DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER

Food and Drug Administration
Rockville MD 20857

Certified Mail
Return Receipt Requested

Reference No. 06-HFD-45-0120

Bruce R. Steffler, Esq.
Chairman
Human Investigation Committee of Houston, Texas
1802 Calumet
Houston, Texas 77004

Dear Mr. Steffler:

Between May 2 and 5, 2005, Mr. Joel Martinez and Dr. Constance Lewin, representing the Food and Drug Administration (FDA), inspected the Human Investigation Committee (HIC) of Houston, Texas, which serves as an Institutional Review Board (IRB). The purpose of this inspection was to determine whether HIC was in compliance with the regulations governing IRBs and those governing the protection of human subjects participating in clinical trials contained in 21 CFR Parts 56 and 50. These regulations apply to clinical investigations of products regulated by FDA. We are aware that at the conclusion of this inspection, our investigators presented and discussed with you a Form FDA 483, Inspectional Observations.

From our evaluation of the establishment inspection report, the documents submitted with that report, and your written response dated May 31, 2005, addressed to FDA's regional office in Dallas, Texas, we conclude that the IRB failed to adhere to certain requirements in 21 CFR Parts 56 and 50 (as described below). The regulatory violations were identified from the review of the IRBs procedures and the review of the following studies:

IRB protocol[ ]"A Multiple-Dose, Steady-State Study Assessing the Relative Bioequivalence of Clozapine 200 mg Tablets[ ]and Two Clozaril® 100 mg (Novartis) Tablets" (also known as[ ]protocol[ ]

IRB protocol[ ]"A Multiple-Dose, Steady-State Study Assessing the Relative Bioequivalence of 3 Formulations of Clozapine[ ]and Clozaril® 100 mg (Novartis) Tablets" (also known as[ ]protocol [ ]

IRB protocol[ ]"A Multiple-Dose, Steady-State, 4-Way Crossover Study Assessing the Relative Bioequivalence of 3 Formulations of Clozapine 200 mg Tablets [ ]and Two Clozaril® 100 mg (Novartis) Tablets" (also known as [ ]protocol[ ]

IRB protocol[ ]"A Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses of an Intramuscular Formulation of[ ]in stable Schizophrenic Subjects" (also known as[ ] protocol[ ]

IRB Protocol[ ]"A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation[ ] and Placebo in the Treatment of Patients with Schizophrenia" (also known as protocol [ ]

IRB protocol[ ]"A Multiple-Dose Steady-State Study Assessing the Relative Bioequivalence of Clozapine[ ]and Clozaril® 100 mg (Novartis) Tablets" (also known as Protocol[ ]

IRB Protocol[ ]"Olanzapine versus Ziprasidone in the Treatment of Schizophrenia" (also known as[ ] protocol[ ]

We wish to emphasize the following:

1. **The IRB failed to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50. [21 CFR 56.111(a)(4)]**

   a. For protocols[ ](protocol and informed consent approved by HIC on 8/28/01), [ ](protocol and informed consent approved by HIC on 6/6/02), and[ ](protocol and informed consent approved by HIC on 9/24/02), the IRB failed to ensure that a description of any reasonably foreseeable risks or discomforts to the subject were included in the informed consent documents (ICDs). [21 CFR 50.25(a)(2)].

      i. The Clozaril® (clozapine) labeling that was in effect in 2001 and 2002 contains the following information in a BOXED WARNING:

      "Because of the significant risk of agranulocytosis, a potentially life-threatening adverse event, Clozaril® (clozapine) should be reserved for use in the treatment of severely ill schizophrenic patients who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment. . . .."

      The WARNINGS section also indicates that agranulocytosis associated with Clozaril use can "prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with Clozaril® (clozapine) use as of December 31, 1989, 32% were fatal."

      The HIC-approved ICDs for protocols[ ](approved on 6/6/02),[ ]approved on 8/28/01), and[ ]approved on 9/24/02), fail to adequately describe this risk.

These ICDs mention only a potential "drop in the white blood cell count." They fail to disclose that there is a significant risk of agranulocytosis associated with Clozaril®, and that this condition can be fatal.

ii. On January 14, 2002, FDA recommended that a BOXED WARNING regarding an increased risk of fatal myocarditis, especially during the first month of therapy, be placed in the Clozaril® labeling, and that additional detail about this risk be placed in the WARNINGS section. In February 2002, Novartis (the manufacturer of Clozaril®), sent a letter to medical practitioners informing them about the addition of this warning to the Clozaril® labeling.

The BOXED WARNING states that:
"Analyses of post-marketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued."

