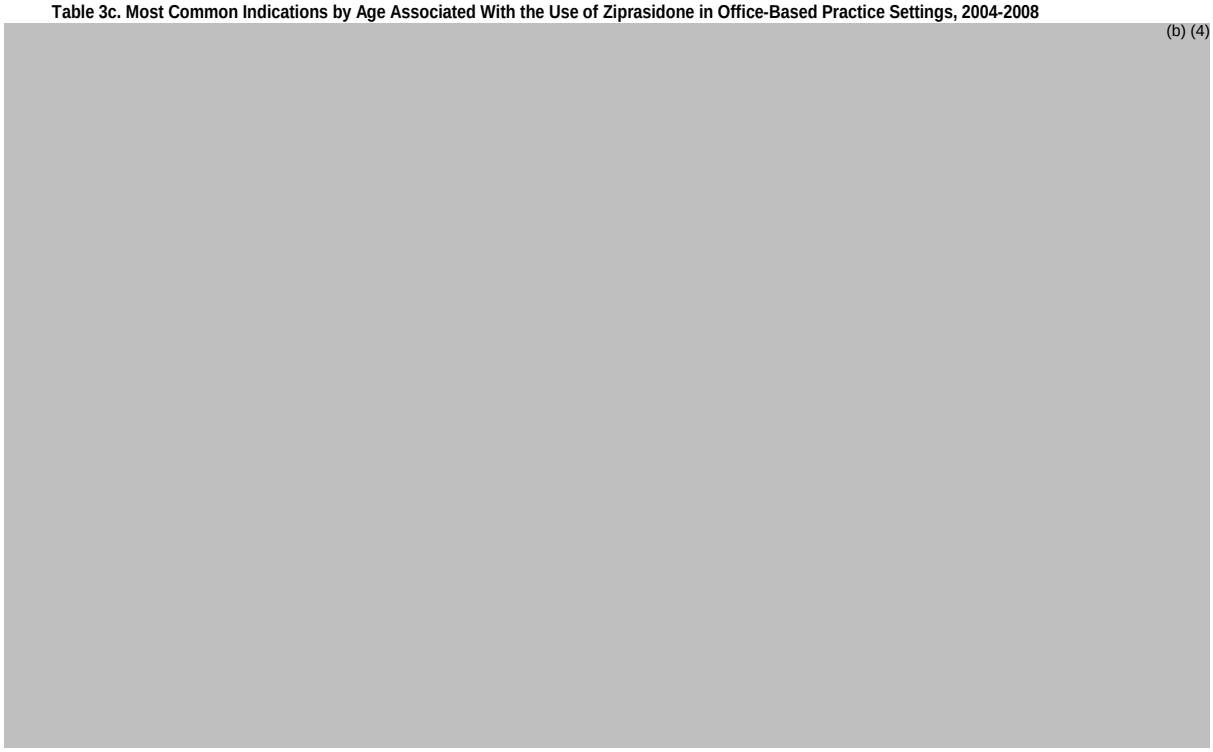
(b) (4)

[redacted]

Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 3c. Most Common Indications by Age Associated With the Use of Ziprasidone in Office-Based Practice Settings, 2004-2008

(b) (4)



Source: SDI: Physician Drug and Diagnosis Audit, Extracted 4-1-09. File: PDDA 2009-439 TRx by Diagnosis 4-1-09.xls

Table 4. Estimated Number of Prescriptions Dispensed for Selected Antipsychotic Agents by Top 10 Physician Specialty, 2004-2008

	2004		2005		2006		2007		2008	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%

(b) (4)

Source: SDI Vector One®: National Years 2004-2008 Extracted 4-1-09 File: VONA 2009-439 TRx by Physician Specialty 4-1-09 xls

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/s/

Hina S Mehta
5/11/2009 10:16:41 AM
DRUG SAFETY OFFICE REVIEWER

Laura Governale
5/11/2009 11:09:00 AM
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 Assessements 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 Espectations 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 (b) (4) 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: (b) (4)

      We have revised the statement to indicate that it is not known if Zyprexa is safe and works in children under 18 years of age, both as monotherapy and with fluoxetine.

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, not (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.

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

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 Managment** 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 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 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 Assessements 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 Assessements 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 (b) (4)

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 asesss 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 "associated with." 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: (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 (b) (4) 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 "and/or" 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 "Zyprexa can cause serious side effects." 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 2009[1], 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)" (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 remove important information about (b) (4) happening. 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 "Trouble swallowing and drawing foreign material such as food or fluid into the lungs," the sponsor's change removes information about the (b) (4) 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 delete the common side effect information in adolescents. 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
3/12/2009 02:54:37 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
3/12/2009 02:57:32 PM
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3/12/2009 03:33:34 PM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 4/12/2007

TO: Doris Bates, Ph.D., Regulatory Project Manager
Ni Khin, M.D. , Medical Team Leader
Division of Psychiatric Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Khairy Malek, Medical Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-592:SE5-040 and SE5-041

APPLICANT: Eli Lilly & Co., Inc.

