DEPARTMENT OF HEALTH & HUMAN SERVICES

JUL 25 2000

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

Certified Mail - Restricted Delivery
Return Receipt Requested

Ref. No.: 01-HFD-45-0301

Candace S. Brown, Pharm.D., FNP
University of Tennessee Medical Group
Dept. OB/GYN, 909 Ridgeway Loop Road
Memphis, Tennessee 38120

Dear Dr. Brown:

Between April 12 and April 14, 2000, Ms. Patricia S. Smith, representing the Food and Drug Administration (FDA), met with you to review your conduct of the following clinical study of the investigational drug[ ] Protocol[ ] *in the Treatment of Female Sexual Disorder: Effect of Dosage Route on Pharmacokinetics and Safety*, performed for[ ] under IND[ ] This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

Ms. Smith presented and discussed with you her findings, which were listed on Form FDA 483, Inspectional Observations. From our evaluation of the inspection report, the documents submitted with that report, and your letter of April 26, 2000, responding to the findings of the inspection, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We wish to emphasize the following:

I. SUMMARY OF VIOLATIONS RELATED TO YOUR FAILURE TO CONDUCT THE INVESTIGATION ACCORDING TO THE SIGNED INVESTIGATOR STATEMENT (21 CFR 312.60 AND 312.53)

a) You failed to personally conduct or supervise the investigation, which led to an overdose of study drug in two subjects [21 CFR 312.53(c)(1)(vi)(c)].

In a single-dose pharmacokinetic study in which you were the principal investigator, two subjects,[ ]101[1] and[ ]102, each received a 10-fold overdose of study drug within approximately 20 minutes of one another. As a

[1] The randomization code for Subject[ ]is shown as "101" in the subject's lab reports, as "009" on the Visit 1 "ASEX" [Arizona Sexual Experiences Scale] Form, as "001" in the[ ]Study Flow Sheets.

result, these subjects experienced significant drug-related toxicities, which could have been avoided.

Your written response of April 26, 2000, which states that you "were in the [ ] unit, but not in the subject's [*sic*] room when the study drug overdose was administered" and that after the overdose, you "discovered that a dosage calculation error had occurred," does not provide an acceptable explanation. We request that you address whether the dosage calculation was made in writing, and whether you made or checked this calculation, which resulted in the medication error, prior to study drug administration.

In addition, your letter discusses only the overdose given to subject[ ]/101, who received the study drug 20 minutes *after* subject[ ]/102. Given the time interval between administration of study drug overdoses to these two subjects, please explain why subject[ ]/101 was treated prior to resolving the medication error in subject[ ]/102.

b) You failed to conduct the study in accordance with the relevant current protocol and you failed to notify the sponsor prior to making changes in the protocol [21 CFR 312.53(c)(1)(vi)(a)].

(1) The protocol, dated July 23, 1999 and approved by the IRB on August 18, 1999, states that "Subcutaneous[ ]will be supplied in a 2 mL vial containing 10 mg/mL [ ]in aqueous solution. The 1 mg (0.1mL) dose will be administered with a 1 cc tuberculin syringe in the anterior abdominal wall... [ ]is manufactured by [ ] and will be available for study use."

[ ] manufactured by[ ] was substituted for the protocol specified drug, and was administered at your site to subjects[ ]/101 and [ ]/102 on 1/12/00, to subject[ ]/401 on 2/2/00, and to subject [ ]/201 at 7:10 a.m. on 2/16/00. The protocol, however, was not amended to reflect the use of[ ]as study drug until 2/4/00 and the amended protocol was not approved by the IRB until 2/16/00.

(2) You amended the original 6/16/99 protocol on 7/23/99, 11/2/99, 1/13/00, and 2/4/000. There was no documentation however to show that any of these amended protocols were formally reviewed and approved by the sponsor prior to implementation.

In fact, written evidence of sponsor approval of the amended 2/4/00 protocol is dated March 7, 2000, after the administration of[ ]to all four subjects listed in (1) above. In addition, the approval coversheet identifies the 2/4/00 protocol as "Revision #1, Dated 2/4/00," suggesting

that the sponsor neither formally reviewed nor approved the amended protocols dated 7/23/99, 11/2/99, and 1/13/00.

We request that you address whether you (as the protocol author) indeed obtained sponsor review and written acknowledgement of any of the changes in the protocol prior to your implementation (as the clinical investigator).

Although your letter dated April 26, 2000, states that you "will obtain IRB approval of all protocol changes before institution, including ... "sponsor-approved protocol deviations," you have not stated that, in the future, you will comply with FDA's requirement to obtain ***sponsor*** approval of all protocol changes before implementation. Please address.

II. SUMMARY OF VIOLATIONS RELATED TO REQUIREMENTS FOR INVESTIGATOR REPORTING TO THE IRB (21 CFR 312.66)

You failed to promptly report to the IRB of a change in study plan, specifically a change in the test article from [redacted] to [redacted] You administered [redacted] to three study subjects before submitting an amended protocol to the IRB on 2/4/00. The IRB did not approve the amended protocol until 2/16/00, by which date you had administered [redacted] to a fourth subject.

You promise, in your summary of corrective actions included in your letter dated April 26, 2000, that in the future you will obtain IRB approval of all protocol changes before implementation. Your letter, however, does not acknowledge your responsibility for failure to obtain IRB review and approval for this change in study plan. Please address this in your response to this Warning Letter.

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. Your letter of April 26, 2000, does not address our concerns regarding lack of adequate investigator oversight, failure to adhere to protocol, failure to obtain sponsor approval of changes in a protocol prior to institution, and failure to obtain IRB approval for changes to the protocol. Please address these issues in detail and in the context of meeting all applicable Federal regulations. Failure to adequately and promptly explain the violations noted above may result in further regulatory action.

If you have any questions, please contact Dr. John R. Martin, at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

Martin H. Cohen, MD

Martin H. Cohen, M.D.
Acting Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Enclosure: 21 CFR 312