DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Surendra Chaganti, M.D.
2639 Miami St., Suite S-20
MedClin Research Inc.
St. Louis, MO 63118

Ref: 08-HFD-45-1003

Dear Dr. Chaganti:

Between March 6 and 23, 2007, Ms. Pamela Vega and Ms. Kathleen Swat, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

- Protocol [ ] entitled "A Randomized, Double-Blind, Parallel- Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Subjects with Schizophrenia," involving the investigational drug Paliperidone Palmitate, performed for Johnson and Johnson Pharmaceutical Research Development, LLC;

- Protocol [ ] entitled "A Multicenter, Randomized, Parallel-Group, Double-Blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (oral tablets 400 mg to 800 mg daily in divided doses) to Placebo When Used as Adjunct to Mood Stabilizers (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients," involving the investigational drug Quetiapine Fumarate, performed for AstraZeneca Pharmaceuticals LP; and

- Protocol [ ] entitled "The Efficacy of [ ] as Adjunctive Therapy in Subjects with Insomnia Related to Generalized Anxiety Disorder (GAD)," involving the investigational drug [ ] performed for [ ]

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your April 27, 2007, written response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of

clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Vega and Ms. Swat presented and discussed with you items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to conduct the clinical investigation according to the investigational plan [21 CFR 312.60].**

   Protocol [ ]

   a. The protocol required that all serious adverse events (SAEs) were to be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event. The protocol required that information regarding SAEs be transmitted to the sponsor using the Serious Adverse Event Form. The protocol also stated that any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a SAE. The following were noted during the inspection:

      i. During clinic visit 9 on 10/14/05, subject 201 notified the clinical site of her breast cancer diagnosis and scheduled surgery date of 10/28/05 to remove her left breast. The subject returned to the clinical site on 11/11/05 and 12/7/05 for visit 10 and 11, respectively. However, no SAE was documented on the SAE form. Dr.[ ](sub-investigator) reported the SAE to the sponsor via phone on 12/9/05, two months after you became aware of the SAE. The SAE form indicates that the investigator/investigational staff became aware of SAE on 12/7/05, which is not accurate.

      ii. During clinic visit on 5/1/06, subject 209 notified the clinical site of his hospitalization on 4/27-29/06 for an infected neck lymph gland. Dr.[ ] documented this SAE on the SAE form on 5/24/06, more than three weeks after you became aware of the SAE. The SAE form indicates that the investigator/ investigational staff became aware of the SAE on 5/23/06, which is not accurate.

   You state in your April 27, 2007, response that while "AEs are not supposed to be reported to the sponsor within 24 hours" SAEs are. We consider breast cancer diagnosis and mastectomy, as well as infected neck lymph gland to be SAEs. Therefore we find your response to be inadequate.

   b. The protocol required that all adverse events (AEs) that occur between the first study-related procedure and the last study-related procedure were to be reported. This included any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. The protocol also required that all AEs, regardless of seriousness, severity, or presumed relationship to study therapy were to be recorded in the source document and the case report form (CRF). The following subjects had laboratory results that you determined to be clinically significant; however, these AEs were not reported to the sponsor as required by the protocol:

Subject No.	Laboratory Test Clinically Significant	Lab Report Date(s)
121	alkaline phosphatase	2/15/2006
123	cholesterol, LDL, triglycerides, glucose	2/8/2006 6/30/2006
125	glucose, insulin, SGPT	2/8/2006
127	GGT, alkaline phosphatase, triglycerides, urinalysis – micro squamous epithelial cells	9/4/2005
	SGOT, GGT, cholesterol, LDL, glucose, insulin, c-peptide	7/13/2006
128	alkaline phosphatase, GGT	4/24/2005
	alkaline phosphatase, GGT	6/26/2005
	SGOT, nitrite	10/2/2005
202	Glucose	10/17/2006
209	GGT, white cell count, lymphocytes	7/15/2006
223	glucose, nitrite, leukocytes, occult blood, insulin	9/28/2005
	uric acid, nitrate, leukocytes	3/15/2006

We find your April 27, 2007, response inadequate because it does not explain why these AEs were not promptly reported to the sponsor. Timely, accurate, and complete reporting of required safety information from clinical studies is crucial for the protection of subjects.

c. According to the protocol, randomization was to be used in the double-blind recurrence prevention period and the study drug administrator was the only person to be responsible for study drug injections, drug accountability, and contacting the [ ]system[ ]to receive the subject's medication kit information. The medication kit number obtained by subjects was based upon a computer-generated schedule prepared by the sponsor before the study.

i. The inspection revealed the following dosing errors:

1. Per[ ] study medication kit number 150780 was assigned to subject 123; however, the subject's medication worksheet and drug accountability log document that study medication kit number 150779 was administered to subject 123.

2. Per[ ]study medication kit number 150779 was assigned to subject 125; however, the subject's medication worksheet and drug accountability log document that study medication kit number 150780 was administered to subject 125.

ii. The inspection also revealed that there were entries/changes that were made in the drug accountability log by someone other than the study drug administrator.

d. The protocol required that subjects must be provided with a "study card" indicating the name of the investigational product, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications. The inspection revealed that study cards were not provided to any subjects as required by the protocol.

