Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee
April 8, 2009

Topic: The committee discussed issues related to the safety and efficacy of supplemental new drug application (sNDAs) 22-047/S-010/S-011/S-012,Seroquel XR (quetiapine fumarate), Astra Zeneca Pharmaceuticals LP, proposed for the treatment of major depressive disorder and 22-047/S-014/S-015, Seroquel XR (quetiapine fumarate), Astra Zeneca Pharmaceuticals LP, proposed for the treatment of generalized anxiety disorder.

These summary minutes for the April 8, 2009 Psychopharmacologic Drugs Advisory Committee were approved on April 15, 2009.

I certify that I attended the April 8, 2009 Psychopharmacologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Yvette Waples, Pharm.D.
(Designated Federal Official)

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Wayne K. Goodman, M.D.
(Acting Chair)

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
April 8, 2009

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on April 8, 2009. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder09.html#Psychopharmacologic

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 met on April 8, 2009 at the Hilton Washington DC/ Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Wayne K. Goodman, M.D. (Acting-Chair); the conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Designated Federal Official). There were approximately 240 persons in attendance. There were 15 speakers for the Open Public Hearing session.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members present (voting):
Gail W. Griffith, M.L.S. (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members absent:
Jorge Armenteros, M.D.(Chair); Robert W. Buchanan, M.D.; Matthew Byerly, M.D.; Rochelle Caplan, M.D.; Susan K. Schultz, M.D.; Marcia J. Slattery, M.D., M.H.S.; Robert F. Woolson, Ph.D.

Temporary Voting Members:
Wayne K Goodman, M.D. (Acting-Chair); Richard P. Malone, M.D.; Daniel S. Pine, M.D.; Delbert Robinson, M.D.; Margy Lawrence (Patient Representative)

Industry Representative (non-voting):
William Z. Potter, M.D., Ph.D. (PDAC)

Guest Speaker (non-voting):
Wayne A. Ray, Ph.D.

Cardiovascular and Renal Drugs Advisory Committee Member (voting):
Robert Harrington, M.D., F.A.C.C.; James Neaton, Ph.D.

Temporary Members (voting):
Christopher B. Granger, M.D., F.A.C.C.; Frank L. Greenway, M.D.; Sheryl Kelsey, Ph.D.

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

Open Public Hearing Speaker:
Vince Boehm; Eileen McGinn, M.P.H.; Fred Baughman, M.D.; Allen Jones; Diane Zuckerman, Ph.D.-President, National Research Center for Women and Families; Stan and Shirley White, Diane Vande Burgt; Janette Layne; Laurence Greenhill, M.D.-President-Elect, American Academy of Child and Adolescent Psychiatry; Dr. Patricia Partridge-International Coalition for Drug Awareness; William Wirshing, M.D.; Kim Witczak; Laura Galbreath, MPP; Ellen B. Liversidge

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On April 8, 2009, the committee met to discuss safety and efficacy of supplemental new drug application (sNDAs) 22-047/S-010/S-011/S-012,Seroquel XR (quetiapine fumarate), Astra Zeneca Pharmaceuticals LP, proposed for the treatment of major depressive disorder and 22-047/S-014/S-015, Seroquel XR (quetiapine fumarate), Astra Zeneca Pharmaceuticals LP, proposed for the treatment of generalized anxiety disorder. Particular safety issues discussed on April 8, 2009, regarding the Seroquel XR applications were concerns regarding exposing a greatly expanded population to a drug with known metabolic side effects and a possible risk of tardive dyskinesia.

On April 8, 2009, Wayne K. Goodman, M.D., (Acting Chair) called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Yvette Waples, Pharm.D., Designated Federal Official (DFO). The agenda for the meeting was as follows:

8:00 a.m.	Call to Order and Opening Remarks	**Wayne K. Goodman, M.D.** Acting Chair, Psychopharmacologic Drugs Advisory Committee
	Introduction of Committee	
	Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Designated Federal Official
8:10 a.m.	FDA Introductory Remarks	**Thomas Laughren, M.D.** Director, Division of Psychiatry Products, Office of Drug Evaluation I, OND, CDER, FDA

INDUSTRY PRESENTATION

8:15 a.m.	Introduction and Background on Quetiapine	**Mark Scott, Ph.D.** AstraZeneca Pharmaceuticals LP
8:30 a.m.	Efficacy and General Safety Profile in MDD and GAD	**Hans Eriksson, M.D.** AstraZeneca Pharmaceuticals LP
9:25 a.m.	Benefit/Risk Assessment Risk Management	**Howard G. Hutchinson, M.D., F.A.C.C.** AstraZeneca Pharmaceuticals LP

9:35 a.m.	Clinical Context	**Alan J. Gelenberg, M.D.** University of Wisconsin
9:50 a.m.	Concluding Remarks	**Mark Scott, Ph.D.** AstraZeneca Pharmaceutical LP
9:55 a.m.	Clarifying Questions	
10:10 a.m.	**BREAK**	

