DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 19 2005

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Raymond E. Tidman, M.D.
101 Riverstone Vista
Suite 206
Blue Ridge, Georgia 30513

Ref: 05-HFD-45-1202

Dear Dr. Tidman:

Between April 21 and 29, 2003, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #[ ]entitled: "A Multicenter, Investigator-Blinded, Randomized Study to Compare the Safety and Efficacy of IV Daptomycin with That of Vancomycin or a Semi-Synthetic Penicillin in the Treatment of Complicated Bacterial Skin and Soft Tissue Infections Due to Gram-Positive Bacteria") of the investigational drug[ ]now known as Cubicin (daptomycin for injection), performed for Cubist Pharmaceuticals, Inc. This inspection was a part of 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 in the study have been protected.

At the conclusion of the inspection, Ms. Hubbard presented and discussed with you the items listed on the Form FDA 483, Inspectional Observations. Based on our evaluation of the information obtained by the agency and your April 30, 2003, written response to the Inspectional Observations, we conclude that you violated the Federal, Food, Drug, and Cosmetic Act (the Act) and FDA regulations governing the use of investigational new drugs, by your failure to protect the rights, safety, and welfare of human subjects and failure to adhere to the investigational plan. We wish to emphasize the following:

1. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

   a. For monitoring the safety of subjects, the protocol required that hematology, serum chemistries (including creatinine phosphokinase (CPK)), and urinalysis be obtained at study admission (Day 1) and at the end-of-therapy (EOT) visit, and that serum CPK be monitored throughout the study (Day 3, Day 5, Day 7, and daily thereafter, if drug therapy was continued beyond 7 days).

In addition, the protocol provided detailed instructions about what to do if subjects experienced elevated CPK levels:

"If CPK levels exceed the upper limit of normal by twofold at any time of the trial, the central laboratory will automatically evaluate CPK isoenzymes to determine if the elevated fraction is M/M. Venous blood samples will then be obtained on a daily basis and sent to the central laboratory for CPK monitoring (i.e., CPK will be determined each day, with other serum chemistries determined every other day). If CPK levels subsequently decline to within the normal range, then venous blood samples should be obtained according to the original schedule. If CPK levels exceed [ ] U/mL, the unblinded investigator will call the medical monitor. A decision to discontinue or continue the subject will be jointly made and will be based on the risk/benefit of continued therapy for the subject. If the subject continues in the trial and CPK levels increase another twofold, the subject must be withdrawn from the study and CPK isoenzymes, serum myoglobin, and urinary myoglobin will be evaluated at the termination visit." (emphasis in original)

Despite the importance for subject safety of monitoring CPK levels, and the protocol's explicit requirements to do so, you did not obtain all required CPK levels or other required laboratory results for any subject you enrolled (see table below). For some subjects, you failed to obtain most of the required CPK levels. Elevations in serum CPK activity provide an early indication of muscle toxicity and rhabdomyolysis, a disease resulting from skeletal muscle injury with release of muscle fiber contents into the systemic circulation that may lead to kidney failure. Failure to obtain required laboratory results may have exposed your subjects to an increased and unnecessary risk of serious toxicity.

Subject	Missing Laboratory Evaluations		
	Chemistries (including CPK)	Urinalysis	Hematology
168141	Days 3, 5, 7, 8, 9, 10, 13, 14	EOT*	-
168142	Days 3, 5, 7	-	EOT
168143	Days 3, 5, 7, 8, 9, EOT	EOT	EOT
168144	Days 2, 3, 5, 7-11	EOT	-
168145	Day 5	-	-
168146	Days 1, 3, 5	-	-
168147	Days 1, 3, 7	-	-
168148	Days 5, 7	-	-
168149	Days 3, 5, 7-9	Admission, EOT	EOT
168150	Days 3, 5, 7	-	-
168151	Days 3, 5, 7	Admission, EOT	-
168152	Days 3, 5, 7	Admission	EOT
168153	Days 5, 7, 8-20**	Admission, EOT	EOT
168154	Days 3, 5, 7	EOT	EOT

* EOT = End-of-Therapy

** See violation 2.e below

b. The protocol excluded subjects who were taking HMG Coenzyme A reductase inhibitors (statins). There is an established association between statins and incidence (albeit rare) of rhabdomyolysis, and a possible association with the study drug. Subject 168151 was taking Lipitor (a statin) at the time she was enrolled in the study and continued to take it throughout her participation in the study. Exposing this subject to two drugs with the potential to cause this condition may have increased this subject's risk of serious toxicity.