The WARNINGS section was also revised to include, among other things, the following discussion of the signs and symptoms of myocarditis:

". . . the possibility of myocarditis should be considered in patients receiving CLOZARIL who present with unexplained fatigue, dypsnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias . . . Tachycardia, which has been associated with CLOZARIL treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis." The WARNINGS section also indicates that, as of August 2001, there had been 30 reports of myocarditis in the United States and 17 fatalities.

The HIC-approved ICDs for protocols[ ](approved on 6/6/02) and[ ] (approved on 9/24/02) failed to include a description of the increased risk of fatal myocarditis associated with Clozaril® therapy or a discussion of the signs and symptoms of myocarditis about which subjects taking clozapine should be aware.

b. For protocols[ ]the IRB failed to ensure that the ICDs disclosed appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. [21 CFR 50.25(a)(4)]

The INDICATIONS section of the Clozaril labeling states that:

"Clozaril is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, Clozaril should be

used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from the drug."

The WARNINGS section further states that:

"Before initiating treatment with CLOZARIL, it is strongly recommended that a patient be given at least 2 trials, each with a different standard drug product for schizophrenia, at an adequate dose, and for an adequate duration."

The ICDs for protocols[ ]state only that "[o]ther treatments and therapies for schizophrenia are available. Those might include other medications and psychotherapy." These ICDs failed to point out that there are several drugs indicated for the treatment of schizophrenia for which the labeling does not recommend that use be restricted to patients who have failed other schizophrenia treatments and that might have been beneficial in treating the subjects' condition. These ICDs also failed to point out that, because of the significant risk of agranulocytosis and seizure, the approved labeling for Clozaril® strongly recommended that this drug be used only in severely ill schizophrenic patients who failed to have an adequate response to at least two of these other therapies.

In your written response to the above items, you state that you will recommend that in the future the IRB require that a medical or scientific IRB member ensure that medical monitoring of subjects comply with boxed warnings for drugs that have such warnings and that medical monitoring comply with manufacturers' warnings for investigational drugs. We are concerned that this response does not address whether the IRB will actually ensure that informed consent is sought in accordance with FDA regulations and, more specifically, does not address the IRB's failure to ensure disclosure of all reasonably foreseeable risks and appropriate alternative procedures or courses of treatment that might be advantageous to the subject.

2. **The IRB failed to ensure that risks to subjects were minimized by using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk. [21 CFR 56.111(a)(1)]**

The approved Clozaril® labeling states that "[p]atients who are being treated with Clozaril must have a baseline white blood cell (WBC) and differential count before initiation of treatment, and a WBC count every week for the first six months. Thereafter, if acceptable WBC counts have been maintained during the first six months of continuous therapy, WBC counts can be monitored every other week." The product labeling further states that "WBC counts must be monitored weekly for at least four weeks after the discontinuation of Clozaril®." HIC approved protocols[ ]with the following WBC monitoring schedule:

a. Protocol[ ]requires WBC counts pre-study, prior to period 2 (Day 16), and post-study (Day 26)
b. Protocol[ ]requires WBC counts pre-study, prior to period 2 (Day 15), and post-study (Day 25)
c. Protocol[ ]requires WBC counts pre-study, prior to period 3 (Day 26), and post-study (Day 46).

The monitoring frequencies for WBC counts in these protocols (ranging from 10 to 26 days) were not adequate to ensure that risks to subjects were minimized.

In your written response, you state that you will recommend that in the future the IRB require that a medical or scientific IRB member ensure that medical monitoring of subjects comply with boxed warnings for drugs that have such warnings and that medical monitoring comply with manufacturers' warnings for investigational drugs. We are concerned that this limited response, with only a promise for a recommendation to the IRB, does not provide sufficient assurance that in the future the IRB will in fact ensure that risks to subjects are minimized in all FDA-regulated research under the IRB's review.

3. **The IRB failed to have a written procedure in place to ensure prompt reporting to FDA of any unanticipated problems involving risks to human subjects or others. [21 CFR 56.108(b)(1)]**

   While your IRB's written procedures do mention reporting to the IRB, they do not contain a procedure for ensuring prompt reporting to FDA of any unanticipated problems involving risks to human subjects or others.

In your written response, you state that you will recommend that the IRB amend its bylaws to provide for prompt reporting of unanticipated problems to FDA. We are concerned that this response, with only a promise for a recommendation to the IRB, does not provide sufficient assurance that the IRB will in fact amend its procedures to incorporate the above written procedure, which the IRB is required to have for FDA-regulated research.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB.

Because of the departures from FDA regulations discussed above, please inform this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action.

If you have any questions, please contact Dr. Constance Lewin at (301) 827-7279, FAX (301) 594-1204. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

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