FDA PRESENTATION

10:20 a.m.	Atypical Antipsychotics and the Risk of Sudden Cardiac Death	**Wayne A. Ray, Ph.D.** **Guest Speaker** Department of Preventive Medicine Vanderbilt University School of Medicine
10:40 a.m.	Estimating Sudden Cardiac Death Rates with Death Certificate Data	**Marc B. Stone, M.D.** Senior Medical Reviewer DPP, CDER, FDA
11:00 a.m.	Clarifying Questions	
11:15 a.m.	**LUNCH**	
12:00 p.m.	Open Public Hearing	
1:00 p.m.	Questions/Clarifications	
2:00 p.m.	**BREAK**	
2:10 p.m.	Committee Deliberations	
3:30 p.m.	**ADJOURNMENT**	

Questions to the Committee:

The questions for discussion and comment are as follows:

1. What are the public health consequences of expanding the use of Seroquel XR into a much larger psychiatric population with MDD and GAD? (Discussion and Comment)
The committee suggests that with expanding the use, non-psychiatrists will be primarily prescribing Seroquel XR. The committee is concerned with general practitioners/non-psychiatrists prescribing Seroquel XR because of the possible lack of expertise in monitoring of Seroquel XR for tardive dyskinesia, akathesia and other motor side effects which can have profound implications. In addition, the committee felt the cardiovascular risks and metabolic

effects are concerning because the documented years of follow-up are low and that the bar should be set higher.
(Please see transcripts for detailed discussion)

2. In particular, how should less well-defined concerns about longer-term metabolic risks, a potential risk for tardive dyskinesia, and a concern for an increased risk of sudden cardiac death be considered in this risk benefit discussion? (Discussion and Comment)
For metabolic risks, the committee felt a year of data is not adequate.

For the potential risk of tardive dyskinesia, the committee was concerned that the data presented were from short-term trials. The committee stated tardive dyskinesia could take many months to years to develop and there is an increase risk of tardive dyskinesia with cumulative years of exposure. As a result, the short-term data is not adequate.

The committee agreed that atypical antipsychotics as a class has shown to have increase risk in QT prolongation. Although QT prolongation is associated with sudden cardiac death, in some patients, the prolongation is not seen. The committee felt that randomized trials with long-term follow-up is needed to adequately identify the risk.

(Please see transcripts for detailed discussion)

The questions for a vote by the committee are as follows:
The committee proposed the following changes to the questions

1. Has Seroquel XR been shown to be effective as a treatment of: (Yes/No/Abstain)
(See Transcript for Complete Discussion)

a. MDD as an adjunct?
Yes: 9 **No: 1** **Abstain: 0**

b. MDD as a monotherapy?
Yes: 8 **No: 1** **Abstain: 1**

The committee members who abstained or voted no were not confident in the data presented

c. GAD as a monotherapy?
Yes: 7 **No: 2** **Abstain: 1**

The committee members who abstained or voted no were not confident in the data presented

*****Please note: Total voting members has decreased by one due to an early departure*****

2. Has Seroquel XR been shown to be acceptably safe as an adjunctive treatment for MDD? (Yes/No/Abstain)
(See Transcript for Complete Discussion)
Yes: 6 **No: 3** **Abstain: 0**

The committee members who voted yes felt there is a need for adjunctive treatment for patients who have failed previous therapy and the benefit outweighs the risk. For those who voted no believed due to the short-term exposure in the clinical studies, the long-term risk has not been adequately studied.

3. Has Seroquel XR been shown to be acceptably safe as a treatment for: (Yes/No/Abstain) *(See Transcript for Complete Discussion)*

    a. MDD as a monotherapy?

Yes: 0 **No: 9** **Abstain: 0**

    b. GAD as a monotherapy?

Yes: 0 **No: 9** **Abstain: 0**

4. Has Seroquel XR been shown to be acceptably safe in certain instances as a treatment for: (Yes/No/Abstain)

(See Transcript for Complete Discussion)

    a. MDD as a monotherapy?

Yes: 4 **No: 4** **Abstain: 1**

The committee was divided. For those who voted yes felt there should be options available for patients who have failed previous treatments. For those who voted no or abstained felt there is not sufficient data in benefit vs. risk for monotherapy.

    b. GAD as a monotherapy?

Yes: 2 **No: 6** **Abstain: 1**

For those who voted yes felt there should be options available for patients who have failed previous treatments. For those who voted no or abstained felt the studies presented did not show sufficient data for monotherapy.

Those who voted yes for MDD, but no for GAD felt that the risk of suicide in patients diagnosed with GAD is not comparable to MDD. In addition, patients usually respond more favorably to the first-line agents for GAD. As a result, the need for additional options is not as great.

The meeting was adjourned at approximately 3:30 p.m. on April 8, 2009.