Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
June 9-10, 2009

Topic: the committee discussed safety and efficacy issues for the following new drug applications (NDAs): 1) NDA 20-639/S-045 and S-046: SEROQUEL (quetiapine fumarate) Tablets, AstraZeneca Pharmaceuticals LP, for the acute treatment of schizophrenia in adolescents from 13 to 17 years of age, and the acute treatment of bipolar mania in children from 10 to 12 years of age and adolescents from 13 to 17 years of age; 2) NDA 20-825/S-032: GEODON (ziprasidone hydrochloride) Capsules, Pfizer Inc., for the acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features in children and adolescents ages from 10 to 17 years of age; and 3) NDA 20-592/S-040 and S-041: ZYPREXA (olanzapine) Tablets, Eli Lilly and Company, for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the acute treatment of schizophrenia in adolescents (13 to 17 years of age).

These summary minutes for the June 9-10, 2009 Psychopharmacologic Drugs Advisory Committee meeting were approved on June 26, 2009.

I certify that I attended the June 9-10, 2009 Psychopharmacologic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____*-signed-*_____	_____*-signed-*_____
Diem-Kieu H. Ngo, Pharm.D., BCPS	Wayne Goodman, M.D.
(Acting Designated Federal Official)	*(Acting Chair)*

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
June 9-10, 2009

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on June 9 and 10, 2009. A verbatim transcript will be available in approximately six weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm126199.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 9 and 10, 2009 at the University of Maryland University College, Marriott Inn and Conference Center, 3501 University Boulevard East, Adelphi, Maryland. Prior to the meeting, the members and temporary voting and non-voting members were provided the background materials from the FDA and the sponsors. Each day, the meeting was called to order by Wayne Goodman, M.D. (Acting Chair); the conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Acting Designated Federal Official). There were approximately 200 people in attendance on June 9 and approximately 300 people in attendance on June 10. There were twenty-three Open Public Hearing (OPH) speakers on June 9.

Issue: The committee discussed safety and efficacy issues for the following new drug applications (NDAs): 1) NDA 20-639/S-045 and S-046: SEROQUEL (quetiapine fumarate) Tablets, AstraZeneca Pharmaceuticals LP, for the acute treatment of schizophrenia in adolescents from 13 to 17 years of age, and the acute treatment of bipolar mania in children from 10 to 12 years of age and adolescents from 13 to 17 years of age; 2) NDA 20-825/S-032: GEODON (ziprasidone hydrochloride) Capsules, Pfizer Inc., for the acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features in children and adolescents ages from 10 to 17 years of age; and 3) NDA 20-592/S-040 and S-041: ZYPREXA (olanzapine) Tablets, Eli Lilly and Company, for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the acute treatment of schizophrenia in adolescents (13 to 17 years of age).

Attendance:
Psychopharmacologic Drugs Advisory Committee Members present (voting): Rochelle Caplan, M.D.; Gail W. Griffith, M.S. (Consumer Representative); Susan K. Schultz, M.D.; Robert F. Woolson, Ph.D.

Psychopharmacologic Drugs Advisory Committee Members absent (voting): Jorge Armenteros, M.D.; Robert W. Buchanan, M.D.; Marcia J. Slattery, M.D., M.H.S.; Matthew J. Byerly, M.D.; Helen Egger, M.D.; Tonya J. White, M.D.

Psychopharmacologic Drugs Advisory Committee Members absent (non-voting): William Z. Potter, M.D., Ph.D.

Pediatric Advisory Committee Member (voting): Marsha D. Rappley, M.D.; Avital Cnaan, Ph.D.

Psychopharmacologic Drugs Advisory Committee Temporary Members (voting): Nitin Gogtay, M.D.; Wayne K. Goodman, M.D. (Acting Chair); Tana Grady-Weliky, M.D.; Mary Lawrence (Patient Representative); Delbert G. Robinson, M.D.; Kenneth Towbin, M.D.; Benedetto Vitiello, M.D.

Psychopharmacologic Drugs Advisory Committee Temporary Member (non-voting): Roy E. Twyman, M.D. (Industry Representative)

Cardiovascular and Renal Drugs Advisory Committee Temporary Members (voting): Christopher B. Granger, M.D.; Edward L.C. Pritchett, M.D.

Drug Safety and Risk Management Advisory Committee Temporary Members (voting): Ruth S. Day, Ph.D.; Timothy S. Lesar, Pharm.D.

Endocrinologic and Metabolic Drugs Advisory Committee Temporary Member (voting): Frank L. Greenway, M.D.

FDA Participants (non-voting): Robert Temple, M.D.; Thomas P. Laughren, M.D.; CDR Mitchell V. Mathis, M.D.

