DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-639

MAY - 1 2000

Zeneca Pharmaceuticals
Attention: W.J. Kennedy, Ph.D.
1800 Concord Pike
POB 15437
Wilmington, DE 19850

2000/142

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TO REGULA

Dear Dr. Kennedy:

Please refer to your new drug application (NDA) for Seroquel (quetiapine fumarate) tablets.

We have recently examined postmarketing surveillance data from the FDA Adverse Event Reporting System for Seroquel as well as for other atypical antipsychotics with respect to spontaneous reports of new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis. Although this examination revealed few of these adverse experiences in association with Seroquel treatment, a larger number of cases with similar agents that have longer periods of postmarketing exposure raises the possibility that more cases associated with Seroquel will emerge as experience accumulates.

To assist us in more fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose regulation, we are requesting that sponsors of these agents provide us with more extensive safety information. Thus, we ask that you submit the following for our consideration:

1) A comprehensive review of all preclinical data pertaining to hyperglycemia. We are particularly interested in any evidence of islet cell pathology observed in animal studies.
2) A thorough assessment of all Phase 1, 2, and 3 studies in the Seroquel NDA for evidence of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia. This should include the frequency of deaths, serious adverse events, total adverse events, and dropouts due to events related to abnormalities of glucose metabolism listed above, data regarding mean changes from baseline in plasma glucose level, and the percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration from an appropriate pool of placebo-controlled Phase 2/3 studies. Any deaths, dropouts, or serious adverse events should have an accompanying detailed narrative summary.
3) A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia.
4) An estimate of patient exposure.
5) Copies of any correspondence with foreign regulatory agencies related to these events in association with quetiapine.

Also, we ask that you investigate the possibility of collaborating with organizations having large pools of treated patients (e.g., HMO or VA databases) that might be examined for evidence of

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hyperglycemia or new-onset diabetes mellitus associated with quetiapine.

Please compile this information and submit it to us within 3 months.

If you have any questions, call Steve Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research