FDA Psychopharmacologic Drugs Advisory Committee Hearings
June 9 – 10, 2009
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On June 9 - 10, the FDA Psychopharmacologic Drugs Advisory Committee reviewed the requests from three pharmaceutical companies for medication approval for the treatment of schizophrenia and/or acute mania bipolar in pediatric populations. AstraZeneca Pharmaceuticals, LP, requested Seroquel (quetiapine fumarate) be granted FDA indication approval for the treatment of schizophrenia in adolescents ages 13 – 17 and acute treatment of bipolar mania in children and adolescents ages 10-17. Pfizer, Inc. requested Geodon (ziprasidone hydrochloride) be granted FDA indication approval for the acute treatment of bipolar mania in children and adolescents ages 10 – 17 years. Eli Lilly and Company requested Zyprexa (olanzapine) be granted FDA indication approval for the treatment of schizophrenia in adolescents ages 13 – 17 years of age and acute treatment of bipolar mania in adolescents ages 13 – 17.

On June 9, the Committee heard a presentation from **Benedetto Vitiello, M.D.**, AACAP member and Chief, Child and Adolescent Treatment and Preventive Intervention Research Branch of the National Institute of Mental Health (NIMH) on the prevalence of early onset schizophrenia and bipolar disorder. Following Dr. Vitiello's presentation, the pharmaceutical companies provided detailed presentations on the study trials completed in order to determine the effectiveness and safety for the new medication approvals. The open public hearing was held late in the afternoon. Twenty-three non-committee public representatives spoke for 4 minutes each. Presentations were provided by family members, consumer organizations, health professionals, lawyers, and researchers. A few of the presenters questioned the diagnosis of pediatric bipolar disorder. Thirteen individuals provided comments encouraging the Committee to ensure an adequate array of treatment options is available to the many individuals suffering from these disorders, encouraged the FDA to consider methods for monitoring these medications and/or indicated a need for additional long-term studies on the side effects of these medications. Many individuals represented consumer organizations such as the Child and Adolescent Bipolar Foundation, Families for Depression Awareness, Mental Health America, and Community Mental Health Organizations. The American Psychiatric Association was represented by AACAP member, **David Fassler, M.D.** AACAP was represented by **Laurence Greenhill, M.D.**, President-elect, who expressed concern about the need for an array of treatment options and additional data on the long-term adverse events of these medications in pediatric populations. (Click here to review the oral comments provided by AACAP.)

On Wednesday, June 10, the Committee members reconvened. The morning began with a presentation by **Kenneth Towbin, M.D.**, AACAP member and Chief, Clinical Child and Adolescent Psychiatry Mood and Anxiety Disorder Program of the NIMH. Dr. Towbin provided the Committee with an overview of the controversial diagnosis of bipolar disorder and the varying characterization of symptoms used to diagnose the disorder. Dr. Towbin stressed the fact that bipolar disorder is real and can be diagnosed in the pediatric population. He also indicated bipolar disorder is very rare in children and

adolescents and that more children and adolescents suffer from severe mood dysregulation. The Committee thanked Dr. Towbin for his presentation and assistance in helping them understand the pediatric bipolar disorder diagnosis controversy. The Committee then continued their discussions and questioning of the data presented on Tuesday.

After thorough discussion, the Committee held the following votes. The Committee found that Seroquel had been shown to be effective (17 – Yes, 1-No) and acceptably safe (16 – Yes, 2 – Abstain) for the treatment of schizophrenia; and they found that Seroquel had been shown to be effective (17 – Yes, 1 – Abstain) and acceptably safe (13 – Yes, 5 – Abstain) for the acute treatment of bipolar mania. The Committee was concerned about the metabolic and cardiac side effects of this medication, specifically the increased weight gain, heart rate and blood pressure. The Committee additionally recommended labeling clarifications regarding the use of this medication only for the narrowly defined mania aspects of bipolar disorder and clear indication that this medication not be used for severe mood dysregulation such as chronic irritability, oppositional defiance and hyperactivity.

The Committee found that Geodon had been shown to be effective (12 – Yes, 4 – Abstain, 2 – No) for the acute treatment of bipolar mania but no conclusion was delivered regarding the safety of this medication (9 – Abstain, 8 – Yes, 1 – No). The Committee members that abstained were concerned about the lack of long-term data, high QTc prolongation intervals, higher rate of side effects in children ages 10 – 14, and unusual number of trial subjects that were lost in the follow-up phase.

The Committee found that Zyprexa had been shown to be effective (11 – Yes, 5 – No, 2 – Abstain) and acceptably safe (10 – Yes, 4 – No, 4 – Abstain) for the treatment of schizophrenia; and they found that Zyprexa had been shown to be effective (17 – Yes, 1 – Abstain) and acceptably safe (11 – Yes, 4 – No, 3 Abstain) for the acute treatment of bipolar mania. The Committee recommended the approval as a second line treatment and recommended labeling clarifications regarding the use of this medication for the narrowly defined mania aspects of bipolar disorder and clear indication that this medication not be used for severe mood dysregulation. The Committee was concerned about the high level of metabolic and cardiac side effects of this medication, specifically the increased weight gain.

AACAP members serving on the Committee included **Rochelle Caplan, M.D.**, Semel Institute for Neuroscience and Human Behavior, UCLA; **Masha Rappley, M.D.**, Michigan State University; **Kenneth Towbin, M.D.**, National Institute of Mental Health; and **Benedetto Vitiello, M.D.**, National Institute of Mental Health.

To view copies of the data and presentations provided during the hearing, please visit the FDA website.

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm126199.htm

Upcoming FDA Committee Meetings of Interest:

- **June 23** – The Pediatric Advisory Committee will review and discuss reports by the Agency, as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, for Alvesco (ciclesonide), Androgel (testosterone), Asmanex (mometasone furoate), Combigan (brimonidine/timolol), Depakote (divalproex sodium), Derma-Smoothe F/S (fluocinolone acetate), Diovan (valsartan), Hepsera (adefovir dipivoxil), Inspra (eplerenone), Moxatag (amoxicillin), Omnaris (ciclesonide), and Zometa (zoledronic acid).

- **July 30** – The Psychopharmacologic Drugs Advisory Committee will discuss the safety and efficacy of new drug application (NDA) 22-117, proposed trade name, SAPHRIS (asenapine maleate) sublingual tablets, Organon, a part of Schering-Plough Corporation, for the following indications: (1) acute treatment of schizophrenia in adults; and (2) acute treatment of manic or mixed episodes of bipolar I disorder in adults.