DEPARTMENT OF HEALTH & HUMAN SERVICES

FOI

Food and Drug Administration
Rockville MD 20857

MAY - 6 1999

TRANSMITTED VIA FACSIMILE

Anthony F. Rogers
Director, Marketed Products Group
Drug Regulatory Affairs
Zeneca Pharmaceuticals
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

RE: NDA #20-639
Seroquel (quetiapine fumarate) Tablets
MACMIS #7914

Dear Mr. Rogers:

Reference is made to Zeneca Pharmaceuticals' (Zeneca) February 9, 1999, response to the Division of Drug Marketing, Advertising and Communications' (DDMAC) request for all materials that Zeneca has continued to distribute following a warning letter dated November 24, 1998. DDMAC has reviewed submitted materials for Seroquel (quetiapine fumarate) Tablets that we have determined to be false, lacking in fair balance, or otherwise misleading, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

DDMAC has the following objections to promotional claims and presentations for Seroquel:

1. Materials that minimize the potential of Seroquel to cause ocular changes are misleading and lacking fair balance. This risk is presented as a bolded precaution in the approved product labeling (PI) for Seroquel, yet Zeneca has distributed materials that directly contradict the precaution (e.g., the fact sheet #SQ1134, Slide Presentation #SQ1067 and the video tape entitled "Ocular Changes in Patients with Psychotic Disorders"). These materials emphasize that ocular changes are probably due to other risk factors common to psychotic patients (including other antipsychotics) and assure doctors that there is nothing to be concerned about with Seroquel. The fact sheet bears a bolded and underlined statement: "A Causal Relationship Between Seroquel and Cataracts Has Not Been Established," yet additional context from the PI, explaining the reasons for concern, is minimized in a subparagraph. The tape further minimizes the importance of this precaution

by providing examples of other drugs that cause cataracts, as well as an example of a drug that carried a similar precaution that was later removed from its PI. Finally, the tape compares the incidence of cataracts in Seroquel patients with the incidence of cataracts in patients on haloperidol. This type of comparison is false and misleading because it is not supported by well-controlled, head-to-head comparative trials that were designed to examine development of cataracts in patients on these drugs.

2. The PI for Seroquel states that lenticular changes should be monitored by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive measures, at the initiation of treatment and at six month intervals during chronic treatment. Zeneca has been distributing materials, including the aforementioned video tape and fact sheet, that emphasize that another appropriately sensitive measure is examination of the lens by direct ophthalmoscopy. Direct ophthalmoscopy is not a sensitive measure of lenticular changes and may miss a developing cataract when it is present. Thus, these materials are false or misleading, and may lead to failure to detect drug-induced lenticular changes.

3. Materials that state or imply that Seroquel is effective in a broader range of mental conditions, including bipolar disorder and schizoaffective disorder, are misleading (e.g., brochures #SQ1035, #SQ1112). Seroquel is indicated for the manifestations of psychotic disorders as determined by clinical trials in schizophrenic inpatients. Application to broader or additional mental disorders would require substantiation from adequate and well-controlled studies designed to examine the specific mental conditions.

4. The mechanism of action of Seroquel, as well as other antipsychotic drugs, is unknown. Therefore, materials that discuss how Seroquel "works" without stressing the theoretical nature of this information, are misleading (e.g., brochures #SQ1059, #PR1048).

5. Materials in which the prominence and readability of the risk information fails to be reasonably comparable to the information regarding the effectiveness of Seroquel lack fair balance (e.g., journal ad #SQ1089, brochure #SQ1139). In addition, materials that fail to disclose the important warnings and precautions (i.e., neuroleptic malignant syndrome, tardive dyskinesia, orthostatic hypotension, risk of cataract development, and seizures) are lacking fair balance because these are considered to be priority safety considerations (e.g., journal #SQ1088).

6. A single-fixed dose haloperidol arm was included as a comparative treatment in one of three clinical trials for Seroquel. This single active arm was inadequate to provide a reliable and valid comparison of the two antipsychotic drugs. Consequently, materials that emphasize comparisons of Seroquel to haloperidol are misleading (e.g., reprint carrier #SQ1133).

To address these objections, DDMAC recommends that Zeneca do the following:

1. Immediately discontinue these and any other materials with the same or similar issues.

2. Provide a written response of Zeneca's intent to comply with this recommendation within 10 business days of the receipt of this letter. This response should include a list of all violative promotional materials that include the same or similar deficiencies, and Zeneca's methods for discontinuing their use.

If Zeneca has any questions or comments, please contact Norman A. Drezin, Esq. or Lisa L. Stockbridge, Ph.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm.17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS 7914 in addition to the NDA number.

Sincerely,

Lisa L. Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing,
Advertising and Communications