DRUG: Zyprexa (olanzapine)

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of mania in adolescents with bipolar 1 disorder and adolescents with schizophrenia.

CONSULTATION REQUEST DATE: December 1, 2006

DIVISION ACTION GOAL DATE: April 30, 2007

PDUFA DATE: April 30, 2007

I. BACKGROUND:

Olanzapine is a psychotropic agent approved by the FDA in 1996 in the treatment of psychotic disorders including schizophrenia and also approved for the treatment of acute manic episode associated with adult bipolar 1 disorder.
The two new supplements are for the same indications in the pediatric population and the protocols included adolescents 13-17 years old. Supplement SE5-040, protocol F1D-MC-HGIU(a) is titled "Olanzapine Versus Placebo in the Treatment of Mania in Adolescents with Bipolar 1 Disorder". Supplement SE5-041, protocol F1D-MC-HGIN(c) is titled "Olanzapine Versus Placebo in the Treatment of Adolescents with Schizophrenia"

Four sites were chosen for inspection; two sites investigated the 2 protocols and two sites, in Moscow, investigated one study, the schizophrenia treatment in adolescents only.

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI (M.D.)	Location	Protocol	Inspection Date	EIR Received Date	Final Classification
Robert Riesenberg	Atlanta, GA	HGIU HGIN	1/29-2/5/07	4/6/07	NAI
Melissa DelBello	Cincinnati OH	HGIU HGIN	2/5-2/21/07	3/19/07	NAI
Leonid Bardenestein	Moscow Russia	HGIN	2/19-2/22/07	Draft only received (not final)	VAI
Valery Kransov	Moscow Russia	HGIN	2/26-3/2/07	Draft only received (not final)	VAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol # HGIU

1. Robert Riesenberg-Atlanta Georgia

At this site 7 subjects were randomized and completed the double-blind period of the study. Four subjects # 2701, 2704, 2705 and 2708 did not complete the open-label period due to adverse events or lost to follow-up.

There was no limitation of the inspection.
The field investigator reviewed the records of three subjects and no violations of the federal regulations were observed.

The data from this site can be used in support of the NDA supplement.

2. Melissa DelBello-Cincinnati, Ohio

At this site 15 subjects were enrolled in the study. The field investigator reviewed all the records of the subjects in the study. No violations were observed.
There was no limitation of the inspection.

The data from this site can be used in support of the NDA supplement.

B. Protocol HGIN:

1. Robert Riesenberg-Atlanta, Georgia

At this site 5 subjects enrolled in the study. Subject # 2002 terminated early during the double-blind phase of the study, subject # 2005 was lost to follow up during the open-label phase of the study, and the other three completed the study. The field investigator reviewed the records of three subjects and no violations were observed.
. There was no limitation of the inspection.

The data from this site can be used in support of the NDA supplement.

2. Melissa DelBello-Cincinnati, Ohio

At this site six subjects enrolled in the study. The field investigator audited all the records in the study. No violations were observed.
There was no limitation to the inspection.

The data generated from this site can be used in support of the NDA.

3. Leonid Bardenstein-Moscow, Russia.

At this site ten subjects were enrolled, but 6 subjects completed the double-blind portion of the study. Four subjects were discontinued during that phase, 2 due to physician perceived lack of efficacy, I due to subject perceived lack of efficacy and one because of elevated liver enzymes. Nine subjects completed the open-label period of the study (all except the one with elevated liver enzymes).
The field investigator reviewed the records of all subjects in the study. Few protocol violations were observed:

- Three subjects (# 9101, 9102 and 9103) were enrolled in the study before all the laboratory reports were available to the CI, but none of them had prolactin levels above 200 ug/L (as it appeared later).

- Subject # 9109 was started at the beginning of the open-label period on 20 mg olanzapine instead of the protocol required 2.5-5 mg with gradual increase.

There was no limitation of the inspection.

The data generated from this site can be used in support of the NDA supplement, and the above stated protocol violations will not affect the validity of the data.

4. Valery Kransov-Moscow, Russia

At this site, 10 subjects were enrolled; 7 subjects completed the double-blind period II. Two subjects had early withdrawal due to perceived lack of efficacy and one for protocol violations. The same 7 subjects completed the open-label portion of the study. The field investigator audited all the records of the subjects. A protocol violation was observed:

- Three subjects (#9101, 9407, and 9408) were enrolled in the study before all the laboratory results were received and reviewed before enrolling in the study as required by the protocol.

