DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

James L. Gaskill, Pharm.D.
Director, Promotional Regulatory Affairs
AstraZeneca LP
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

RE: NDA # 20-639, 22-047
Seroquel® (quetiapine fumarate) Tablets
Seroquel XR™ (quetiapine fumarate) Extended Release Tablets
MACMIS ID #16370

Dear Dr. Gaskill:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by an AstraZeneca LP (AZ) sales representative on January 3, 2008, to a healthcare professional, and a mailing from AZ dated January 4, 2008, to the same healthcare provider, regarding its drugs, Seroquel® (quetiapine fumarate) tablets (Seroquel) and Seroquel XR™ (quetiapine fumarate) Extended Release Tablets (Seroquel XR). The representative and the mailing recommended or suggested a use for Seroquel and Seroquel XR that has not been approved by FDA, and thus created a new "intended use" for Seroquel and Seroquel XR for which the products lack adequate directions. Thus, these promotional activities and materials misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(f)(1), and FDA implementing regulations. 21 CFR 201.100(c)(1) & 201.128.

Background

According to the Indications and Usage section of its FDA-approved product labeling (PI),[1] Seroquel is indicated, among other things, for the following:

> **Bipolar Disorder**
> SEROQUEL is indicated for the treatment of both:
> - depressive episodes associated with bipolar disorder
> - acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex.
>
> The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients. Effectiveness has not been systematically evaluated in clinical trials for more

[1] At the time of this violative action, the approved PI (and the version referred to within this letter) for Seroquel was the version dated July 30, 2007. Although not relevant to the issues cited in this letter, the most recent version of the Seroquel PI was approved on May 13, 2008.

than 8 weeks. The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania. Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy. The efficacy of SEROQUEL as adjunct maintenance therapy to lithium or divalproex was established in 2 identical randomized placebo-controlled double-blind studies in patients with Bipolar I Disorder. The physician who elects to use SEROQUEL for extended periods in Bipolar Disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Schizophrenia
SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients. The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

According to the Indications and Usage section of the FDA-approved PI[2] for Seroquel XR:

SEROQUEL XR is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL XR in schizophrenia was established in part, on the basis of extrapolation from the established effectiveness of SEROQUEL. In addition, the efficacy of SEROQUEL XR was demonstrated in 1 short-term (6-week) controlled trial of schizophrenic inpatients and outpatients.

The effectiveness of SEROQUEL XR in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Promotion of Unapproved Use

On Thursday, January 3, 2008, at approximately 3:00 p.m., a sales representative from AZ in the —b(4)— made an unsolicited sales call to a physician at his office. The representative stated that Seroquel was approved for treatment of major depressive disorder (MDD). This representation was not made in response to a request for such information by the physician. As a result of this representation, the physician requested that AZ provide written information to support the claim that Seroquel has been approved for the treatment of MDD. In response to this request, AZ sent the physician a mailing dated January 4, 2008.

[2] At the time of this violative action, the approved PI (and the version referred to within this letter) for Seroquel XR was the version dated May 17, 2007. Although not relevant to the issues cited in this letter, the most recent version of the Seroquel XR PI was approved on October 8, 2008.

The mailing contained information about Seroquel and Seroquel XR's use for MDD, and included summaries of eight clinical trials with referenced citations. This mailing was not the result of an unsolicited request by the physician, but rather was prompted by the sales representative's statements.

According to their PIs, **Seroquel and Seroquel XR are not FDA-approved for the treatment of MDD.**[3] Therefore, the oral statements made by the sales representative and the information provided in the January 4, 2008, mailing, misleadingly suggest a new "intended use" for Seroquel and Seroquel XR. Because the PIs for Seroquel and Seroquel XR lack adequate directions for this use, the drugs are therefore misbranded. Although the letter to the physician states that "[AZ] does not recommend the use of SEROQUEL or SEROQUEL XR in any other manner than as described in the enclosed prescribing information," this disclaimer is insufficient to mitigate the promotion of a new "intended use" for which the products lack adequate directions.

Conclusion and Requested Action

The oral statements made and information provided by AZ and its representative recommend or suggest a use for Seroquel and Seroquel XR that has not been approved by FDA, and thus misbrand Seroquel and Seroquel XR in violation of the Act, 21 U.S.C. 352(f)(1), and FDA implementing regulations. 21 CFR 201.100(c)(1) & 201.128.

DDMAC requests that AZ immediately cease the dissemination of violative promotional materials for Seroquel and Seroquel XR such as those described above. Please submit a written response to this letter on or before December 15, 2008, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Seroquel and Seroquel XR as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #16370 in addition to the NDA number. We remind you that only written communications are considered official.

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 and Seroquel XR comply with each applicable requirement of the Act and FDA implementing regulations.

[3] Seroquel is approved for the treatment of depressive episodes associated with bipolar disorder, which is a disease state that is distinct from MDD. On October 8, 2008, Seroquel XR was also approved for the treatment of depressive episodes associated with bipolar disorder.

Sincerely,

{See appended electronic signature page}

Amy Toscano, Pharm.D., CPA
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/

Amy Toscano
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