DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

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RE: NDA # 20-639
Seroquel® (quetiapine fumarate) Tablets
MACMIS ID # 14670

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a professional sales aid (238110) for Seroquel® (quetiapine fumarate) tablets (Seroquel) submitted by AstraZeneca under cover of Form FDA 2253. This piece is false or misleading because it minimizes the risk of hyperglycemia and diabetes mellitus and fails to communicate important information regarding neuroleptic malignant syndrome, tardive dyskinesia, and the bolded cataracts precaution. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(6)(i). The promotional material raises significant public health and safety concerns through its minimization of the risks associated with Seroquel.

Background

According to its FDA-approved product labeling (PI), Seroquel is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex and for the treatment of schizophrenia.

The PI includes important warnings and precautions. It states (in pertinent part):

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical

manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing

a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

Orthostatic Hypotension
SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. SEROQUEL should be used with particular caution in patients with known cardiovascular disease, cerebrovascular disease or conditions which would predispose patients to hypotension.

Cataracts
Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures
As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

* * *

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, FDA asked all manufacturers of atypical antipsychotics to include a warning in their PI regarding this risk on September 11, 2003. FDA believes that the safe use of Seroquel can be enhanced by informing prescribers and patients about these events and increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment and thus reduce the risk for the most serious outcomes. The PI including the hyperglycemia and diabetes mellitus warning for Seroquel was approved on January 12, 2004.

Misleading Presentation

Page two of the professional sales aid starts with a prominent header, which states “Diabetes Information,” and then presents the following five bullets:

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL
- The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population
- The results of retrospective studies of SEROQUEL and diabetes have been discrepant
- Postmarketing reports of diabetes or diabetes-related events are very rare (<0.01%) with SEROQUEL. These reports were confounded by preexisting or coexisting risk factors and/or had limited information
- SEROQUEL is an atypical that has had over 16 million patient exposures worldwide since its approval in 1997. AstraZeneca believes that the available scientific and medical data do not establish that SEROQUEL causes diabetes

The first two bullets contain information from the Warning in Seroquel's PI regarding Hyperglycemia and Diabetes Mellitus concerning the observed hyperglycemic events and the areas of uncertainty about the glucose abnormality findings. While the agency acknowledges that it has not been established whether Seroquel causes diabetes, you fail to include information regarding the increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. The increased risk may be due to confounding factors and is not completely understood, but a warning about it was recently added to Seroquel's PI to enhance the safe use of Seroquel and protect public health. Because your bullets about the relationship between the use of Seroquel and hyperglycemia leave out this information, the bullets are misleading and undermine the warning.

Furthermore, the fourth bullet claims that the percentage of diabetes or diabetes-related events in post-marketing reports is "very rare (<0.01%) with Seroquel." In light of the voluntary nature of post-marketing adverse event reporting by healthcare professionals and patients, it is infeasible to obtain an accurate percentage of all diabetes or diabetes-related

adverse events associated with Seroquel based upon these reports. Therefore, quantifying post-marketing adverse events in this manner is misleading.

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Specifically, the professional sales aid fails to include relevant risk information about the Warnings and Precautions that it presents. While the professional sales aid states that "Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia," it fails to reveal that the risk of developing the condition and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered increase. The sales aid also fails to mention that the syndrome may partially or completely remit if antipsychotic treatment is withdrawn. Additionally, the professional sales aid states that "A rare condition referred to as neuroleptic malignant syndrome has been reported with this class of medications, including SEROQUEL." This statement is misleading in that it fails to reveal that NMS is a potentially fatal symptom complex associated with the administration of Seroquel. Furthermore, the professional sales aid fails to convey the important information from the PI regarding the clinical manifestations of NMS and that management of NMS should include immediate discontinuation of antipsychotic drugs.

The professional sales aid states that "Precautions include the risk of seizures, orthostatic hypotension, and cataract development." This statement is misleading because it omits material facts from the PI about these risks. In particular, it fails to mention important information from the bolded cataracts precaution recommending that physicians examine all patients at initiation of Seroquel treatment or shortly thereafter, and at six month intervals during chronic treatment, to detect cataract formation.

Conclusion and Requested Action

For the reasons discussed above, the professional sales aid misbrands Seroquel in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(6)(i).

DDMAC requests that AstraZeneca immediately cease the dissemination of violative promotional materials for Seroquel such as those described above. Please submit a written response to this letter on or before November 30, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Seroquel the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14670 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Seroquel comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Dean

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