There was no limitation of the inspection.

The data obtained from this site can be used in support of the NDA supplement and the protocol violation mentioned above will not affect the validity of the data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies were generally well conducted in all the four sites. We did not receive the final EIRs from the Moscow inspections. An addendum will be generated if there is any conclusion changes.

The data from all the studies can be used in support of the NDA supplement.

I reviewed the EIRs and the few laboratory reports sent by the field investigator from 2 sites (Dr. Riesenberg's site in Moscow and Dr. Brandenstein site in Atlanta, and I observed a tendency of elevation in the liver enzymes in five subjects and probably also the lipids (2 subjects at Dr. Riesenberg's site), in this age group.
The division may have made a more thorough analysis than mine.

Khairy Malek
Medical Officer

{See appended electronic signature page}

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Khairy Malek
4/16/2007 01:29:13 PM
MEDICAL OFFICER

Constance Lewin
4/16/2007 01:53:44 PM
MEDICAL OFFICER

Constance Lewin
4/16/2007 02:00:30 PM
MEDICAL OFFICER

NDA REGULATORY FILING CHECKLIST

NDA #	20-592	Efficacy Supplement Type	SE-	5	Supplement #	040
NDA #	20-592	Efficacy Supplement Type	SE-	5	Supplement #	041

Trade Name: Zyprexa
Established Name: olanzapine
Strengths: 2.5, 5.0, 7.5, 10, 15 and 20 mg
Indication(s): SE5-040, pediatric bipolar disorder
SE5-041, pediatric schizophrenia
Applicant: Eli Lilly & Co., Inc.
Agent for Applicant: none needed, US firm
Date of Application: October 30, 2006
Date of Receipt: October 31, 2006
Date of Filing Meeting: December 15, 2006
Filing Date: December 29, 2006 [but decision made 12-15-06 and conveyed to firm]
PDUFA Date April 30, 2007

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☐ P ☒
Resubmission after withdrawal? original Resubmission after refuse to file? original
Chemical Classification: (1,2,3 etc.) 6
Other (orphan, OTC, etc.) not applicable

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2)

application? YES ☒ NO ☐
If yes, explain:
NDA 21253 intramuscular injection exclusivity expires 29MAR2007,
NDA 21086 orally disintegrating tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007
NDA 20592 tablet exclusivity for long term tx of bipolar disorder expires 14JAN2007

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
If yes, explain:

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
Not included in original submission. Requested and received as an amendment prior to filing date. Forms were requested and received for both indications.

- Exclusivity requested? YES, ☒ 3 three Years NO ☐
Three years of exclusivity were requested for each of the two indications.

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☐ NO ☐
Not applicable; there are no chemistry changes requiring a CMC section, only an EA.

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
Corrected in COMIS per PM request.
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. ***Yes***

- List referenced IND numbers: ***IND 28,705 only***

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? ***Not applicable***
  YES ☐ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☐ NO ☐ ***Not applicable***

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐

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/s/

Doris Bates
1/4/2007 03:35:37 PM
CSO

One filing checklist for both SE5 submissions under a common Written Request.

NDA FILING MEETING MINUTES
NDA 20-592 SE5-040, SE5-041
Zyprexa (olanzapine): Pediatric Bipolar, Pediatric Schizophrenia
Priority Review Supplements

DATE: 15 December 2006

BACKGROUND: Zyprexa is approved as tablets, orally dissolving tablets, and an intramuscular injection, for schizophrenia, agitation associated with schizophrenia (i.m. formulation) and bipolar disorder. These two supplements are submitted in response to a Pediatric Written Request and the firm seeks exclusivity.

Participants and Reviewers (including those [not present] at filing meeting) :

Discipline	**Participants**
Division Director	Thomas P. Laughren, M.D.
Deputy Director	[Mitchell Mathis, M.D.]
Clinical Team Leader and Reviewer:	Ni Aye Khin, M.D. / Cara Alfaro, Pharm.D.
Secondary Medical:	not applicable
Statistical Team Leader: and Reviewer	Peiling Yang, Ph.D. / Fanhui Kong, Ph.D.
Pharmacology Team Leader and Reviewer:	not applicable
Statistical Pharmacology:	not applicable
Chemistry PAL and Reviewer	[Janice Brown, Ph.D.]
Environmental Assessment (if needed):	[Janice Brown, Ph.D.] [categorical exclusion]
Biopharmaceutics Team Leader and Reviewer:	Ray Baweja, Ph.D. / Andre Jackson, Ph.D.
DSI:	[Khairy Malek, Ph.D.]
Regulatory Project Management:	Doris J. Bates, Ph.D.
HFD-130 Clinical Safety:	not applicable
ODS Clinical Safety (RiskMAP-IO):	Mary Dempsey
DDMAC:	not applicable

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES, consult sent ☒ NO ☐
  international sites need to be inspected; DSI was notified.
- RiskMAP Consult Needed? YES, consult sent ☒ NO
  screening review by ODS-IO: RiskMAP is routine pharmacovigilance, and acceptable; a detailed review will not be needed.
- Advisory Committee Meeting needed? YES, date if known NO ☒

STATISTICS FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

Categorical exclusion was omitted, has been requested and received.