Protocol [ ]

a. According to the protocol, the use of sedative hypnotics including non-benzodiazepines was disallowed during the study participation and must not have been used for minimum of 1 week prior to Visit 1. Subject 003 met this exclusion criterion; however, the subject was enrolled in the study. The subject 003's concomitant medication worksheet documents that the subject stopped taking Ambien (zolpidem tartrate) on 10/30/05. Study visit 1 for subject 003 occurred on 10/31/05. In your April 27, 2007, response you acknowledge that the subject was on a medication that required a one week washout period prior to starting the study, which should have excluded the subject from the study.

b. According to the protocol, the Montgomery Asberg Depression Rating Scale (MADRS) was to be administered by a trained clinician at visit 1. The inspection revealed that Dr. [ ] Study Coordinator, performed the MADRS assessment for four of the six subjects enrolled in the study. He was not a qualified rater as required by the protocol. In your April 27, 2007, response, you acknowledge that Dr. [ ] was not a qualified rater to do some of the assessments, but claim that the sponsor provided a waiver making him eligible to do these assessments. There is no documentation to indicate that the sponsor provided such a waiver. Therefore we consider your response to be inadequate.

Subject	Date of MADRS
001	10/24/05
002	10/31/05
003	10/31/05
004	11/1/05

c. Dr. [ ] performed the Clinical Global Impression-Severity (CGI-S) assessment for subject 003 on 10/31/05. He was not a qualified rater as required by the protocol.

d. The protocol required that all subjects were to receive a Medical Events Calendar (MEC) to be completed throughout their time on study to record changes in their health status or medications. At each return visit, the MEC was to be reviewed, collected, and a new MEC was to be dispensed. There is no documentation to indicate that the MEC was given to subjects for the months of October, November and December. In addition, MECs were found in subjects' files for the month of January; however, MECs were not completed other than subject's name, number, and signature. You acknowledge in your April 27, 2007, response that MECs were "not used by the site in the beginning of the study."

2. **You failed to report promptly to the Institutional Review Board (IRB) all unanticipated problems involving risk to human subjects or others [21 CFR 312.66].**

   Protocol [ ]

   a. Subject 128 was admitted to the hospital on 9/10/05 for exacerbation of schizophrenia. You were notified of the SAE on 9/16/05 and reported the SAE to the sponsor the same day; however, you did not report the SAE to the IRB until 8/25/06, eleven months later.

   b. Subject 209 was admitted to the hospital on 11/3/05 for pneumonia. You were notified of the SAE on 11/28/05 and reported the SAE to the sponsor on 11/29/05; however, you did not report the SAE to the IRB until 8/25/06, nine months later.

   c. Subject 201 was admitted to the hospital on 10/28/05 for removal of left breast secondary to breast cancer. Your clinical site contacted the sponsor to report the SAE on 12/7/05; however, you did not report the SAE to the IRB until 8/25/06, eight months later. In your April 27, 2007, response, you claim that failure to promptly report the SAEs for subjects 128 and 209 to the IRB was "due to failure of fax transmission;" however, you did not explain the delay in your reporting of subject of 201's SAE to the IRB. We find your response to be inadequate.

3. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].**

   Protocol [ ]

   On May 4, 2005, [ ] Institutional Review Board approved an addendum to the informed consent form (Version date: 04 April 2005), updating the risks to incorporate new information regarding an allergic reaction to the oral medication. You received and reviewed the addendum on 5/12/2005. Subject 122 did not sign the addendum. In your April 27, 2007, response, you acknowledge that you could not find a signed addendum for subject 122. Therefore, there is no evidence that subject 122 was informed of the additional risk outlined in the addendum.

   Protocol [ ]

   The IRB issued a memorandum on May 26, 2006, informing you that the IRB approved informed consent form (ICF), version 3, on April 13, 2006, for the above mentioned study. The revised consent form contained medical information disclosing potential additional serious risks to subjects. You signed and dated the IRB memorandum on June 6, 2006. There is no evidence that subjects 003, 010, 011, 025, 026, 031, 033, and 034 were informed of these additional risks. In your April 27, 2007, response, you state that the site did not receive ICF version 3 until August 4, 2006. We find your response to be inadequate because on June 6, 2006, you signed and dated the IRB memorandum that enclosed the revised consent form, version 3, for the above mentioned study.

4. You failed to conduct the investigation in accordance with the signed investigator statement [21 CFR 312.60].

You failed to list the names of all sub-investigators who would be assisting in the conduct of the investigation, as required by the Form FDA 1572. Review of records at the site revealed that the Form FDA 1572, Statement of Investigator, dated 1/20/05 and 2/25/05, did not include Ms. [ ](Study Drug Coordinator). According to the study records, Ms. [ ]treated subjects on protocol [ ]specifically, Ms. [ ]administered the study drug for the following subjects from 3/28/05-4/29/05:

Subject	Date(s) of study drug injection
121	4/11/05
122	3/28/05, 4/4/05
123	3/28/05, 4/4/05
124	4/4/05, 4/11/05
125	3/28/05, 4/4/05
126	3/28/05, 4/4/05
127	4/11/05
128	4/22/05, 4/29/05
129	4/22/05, 4/29/05
130	4/22/05, 4/29/05
201	4/22/05, 4/29/05
203	4/26/05
204	4/27/05
205	4/27/05

The inspection revealed that Ms. [ ]was not added to Form 1572 until May 1, 2005.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at (240) 276-8829; FAX (240) 276-8844. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

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

/s/

Leslie Ball
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