Open Public Hearing Speakers: Vince Boehm; David Fassler, M.D.; Diana Zuckerman, Ph.D.; Stephen Mack; Laurence Greenhill, M.D.; Susan Resko, M.M.; Liza Ortiz; Mary Kitchens; Elizabeth V. Earls; Carl Clark, M.D.; Shirley Havenga, M.A., M.P.A.; Marc Peters; Renee' Lynn Rosolino; Stephanie Portes-Antoine; David Shern, Ph.D.; Glenda Ring, R.N.; Daniel S. Safer, M.D.; Allen Jones; Christina M. Bagno; Polly D. Sherard; Julie M. Zito, Ph.D.; Robert T. Brown, Ph.D.; Lee Spiller

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The agenda was as follows:

DAY 1: June 9, 2009

8:00 a.m.	Call to Order and Opening Remarks	**Wayne Goodman, M.D.** Acting Chair PDAC
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Acting Designated Federal Official
8:15 a.m.	FDA Introductory Remarks	**Thomas Laughren, M.D.** Director, Division of Psychiatry Products (DPP), Office of Drug Evaluation I (ODEI) Office of New Drugs (OND) CDER, FDA

FDA PRESENTATION

8:30 a.m.	Early Onset Schizophrenia and Bipolar Disorder	**Benedetto Vitiello, M.D.** Chief, Child and Adolescent Treatment and Preventive Intervention Research Branch, National Institute of Mental Health, National Institutes of Health

INDUSTRY PRESENTATIONS

9:00 a.m. **ASTRAZENECA PHARMACEUTICALS LP**

	Introduction and Background on Quetiapine	**Ihor Rak, M.D.** Vice President, Clinical Neuroscience AstraZeneca Pharmaceuticals LP
	Overview of the Clinical Development Program, Clinical Pharmacology, and Efficacy	**Hans Eriksson, M.D., Ph.D.** Medical Science Senior Director Research and Development AstraZeneca Pharmaceuticals LP
	Summary of Safety Data – Pediatric Schizophrenia and Bipolar Mania	**Liza O'Dowd, M.D.** Vice President, Clinical Development Neuroscience AstraZeneca Pharmaceuticals LP
	Schizophrenia and Mania in Youth: A Clinician's Perspective	**Lili Kopala, M.D., FRCPC** Professor, Center for Complex Diseases University of British Columbia
	Risk Management and Benefit Risk Assessment	**Ihor Rak, M.D.** Vice President, Clinical Neuroscience AstraZeneca Pharmaceuticals LP

10:10 a.m. Clarifying Questions

10:30 a.m. **BREAK**

10:45 a.m. **PFIZER, INC.**

	Geodon® (Ziprasidone HCl) – Safety and Efficacy in Bipolar I Disorder (acute manic or mixed episode) in children and adolescents ages 10 – 17 years	**Phillip B. Chappell, M.D.** Executive Director, Clinical Affairs Group Lead, Psychiatry Pfizer, Inc.

11:30 a.m. Clarifying Questions

12:00 p.m. **LUNCH**

1:00 p.m.	**ELI LILLY AND COMPANY**	
	Introduction	**Robert W. Baker, M.D.** Team Leader Psychosis Global Product Development Eli Lilly and Company
	Efficacy in Adolescents with Schizophrenia and Bipolar Type 1, Acute Mania or Mixed Episodes	**Olawale O. Osuntokun, M.D.** Medical Advisor, Psychosis Global Product Development Eli Lilly and Company
	Safety of Olanzapine in Adolescents and Risk Management Plans	**Robert R. Conley, M.D.** Distinguished Lilly Scholar US Medical Division Eli Lilly and Company
	Benefit/Risk and Conclusions	**Robert W. Baker, M.D.** Team Leader Psychosis Global Product Development Eli Lilly and Company
2:10 p.m.	Clarifying Questions	
2:30 p.m.	**BREAK**	
3:00 p.m.	Open Public Hearing	
5:00 p.m.	**ADJOURNMENT**	

DAY 2: June 10, 2009

8:00 a.m.	Call to Order and Opening Remarks	**Wayne Goodman, M.D.** Acting Chair PDAC
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Acting Designated Federal Official
8:15 a.m.	FDA Introductory Remarks	**Thomas Laughren, M.D.** Director, DPP ODEI, OND, CDER, FDA
8:30 a.m.	Panel Discussion/Questions	
10:00 a.m.	**BREAK**	
10:15 a.m.	Panel Discussion/Questions	

12:00 p.m. **LUNCH**

1:00 p.m. Panel Discussion/Questions

3:00 p.m. **BREAK**

3:15 p.m. Panel Discussion/Questions

5:00 p.m. **ADJOURNMENT**

Committee Discussion (June 10):
Before voting on the questions, the committee discussed several topics that were pertinent to all three drug products:

- Diagnostic criteria for pediatric bipolar disorder and trends leading to a broadening of this diagnosis in children
- Metabolic side effects: weight gain, hyperlipidemia, hyperglycemia, increase prolactin
- Cardiovascular risks: increase blood pressure, increase heart rate, QT prolongation
- Extrapyramidal symptoms: tardive dyskinesia, akathisia
- Need for withdrawal and maintenance studies and ethical issues with such studies
- Need for labeling to state the need for re-assessment of patients in order to determine the need for continued therapy
- Assumption that the committee questions refer to only acute treatment

Questions to the Committee (June 10):

1. Has Seroquel been shown to be effective for the treatment of schizophrenia in pediatric patients ages 13-17?

   YES: 17 NO: 1 ABSTAIN: 0

   Committee Discussion: In voting on this question, the committee assumed that the question referred to the *acute* treatment of schizophrenia in pediatric patients (13-17 years of age) and that language in the product's label will clearly indicate the studies used for approval (if approved).