ELECTRONIC SUBMISSION: No comments.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be sufficiently well-organized and indexed to be suitable for filing.

☐ No filing issues have been identified.
☒ Clinical review issues have been identified and are to be communicated by Day 74.

Comments: The RPM determined that the application, when submitted, was lacking Patent Information [form 3542a] and Environmental Assessment information. These are filing issues [submission materially complete on face]. The RPM contacted the firm and both missing components were submitted and received prior to the filing meeting.

Clinical review comments will be incorporated into the filing letter, which must be signed by the DD to issue on or before January 12, 2007.

Milestones for this project:
Filing date: 12-29-06.
74-day letter date: 1-12-2007.
Pediatric Exclusivity Board Date: 1-10-07. Exclusivity Pkg due to PEB: 1-1-07.
PEB Exclusivity Finding Due Day 90: 1-29-07.
Midcycle meeting: 2-12-2007.
Internal Deadline for reviews to Team Leaders: 3-26-07
Internal Deadline for reviews to Clinical TL: 4-09-07
Internal Deadline for package to Dr. Laughren:: 4-16-07
Clinical and Clinical Pharmacology Summaries Due for Web Release by Day 175: 4-24-2007
PDUFA date: 4-30-2007

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

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/s/

Doris Bates
1/4/2007 03:39:57 PM
One meeting for both submissions under a common Written Request.

DSI CONSULT: Request for Clinical Inspections

Date: December 1, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

CC: Gary Della'Zanna, Director, DSI, HFD-45
Thomas Laughren, M.D., Director, DPP, HFD-130

From: Doris J. Bates, Ph.D., Regulatory Project Manager, DPP, HFD-130
(with concurrence)

Subject: **Request for Clinical Site Inspections**
NDA 20-592: SE5-040 and SE5-041
Zyprexa (olanzapine): Eli Lilly & Co., Inc.
Pediatric Exclusivity Efficacy Supplements
Bipolar Disorder [S-040] and Schizophrenia [S-041]

Protocol/Site Identification:

As previously communicated, the following protocols/sites essential for approval have been identified for inspection. There are two pediatric exclusivity supplements under one Written Request; the shaded sites include both indications, and are therefore of higher priority.

Please note that we have included two international sites. However, these sites are ***optional.***

Site # (Name and Address)	Protocol #	No. of Subjects	Supplement Number and Indication
Robert Riesenberg Atlanta Center of Medical Research 811 Juniper Street Atlanta, GA 30308	HGIU	7	SE5-040, Bipolar Disorder
	HGIN	5	SE5-041, Schizophrenia
Melissa DelBello U. of Cincinnati Med. Center 231 Albert B. Sabin Way Dept. of Psychiatry Cincinnati, OH 45267	HGIU	15	SE5-040, Bipolar Disorder
	HGIN	6	SE5-041, Schizophrenia
Leonid Bardenstein Moscow Medical University N.A. Semashko Moskvorechye 7 City Psychiatric Hospital #15 Moscow, 115522 RUSSIA	HGIN	10	SE5-041, Schizophrenia

Site # (Name and Address)	Protocol #	No. of Subjects	Supplement Number and Indication
Valery Kransov Moscow Research Institute of Psychiatry UL. Poteshnaya 3 Moscow 107076 RUSSIA	HGIN	10	SE5-041, Schizophrenia

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by March 26, 2007. We intend to issue an action letter on this application by April 30, 2007. The PDUFA due date for this application is April 30, 2007.

Should you require any additional information, please contact the clinical reviewer, Cara Alfaro, Pharm.D., via email at cara.alfaro@fda.hhs.gov, or the Project Manager, Doris J. Bates, Ph.D., via email at doris.bates@fda.hhs.gov .

Concurrence: (see attached electronic signature page)

Ni Aye Khin, M.D., Medical Team Leader

Mitchell Mathis, M.D., Deputy Director

Thomas P. Laughren, M.D., Division Director (for foreign inspection requests only)

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/s/

Doris Bates
12/6/2006 12:31:05 PM
Dr. Laughren's signature also covers Drs. Mathis and Khin for this consult request

Thomas Laughren
12/6/2006 05:46:51 PM