

One Year Post-Exclusivity Adverse Event Review: Olanzapine

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Felicia L. Collins, M.D., M.P.H., FAAP
CDR, US Public Health Service
Medical Officer
Pediatric and Maternal Health Staff
Center for Drug Evaluation and Research
Food and Drug Administration



Background Drug Information

Drug: Zyprexa[®] (olanzapine)

Formulation: Tablets and orally disintegrating tablets

Therapeutic Category: Antipsychotic (atypical)

Sponsor: Eli Lilly

Original Market Approval: September 30, 1996

Pediatric Exclusivity Granted: January 10, 2007

Background Drug Information

Indications Prior to the Exclusivity Studies:

- Acute and maintenance treatment of schizophrenia in adults
- Acute and maintenance treatment of mixed or manic episodes associated with Bipolar I Disorder in adults

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Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

4 million dispensed prescriptions for all age groups

- 101,000 (2.5%) for patients 13 to 17 years old
- 73,000 (1.8%) for patients 0 to 12 years old

5% decrease in prescriptions for all age groups between the 12 month pre- and post-exclusivity periods

- 8% decrease for patients 0 to 17 years old

SDI Vector One®: National. Feb 2007 – Jan 2008. Data extracted 5-12-2008. 4

Drug Use Trends in Outpatient Settings During the Post-Exclusivity Period

Psychiatry was the top prescribing specialty[†]

- All psychiatrists - 52.6%
- Child psychiatrists - 4.9%
- Pediatricians - 0.7%
- Child neurologists - 0.1%

Top diagnosis codes [‡]

- 13 to 17 years old: depressive disorder
- 0 to 12 years old: anxiety states and early child psychoses

[†]SDI Vector One®: National. Feb 2007 – Jan 2008. Data extracted 5-12-2008. 5

[‡]SDI Physician's Drug and Diagnosis Audit. Feb 2007 – Jan 2008. Extracted 5-13-08.

Pediatric Exclusivity Studies: Overview

Uses

- Schizophrenia (acute treatment)
- Mania in Bipolar I Disorder (acute treatment)

Ages of Pediatric Patients

- Adolescents, 13 to 17 years old

Study Types

- 1 Pharmacokinetic (PK) Study
- 2 Efficacy and Safety Studies
(including open-label safety extension studies)

Dosing

- Flexible dosing from 2.5 to 20 mg/day

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Pediatric Exclusivity Studies: Findings

- Studies demonstrated a statistically significant effect of olanzapine for the proposed uses in adolescents.
- Additional safety information was needed to adequately describe relevant risk information for adolescents in the labeling.
 - Weight gain
 - Hyperglycemia
 - Hyperlipidemia

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Pediatric Exclusivity Studies: Outcomes

- Olanzapine has not been approved for the studied uses in pediatric patients.
- Safety data from the pediatric exclusivity studies have been incorporated into the drug labeling.

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Pediatric Exclusivity Studies: Labeling Changes

Warnings

Weight Gain, Monotherapy in Adolescents

- 1) Average weight gain with a 3 week median exposure:
4.6 kg for olanzapine vs. - 0.3 kg for placebo*
- 2) Percentage of patients gaining at least 7% of their
baseline body weight with a 4 week median exposure:
40.6% for olanzapine vs. 9.8% for placebo*

Hyperglycemia, Monotherapy in Adolescents

- 1) Mean change in fasting glucose:
2.68 mg/dL for olanzapine vs. - 2.59 mg/dL for
placebo*

* Statistically significant difference

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Pediatric Exclusivity Studies: Labeling Changes

Warnings

Hyperlipidemia, Monotherapy in Adolescents

- 1) Percentage of patients with fasting triglycerides that
increased by ≥ 50 mg/dL:
37% for olanzapine vs. 15.2% for placebo*
- 2) Percentage of patients with fasting total cholesterol
that increased by ≥ 40 mg/dL:
14.5% for olanzapine vs. 4.5% for placebo*
- 3) Percentage of patients with fasting LDL cholesterol
that increased from borderline to high:
48.3% for olanzapine vs. 0% for placebo*

* Statistically significant difference

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Adverse Event Reports Since Marketing Approval