2. You failed to adhere to the protocol [21 CFR 312.60].

a. Protocol inclusion criteria required a diagnosis of skin and soft tissue infection known or suspected (based on Gram stain) to be due to gram-positive bacteria. Subjects 168145, 168146, 168147, 168148, and 168154 were enrolled in the study despite Gram stains that showed no gram-positive bacteria.

b. The protocol required that one investigator be blinded to the treatment that subjects were receiving to be able to objectively evaluate the subjects' clinical response to treatment and the relationship of adverse events to the study drug. The protocol required an unblinded investigator to manage the subjects' care and note any adverse events during the course of the study. In your written response to the 483 dated April 30, 2003, you stated that your study coordinator, Ms. [ ] acted as the unblinded investigator. However, source records demonstrate that you performed both roles. You prescribed home IV Daptomycin treatment for subject 168150, wrote inpatient orders for Vancomycin treatment for subjects 168142, 168143, and 168153, and wrote inpatient orders concerning the Vancomycin trough level for subject 168146. These orders indicate that you were aware of these subjects' treatment during the course of the study (i.e., had broken the blind) and had thus violated the protocol and compromised your ability to objectively evaluate clinical response. Of note, during the inspection, you agreed that it looked like the blind was broken for subject 168153.

c. The protocol required that appropriate specimens for Gram stain and culture be obtained at the End-of-Therapy (EOT) and Post-Therapy (PT) visits if clinically significant lesions and/or drainage persisted. Subject 168141 had wound drainage at the EOT and PT visits, and you failed to obtain a Gram stain and culture at both visits.

d. The protocol required that subjects be treated with intravenous therapy throughout the study unless all criteria were met to convert to oral therapy, including permission from the sponsor's Medical Monitor. You converted subjects 168142, 168143, and 168146 to oral therapy without obtaining permission from the Medical Monitor.

e. The protocol required that the investigator obtain permission from the sponsor's Medical Monitor to extend therapy past 14 days. You failed to obtain permission from the Medical Monitor to treat subject 168153 beyond 14 days. The subject was treated for 20 days.

f. Four subjects received concomitant medications that were prohibited by the protocol:

- Subject 168141: Neosporin topical ointment
- Subject 168143: betadine dressings
- Subject 168150: hydrogen peroxide and betadine dressings
- Subject 168153: Augmentin, hydrogen peroxide, and betadine dressings.

g. The protocol required that On-Therapy Evaluations occur on study day 3-4, EOT Evaluations occur 1-3 days after completion of study drug or upon early termination from study, and Posttherapy Visits occur 7-12 days after completion of study drug. In addition, subjects with successful clinical outcome (cure or improved) at the Posttherapy Visit were required to have a Poststudy Visit at 3-4 weeks after completion of the drug. The following study visits occurred outside the protocol-specified time frames:

Subject	Visit	Due Date	Actual Visit
168143	Post-therapy	10/10/00 - 10/15/00	10/18/00
168144	Post-study	11/20/00 - 11/27/00	11/14/00
168146	On-Therapy	1/25/01 - 1/26/01	1/24/01
	EOT	1/29/01 - 1/31/01	2/5/01
	Post-therapy	2/4/01 - 2/9/01	2/19/01
	Post-study	2/18/01 - 2/25/01	2/27/01
168147	Post-study	3/7/01 - 3/14/01	2/28/01
168152	EOT	5/2/01 - 5/3/01	5/1/01
168154	EOT	7/6/01 - 7/8/01	7/9/01

h. The protocol inclusion criteria required that specimens for a Gram stain be obtained from subjects $\leq$ 48 hours prior to initiating study drug. For subject 168147, the Gram stain was obtained one day after starting the study drug. In addition, for subject 168153, the Gram stain was obtained three days after starting the study drug.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. Your written response to the 483 dated April 30, 2003 attributed most of the deficiencies to the study coordinator or the hospital laboratory, and you stated that you planned to ensure more strict compliance in the future; we do not find your explanations acceptable in addressing the matters under complaint. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must 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, please 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 Leslie K. Ball, M.D., at (301) 827-5455, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

Joanne L Rhoads MD

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research