

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 3 December 2009

FROM: Mitchell V. Mathis, M.D.
Deputy Director
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TO: File NDA 20-592 S-040, S-041

SUBJECT: Approval Recommendation for Zyprexa [olanzapine] Tablets for the Treatment of Schizophrenia and the Acute Treatment of Manic or Mixed Episodes Associated with Bipolar Disorder in Adolescents (ages 13-17)

BACKGROUND AND REGULATORY HISTORY

Zyprexa is an atypical antipsychotic approved (as an oral formulation) in adults for the treatment of schizophrenia, and the acute treatment of manic or mixed episodes associated with bipolar I disorder (monotherapy or adjunctive therapy to lithium or valproic acid). The sponsor submitted one positive short-term trial in adolescents with schizophrenia (ages 13-17) and in one trial of adolescents with manic or mixed episodes associated with bipolar I disorder (ages 13-17), as well as pharmacokinetic data to support dosing in this population, and longer-term (6 months) safety data.

The Division was prepared to approve these applications after reviewing the data (see team member reviews, this NDA), but decided to first take this application (along with two others pending for similar indications) to the Psychopharmacologic Drugs Advisory Committee (PDAC) for a public discussion among experts in the fields of child psychiatry, general psychiatry, drug safety, cardiology, and endocrinology. We were specifically interested in expert opinion about expanding the indications of atypical antipsychotics into broader populations, especially given the adverse metabolic profile and yet unquantified risk of tardive dyskinesia with this class of medications.

Zyprexa (and others in the atypical antipsychotic class) has an adverse impact on glucose, lipids, and weight gain. In fact, although there are limited comparative safety data, it is our impression from having evaluated the controlled trial data for each of the atypicals that Zyprexa poses a greater risk of metabolic changes than do the others in the class (except for perhaps clozapine). Since schizophrenia and bipolar I disorder are life-long illnesses, our concern was that pediatric patients with these disorders would be treated earlier in life and for an extended period of time compared to adults, therefore increasing exposure-related risks of adverse reactions associated with drugs in this class. Zyprexa appears to have a greater adverse metabolic impact than the other drugs being evaluated in children/adolescents, and we felt like a public discussion of how to differentially label this drug would be in order.

Our safety review revealed that younger patients experienced qualitatively similar adverse reactions as adults, but there were some quantitative differences related to adverse changes in metabolic

parameters, as well as other adverse events. Our belief has been that pediatric patients represent a more treatment-naïve population, and so effects on glucose, lipids and weight are more apparent in this population, but we wanted to hear from experts and discuss these issues in public before taking a final action.

PEDIATRIC ADVISORY COMMITTEE MEETING (PDAC)

The PDAC met on June 9-10, 2009. The members agreed with us that efficacy had been established in the studied populations for both indications. We then discussed the safety issues of concern with the committee. From a discussion of the facts and from the experience of treating physicians, it was obvious that schizophrenia and bipolar I disorder affect the pediatric population (in fact these diseases often onset during the pediatric years) and that the availability of multiple treatment options is important to the clinical management of these routinely devastating disorders. It was noted that the American Academy of Child and Adolescent Psychiatry (AACAP) recommends in its practice guidelines that antipsychotics be used in both disorders, and it was routinely accepted as fact that children and adolescents were already being treated with atypical antipsychotics, including Zyprexa, because their safety profiles are considered by many clinicians to be superior to the typical antipsychotics which have a known exposure-related risk of tardive dyskinesia. The Sponsor presented their data, and also indicated their acceptance of the Division's proposed labeling language which states that the increased potential in adolescents compared to adults for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first.

The votes of the PDAC were as follows:

- Schizophrenia
 - Effective? 11 yes; 5 no, 2 abstain
 - Safe? 10 yes; 4 no; 4 abstain
- Bipolar mania/mixed episodes
 - Effective? 17 yes; 0 no; 1 abstain
 - Safe? 11 yes; 4 no; 2 abstain

LABELING/MEDICATION GUIDE

The labeling and Medication Guide were updated to include the pediatric indications, and pediatric safety data (which had already been included in labeling prior to our evaluation of these supplements). We also included a new section in labeling entitled *Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder*, which states that diagnosing these illnesses in children/adolescents is difficult, and that medication management is but one part of a comprehensive treatment program necessary to provide optimal care. *Dosing and Administration* describes what we learned from the trials about dosing younger patients, and is presented in an easy to read tabular form in Highlights. The Medication Guide was updated to include a comprehensive description of what can be expected when using the drug, and when the patient/parent should call the prescriber. The Office of Safety and Epidemiology were consulted to evaluate the Medication Guide and the safety review team reviewed the final REMS documents.

CONCLUSIONS

The safety and efficacy of Zyprexa has been established in pediatric patients with schizophrenia and manic or mixed episodes associated with bipolar I disorder. My recommendation to the Director is to approve these indications, with the expanded labeling and Medication Guide. This action will provide clinicians treating these patients with the proper information about dosing, a complete description of the risks of treating pediatric patients with Zyprexa (including our labeling stating that other drugs should be tried first in adolescent patients secondary to adverse metabolic effects), and a comprehensive Medication Guide to provide to patients with their prescription. These approvals would provide another treatment option for clinicians treating pediatric patients suffering from these debilitating diseases.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/

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/s/

MITCHELL V Mathis
12/04/2009