DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Springs, MD 20993-0002

TRANSMITTED BY FACSIMILE **November 14, 2008**

Saul Komisar, M.B.A.
President, Protherics Inc.
5214 Maryland Way
Suite #405
Brentwood, TN 37027

RE: IND # —— b(4)
Voraxaze™ (glucarpidase)
MACMIS ID # 16901

Dear Mr. Komisar:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a webpage titled, "Voraxaze™ – an enzyme that breaks down methotrexate (MTX)," found at http://www.macromed.com/products/Voraxaze.aspx, (webpage) and a Product Fact Sheet titled, "Voraxaze™ for methotrexate toxicity," found at http://www.macromed.com/Documents/Fact%20sheets/Voraxaze%20FINAL%2018%2006%2008.pdf, (fact sheet) for your investigational new drug Voraxaze (glucarpidase) (Voraxaze). The webpage and product fact sheet contain statements that represent Voraxaze in a promotional context as safe or effective for the purposes for which it is being investigated, or otherwise commercially promote the drug. As a result, these materials misbrand your investigational new drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n) and 321(n), and FDA's implementing regulations. See 21 CFR 312.7(a) and (d)(2). This is problematic from a public health perspective because it suggests Voraxaze is safe and effective when the product has not yet been approved by FDA and the promotional claims made have yet to be demonstrated by substantial evidence or substantial clinical experience.

Promotion of an Investigational New Drug

Voraxaze is an investigational new drug that is available in the U.S. under a treatment IND for patients receiving high dose methotrexate (≥ 1 g/m^2) who are experiencing, or at risk of, methotrexate toxicity. High dose methotrexate is used to treat or prevent the recurrence of certain types of cancer. Patients are considered at risk of methotrexate toxicity if they have impaired renal function, which can lead to a delay in methotrexate elimination, or have evidence of delayed elimination based on methotrexate levels. Additionally, pursuant to 21 CFR 312.7(d), the FDA has authorized the manufacturer of Voraxaze, Protherics Inc. (Protherics), to charge for Voraxaze for this use.

According to 21 CFR 312.7(d)(2), in pertinent part, "A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided . . . (iii) the drug is not being commercially promoted or advertised . . . ." Furthermore, promotion of an investigational new drug is prohibited under 21 CFR 312.7(a), which states that "A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug."

However, the webpage and product fact sheet contain the following misleading claims that either promote the safety or efficacy of, or that otherwise promote, your investigational new drug for the reduction of methotrexate levels in patients who are experiencing, or at risk for, methotrexate toxicity due to impaired or delayed methotrexate elimination. This list is not all-inclusive:

- "Voraxaze™ (glucarpidase, previously known as carboxypeptidase G2 or CPG2) is a biological product designed to rapidly reduce the amount of blood levels of methotrexate (MTX), a commonly used cancer drug in the blood."

- "Voraxaze™ is the only drug which can remove MTX from the blood; dialysis is the only other way to remove MTX from the blood."

- "Voraxaze™ contains a recombinant enzyme (glucarpidase) which rapidly cleaves MTX into a non-toxic form. In one pivotal and two supportive studies, Voraxaze™ was able to achieve a clinically important reduction (CIR) in MTX concentration to ≤1 μmol/L in the majority of patients treated. . . . Voraxaze™ consistently reduced plasma or serum MTX concentrations by an average of >98% by the time of the first sample point, which was usually 15 minutes after Voraxaze administration in each of the three studies."

- "Voraxaze is well tolerated. In clinical studies, a total 25/329 (8%) patients reported 50 adverse events with a possible relationship to Voraxaze™; about a third of these were considered transient allergic reactions (burning sensation, flushing, hot flush, allergic dermatitis, feeling hot, pruritis, hypersensitivity). Only 2 of these adverse events were considered serious, one case each of hypertension and arrhythmia, but neither was definitively associated with use of Voraxaze and the latter was considered more likely to be associated with MTX."

- "Voraxaze is a unique drug that allows clinicians to control patient exposure to methotrexate (MTX)."

- "Voraxaze may also prove suitable for more routine adjunctive use ("planned use") with high-dose MTX (HDMTX) to optimize the HDMTX therapy."

- "Protherics believes that Voraxaze could potentially be used as an adjunctive therapy with each cycle of high dose MTX therapy . . ."

- "Clinical trials in the US and EU have shown that Voraxaze rapidly and predictably reduces MTX levels in the blood of patients in whom its elimination has been delayed."

- Figure 1, titled "Voraxaze (previously CPG2) rapidly reduces blood levels of MTX," shows MTX (μmol/L) before and approximately 15 minutes after CPG2 dosing in 70 patients with paired data from the US NCI Special Exception Protocol.

In addition to promoting Voraxaze for the reduction of methotrexate levels in patients who are experiencing, or at risk for, methotrexate toxicity, some of the above claims promote that Voraxaze may be effective for "routine" or "planned" use with high-dose methotrexate (HDMTX) to optimize the HDMTX therapy. In combination with the other claims about the safety and efficacy of Voraxaze, the webpage and product fact sheet strongly suggest that the drug will be safe and effective for this use as well. These claims are misleading because neither the webpage nor the product fact sheet reveals that there is no data to support the efficacy of the drug for this use or that the risks for routine, planned use are unknown. This is particularly problematic from a public health perspective because routine administration of Voraxaze could have serious safety and efficacy implications. Voraxaze is a protein that is foreign to the body, and the risk of an allergic reaction and/or anaphylaxis may increase following repeat doses. Voraxaze may also become ineffective after repeated doses (i.e., routine use) due to the presence of neutralizing antibodies. Additionally, patients receiving Voraxaze routinely after a cycle of high dose methotrexate may be exposed to a sub-optimal dose of methotrexate, potentially reducing effectiveness of methotrexate for treating or preventing recurrence of certain types of cancer.

Conclusion and Requested Action

For the reasons discussed above, the webpage and product fact sheet misbrand your investigational drug in violation of the Act, 21 U.S.C. 352(a) & (n) and 321(n), and FDA's implementing regulations, 21 CFR 312.7(a) and (d)(2).

DDMAC requests that Protherics immediately cease the dissemination of violative materials for Voraxaze such as those described above. Please submit a written response to this letter on or before November 28, 2008, stating whether you intend to comply with this request, listing all violative materials for Voraxaze, such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301.847.8444. In all future correspondence regarding this matter, please refer to MACMIS ID #16901 in addition to the IND number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your materials for your investigational drug Voraxaze comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lynn Panholzer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Linked Applications	Sponsor Name	Drug Name
IND [redacted]	b(4) PROTHERICS INC	Glucarpidase [Carboxypeptidase G2]

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

/s/

LYNN M PANHOLZER
11/14/2008