2. Has Seroquel been shown to be acceptably safe for the treatment of schizophrenia in pediatric patients ages 13-17?

   YES: 16 NO: 0 ABSTAIN: 2

   Committee Discussion: The committee had a brief discussion on the product's antidepressant effects and suicide ideation. The committee expressed the need for the product's label to continue to have warnings on suicidality. The committee also had a brief discussion on the reports of cataracts. In response, AstraZeneca presented new data suggesting that Seroquel does not cause cataracts. As such, the committee recommended that the language in the proposed label be revised to exclude the need for a slit lamp exam if, upon review of the new data, FDA agrees with AstraZeneca's conclusions.

3. Has Seroquel been shown to be effective for the treatment of bipolar mania in pediatric patients ages 10-17?

   YES: 17 NO: 0 ABSTAIN: 1

4. Has Seroquel been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 10-17?

   YES: 13 NO: 0 ABSTAIN: 5

   Committee Discussion: Due to concerns raised over the diagnosis of bipolar disorder in the pediatric population, the committee expressed the need for strong language in the product's labeling to indicate which population in which the drug was studied so that it is clear to prescribers which patient population this drug product is intended to treat.

5. Has Geodon been shown to be effective for the treatment of bipolar mania in pediatric patients ages 10-17?

   YES: 12 NO: 2 ABSTAIN: 4

   Committee Discussion: The committee discussed concerns over the results of the subgroup analyses. Some committee members noted that subgroup analyses were not appropriate because the data were not robust enough to detect a true difference between drug and placebo and because these analyses were conducted post hoc. Thus, interpretation of the subgroup analyses should be done with caution.

6. Has Geodon been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 10-17?

   YES: 8 NO: 1 ABSTAIN: 9

   Committee Discussion: The committee expressed concerns regarding the patients lost to follow-up. Additionally, the committee noted that more data in the 10-14 year old age group would be useful.

7. Has Zyprexa been shown to be effective for the treatment of schizophrenia in pediatric patients ages 13-17?

   YES: 11 NO: 5 ABSTAIN: 2

   Committee Discussion: The committee expressed concern over the disparity between the data from the Russian study sites versus the data from the U.S. study sites (greater placebo effect seen with the U.S. data). It was noted that there is a difference in the management of these patients in the U.S. versus Russia as there are more products available and better access to care in the U.S. Also, some committee members stated that placebo-controlled trials for this indication are hard to perform in the U.S.

8. Has Zyprexa been shown to be acceptably safe for the treatment of schizophrenia in pediatric patients ages 13-17?

   YES: 10 NO: 4 ABSTAIN: 4

   Committee Discussion: The committee stressed the need for the labeling to clearly state that prescribers consider other treatment options first before prescribing Zyprexa. Some committee members expressed concern over the lack of knowledge on the long-term effects of Zyprexa on the brain of pediatric patients.

9. Has Zyprexa been shown to be effective for the treatment of bipolar mania in pediatric patients ages 13-17?

   YES: 17 NO: 0 ABSTAIN: 1

10. Has Zyprexa been shown to be acceptably safe for the treatment of bipolar mania in pediatric patients ages 13-17?

    YES: 11 NO: 4 ABSTAIN: 3

    Committee Discussion: Weight gain and metabolic effects were the primary concerns of the committee; however, it was noted that patients/consumers want to have more treatment options despite these side effects. The committee recommended that the product's labeling provide guidance on monitoring for these side effects and clearly indicate the patient population that was studied for this indication.

The committee provided the following overall recommendations to the Agency after the voting was completed:

- Labeling for these drug products should clearly indicate that patients be reassessed during prolonged use
- Labeling for these drug products should recommend monitoring of pediatric patients for side effects (metabolic, cardiovascular, etc.)
- Labeling should indicate the exact patient population these drug products are intended for.
- Need for phase IV studies for long-term efficacy and safety
- Need for head-to-head clinical trials
- Moratorium on Direct-to-Consumer advertising
- Need for effective communication plans to prescribers and professional organizations to ensure safe use of these drug products
- Need for long-term follow-up studies (may have high drop-out rates)

The meeting was adjourned at approximately 4:30 p.m. on June 9 and 5:00 p.m. on June 10.