09/30/1996 – 02/10/2008

Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	16,819 (11,047)	13,594 (8,578)	2,792 (1,577)
Pediatrics (0 to 16)	949 (732) [4.4% of all reports]	631 (444)	60 (41)
Age unknown	3,667	2,616	603
All ages	21,435	16,841	3,455

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

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Source: Adverse Event Reporting System, FDA

Pediatric Deaths Since Marketing Approval

60 Crude count reports

- 14 Duplicates
- 2 Miscoded adult reports

44 Unique pediatric cases

- 12 Drug exposure during pregnancy
- 8 Indeterminant cause of death

24 Remaining cases

- 6 Suicide
- 5 Metabolic
- 4 Cardiac
- 5 Unusual use of olanzapine
- 4 Others

No new safety concerns were identified.

Source: Adverse Event Reporting System, FDA

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Labeling Relevant to the Death Cases

Warnings

- Hyperglycemia (associated with diabetes mellitus, ketoacidosis, and/or coma)

Precautions

- Suicide

Adverse Events

- Bradycardia, atrial fibrillation, and heart arrest

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Pediatric Deaths Since Marketing Approval

6 Suicide Cases

12, 14 & 15 year old ingested unknown amounts of olanzapine.

- These adolescents did not have a known olanzapine prescription.

13, 14 & 16 year old with depression, agitation, and/or anxiety committed suicide within two months of initiating olanzapine treatment or increasing the dose.

- Concomitant medications (sertraline, clonazepam, venlafaxine, isotretinoin).

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

5 Metabolic Cases

6, 12, 13, 15, and 16 year old experienced diabetic ketoacidosis and/or coma with known olanzapine doses ranging from 5 to 15 mg.

- Three cases reported bipolar disorder or unspecified psychiatric illness.
- Concomitant medications (ziprasidone, methylphenidate, dexamethylphenidate, sertraline, valproate, topiramate, amphetamine/dextroamphetamine, risperidone, and gabapentin).

Source: Adverse Event Reporting System, FDA

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Pediatric Deaths Since Marketing Approval

4 Cardiac Cases

7, 11, & 16 year old males experienced cardiac arrhythmia or arrest while on olanzapine for psychosis, autism, or bipolar disorder.

- In two cases, death occurred 4 to 8 days after increasing the olanzapine dose to 10 or 30 mg.
- Concomitant medications (alprazolam, diphenhydramine, droperidol, or carbamazepine).

11 year old male experienced myocardial infarction 2 ½ years after initiating olanzapine therapy 2.5 mg qd for insomnia and depression.

- Concomitant medications (doxepin, prednisone, and fluticasone).

Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined. ¹⁶

Pediatric Deaths Since Marketing Approval

5 Unusual Use of Olanzapine Cases

2 year old female died possibly due to a drug interaction between olanzapine and atomoxetine used to treat hyperactivity and possible bipolar disorder according to the medical examiner.

15 year old male drowned while on olanzapine and dextroamphetamine for Asperger Syndrome and attention deficit hyperactivity disorder (ADHD).

- Olanzapine dose was increased to 10 mg qd 2 weeks prior to death.

Source: Adverse Event Reporting System, FDA

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Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

5 Unusual Use of Olanzapine Cases (continued)

4, 1, & 12 year old experienced fatal injuries inflicted by parents

- Asphyxiated after being given olanzapine to sleep
- Fed morphine and hydromorphone*
- Killed by other means*

*Olanzapine was noted on autopsy

Source: Adverse Event Reporting System, FDA

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Unlabeled SAEs are underlined.

Pediatric Deaths Since Marketing Approval

4 Other Cases

14 year old male with asthma experienced an acute asthma attack while taking olanzapine 20 mg qd.

16 year old experienced a possible drug interaction and hepatic steatosis and was found dead after initiating olanzapine 5 mg qd one to two years earlier for ADHD and personality disorder.

- Concomitant medication (amphetamine/dextroamphetamine).

Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

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Pediatric Deaths Since Marketing Approval

4 Other Cases (continued)

15 year old male died from necrotizing pancreatitis within three months of initiating olanzapine therapy for Bipolar Disorder and depression.

- Concomitant medications have labeled association with pancreatitis (carbamazepine, paroxetine, and valproate).

Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

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Pediatric Deaths Since Marketing Approval

4 Other Cases (continued)

12 year old female died from unknown causes within one month of discontinuing olanzapine and initiating quetiapine therapy. Diagnosed with diabetes and ketoacidosis three months prior to death.

- Other diagnoses included sickle cell beta thalassemia, thrombocytopenia, endocranial hemorrhage, encephalopathy, hypertension, and anemia. Concomitant medications (clonidine, escitalopram, methylphenidate, and diphenhydramine).

Source: Adverse Event Reporting System, FDA

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Unlabeled SAEs are underlined.

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Source: Adverse Event Reporting System, FDA

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Adverse Event Reports During the Post-Exclusivity Period

01/10/2007 – 02/10/2008

Crude Counts*	All Reports (US)	Serious** (US)	Death (US)
Adults (≥ 17)	2,425 (1,651)	2,256 (1,544)	258 (127)
Pediatrics (0 to 16)	81 (52)	69 (42)	7 (3)
Age unknown	771	707	85
All ages	3,277	3,032	350

* May include duplicate cases

** Serious adverse events include death, hospitalization, life-threatening event, disability, congenital anomaly, and other (unspecified).

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Source: Adverse Event Reporting System, FDA

Serious Adverse Events During the Post-Exclusivity Period

69 Crude count reports

- 3 Duplicates

66 Unique reports

- 7 Miscoded age or adverse event occurred prior to olanzapine use

59 Unique pediatric cases

- 11 Drug exposure during pregnancy

48 Remaining cases

- No new safety concerns identified

Source: Adverse Event Reporting System, FDA

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Labeling Relevant to the Serious Adverse Events

Warnings

- Hyperglycemia (associated with diabetes mellitus, ketoacidosis, and/or coma)
- Weight gain
- Hyperlipidemia
- Neuroleptic malignant syndrome

Precautions

- Seizures

Adverse Events

- Leukopenia

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Serious Adverse Events During the Post-Exclusivity Period

48 Remaining cases

- 27 Metabolic effects
 - Increased weight, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, diabetic coma, elevated triglycerides, and/or metabolic syndrome
- 4 Nervous system
 - 3 Seizures
 - 1 Neuroleptic malignant syndrome
- 3 Blood dyscrasias
 - 2 Leukopenia
 - 1 Hemolytic anemia
- 14 Others

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Source: Adverse Event Reporting System, FDA

Unlabeled SAEs are underlined.

Metabolic Serious Adverse Events During the Post-Exclusivity Period (n=27)

Number of Cases	Metabolic Serious Adverse Event
6	Increased weight
5	Diabetes mellitus
3	Diabetes mellitus + diabetic ketoacidosis
3	Diabetes mellitus + metabolic disorder
2	Diabetes mellitus + diabetic coma + diabetic ketoacidosis + increased weight
2	Diabetes mellitus + increased weight
1	Diabetes mellitus + diabetic coma
1	Diabetes mellitus + diabetic coma + diabetic ketoacidosis + metabolic disorder
1	Diabetes mellitus + diabetic coma + diabetic ketoacidosis
1	Diabetes mellitus + metabolic disorder + increased weight
1	Hyperglycemia + elevated triglycerides
1	Metabolic syndrome + increased weight

Source: Adverse Event Reporting System, FDA

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Other Serious Adverse Events During the Post-Exclusivity Period

14 Other cases

- 8 Cases with labeled events
 - 3 Pancreatitis cases
 - 5 Single case reports
- 6 Cases with unlabeled events
 - 6 Single case reports

No new safety concerns were identified.

Source: Adverse Event Reporting System, FDA

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Summary: Olanzapine

- This completes the one year post-exclusivity adverse event reporting.
- At present, olanzapine is not approved for use in any patient under 18 years of age.
- Safety data from the pediatric exclusivity trials have been incorporated into the drug labeling.

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Summary: Olanzapine

- In view of the potential metabolic effects with the use of olanzapine, especially in pediatric patients, FDA will:
 - Continue to evaluate the safety of olanzapine; and
 - Decide if any additional risk-management regulatory action is needed.
- Does the Advisory Committee concur with this approach?

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