

Pediatric Advisory Committee Summary

December 9, 2009 – Prepared by S. Fleisher

On December 8, 2009, the Pediatric Advisory Committee met to discuss pediatric-focused safety reviews, as mandated by the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, for Abilify (aripiprazole), Argatroban (argatroban), Orencia (abatacept), Humira (adalimumab), Cancidas (caspofungin acetate), Evicel - fibrin sealant (human), Artiss - fibrin sealant (human), Voluven - 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, Reyataz (atazanavir sulfate), Kaletra (lopinavir/ ritonavir), Aptivus (tipranavir), Zetia (ezetimibe), Vytorin (ezetimibe/simvastatin), Ventolin HFA (albuterol sulfate). An update to address some of the committee's questions from the November 18th, 2008 Pediatric Advisory Committee meeting on atypical antipsychotic drugs was provided. In addition to Abilify (aripiprazole), Risperidal (risperidone), Zyprexa (olanzapine), Geodon (ziprasidone), and Seroquel (quetiapine) were included.

AACAP members serving on the Committee included: Kenneth Towbin, M.D., NIMH and Benedetto Vitiello, M.D., NIMH.

Open Public Comment Presentations

There was one registered presenter. The floor was opened to the audience for additional comments and one additional person spoke.

Diana Zuckerman, Ph.D., National Research Center for Women and Families – Dr. Zuckerman expressed concern for the pediatric approval indications granted for atypical antipsychotics. She stated her frustration with FDA approval based on short-term trial use for medication approvals intended to be used for life-long maintenance. She also expressed dismay with the additional approvals granted without additional warnings for side effects that have been shown in various research studies to be of concern for this population including metabolic effects, Tardive Dyskinesia, and weight gain. She also requested the FDA panel to address the mass marketing campaigns that mislead the public into believing these medications are anti-depressants.

Kenneth Smith, lawyer overseeing litigation against the makers of several atypical antipsychotics – Mr. Smith voiced his dismay of the pediatric approval indications granted for the atypical antipsychotics without additional warnings. He also expressed frustration with the use of these medications for treatment of non-approved indications such as conduct disorder, oppositional defiant disorder, pervasive developmental disorders, and other mental health disorders.

Discussion on Atypical Antipsychotics

A series of presentations were provided by federal government officials and representatives. All clarifying questions and discussions were held until all presentations were completed.

Background & Update on the June 9 -10 Psychopharmacological Drugs Advisory Committee Meeting

Mitchell Mathis, M.D., FDA representative for the Psychopharmacological Drugs Safety Advisory Committee, provided an update on the discussion and recommendations of the Advisory Committee in June 2009. The Committee reviewed five requests from industry sponsors for atypical antipsychotic pediatric indications for schizophrenia and bipolar in the adolescent population. Four of the five have subsequently been approved by FDA (Abilify, Zyprexa, Seroquel and Risperidal). Geodon has not been approved for a pediatric indication at this time. The FDA utilized the AACAP Practice Parameters on Schizophrenia and Bipolar and the AACAP Policy Statement on Pharmaceutical Benefit Management and the Use of Psychotropic Medication for Children and Adolescents as supporting documentation for their decision.

Overview of the NICHD/NIH Working Group Recommendations

Julie Zito, Ph.D., Member of the NICHD Working Group, provided an overview of the recommendations of the Working Group on atypical antipsychotic medication use in children and adolescents. The Working Group recognized research gaps exist, recommended a publicly funded mixed model study (stage one: retrospective claims data analysis and stage two: prospective clinical cohort study) be conducted, and suggested FDA make existing data available for independent scientific review.

Atypical Antipsychotic Drugs Utilization Data in Children

Laura Governale, PharmD, MBA, FDA representative, provided a presentation on the current utilization rates of these medications. Based on the analysis of Vector one data, outpatient use from 2004 – 2008 increased by 22% in the 0-17 age group. Over 160 million unique users were identified during this time. The medication with the greatest increase was Abilify at 96%. The greatest age group increases for all class medications were 7-12 (21% increase) and 13-17 (25% increase). There was a 51% decrease for those ages 0-2. Approximately, 1% of prescriptions prescribed during this time frame were for children age 0-6. The data also indicated the number one prescriber of the medications as psychiatrists followed by nurse practitioners and primary care. Additional data on diagnosis for prescriptions was presented using the Physician Drug and Diagnosis Audit from 2004 - 2008. A majority of the prescriptions issued were for affective psychosis and bipolar disorder. The most common concomitant medication use for 7-12 year olds was stimulants and anti-depressants and anticonvulsants for 13-17 year olds.

Clinical Summary of Pediatric Metabolic AERs Reports

Judith Cope, M.D., FDA representative, provided an update on the adverse event reports for atypical antipsychotics for the age 0-17 population. FDA has received 100 adverse event reports (including serious and non-serious). Of

the 100 adverse event reports were 6 deaths and 13 hospitalizations. Additionally, 42% of those reporting adverse events also reported concomitant medication use. It was also noted that from the adverse event reports, there is no conclusive evidence of metabolic side effects from these medications since a majority of the patients had complex medical histories and were or had previously been treated for multiple health related issues. It was noted that other studies have been conducted that provide evidence that atypical antipsychotics impose greater metabolic effects in adolescents than in adults.

The Committee discussed the continued safety concerns regarding the metabolic side effects of the medications. They also requested clarification on the number of prescriptions issued by nurse practitioners. It was clarified that there are psychiatric nurse practitioners and most nurse practitioners are working in conjunction with a physician. It was not able to be determined from the data set what type of physicians the nurse practitioners were working with (psychiatry, pediatrics, primary care, etc.). There were questions regarding the large number of atypical antipsychotic prescriptions for ADHD. It was clarified that the most common comorbidity for bipolar disorder is ADHD and that a physician would be operating outside the realm of professional standards to prescribe atypical antipsychotics as a first line treatment for ADHD.

Abilify Safety Review

The meeting concluded with a safety review of Abilify. A presentation was provided by Felicia Collins, M.D., M.P.H., FDA Representative, on the adverse events for the medication. The Committee members discussed the safety issues.

In conclusion, the Committee voted on the following questions.

Does the Abilify label adequately reflect possible pediatric risk of excessive weight gain?
Yes - 0, No - 12, Abstentions - 0

Does the committee recommend standard ongoing monitoring?
Yes – 10, No – 2, Abstentions - 0

For more information on the Pediatric Advisory Committee meeting, including copies of the background data, presentations and meeting minutes please visit the FDA website.

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm116530.htm>