DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

James Manuso, Ph.D.
Chairman, President, and Chief Executive Officer
SuperGen Incorporated
4140 Dublin Blvd., Suite 200
Dublin, CA 94568

RE: NDA 20-122
Nipent® (pentostatin) for Injection
MACMIS ID# 13203

WARNING LETTER

Dear Dr. Manuso:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a mechanism of action (MOA) booth panel (800P5(501)) ("panel") and handout (800S4(400)) ("handout") for Nipent (pentostatin) for Injection submitted by SuperGen Incorporated (SuperGen) under cover of Form FDA 2253. This panel and handout are false or misleading because they fail to present any risk information for Nipent, contain an unsubstantiated claim regarding the mechanism of action of the drug, and overstate the safety and efficacy of the drug. By failing to include any risk information, making an unsubstantiated claim, and overstating safety and efficacy, SuperGen misleadingly suggests that Nipent is safer or more effective than has been demonstrated by substantial evidence or substantial clinical experience. See 21 CFR 202.1(e)(6)(i). This panel and handout thus misbrand Nipent in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n).

Background

Approved Product Labeling

According to the FDA-approved labeling (PI), Nipent is indicated as single-agent treatment for both untreated and alpha-interferon-refractory hairy cell leukemia (HCL) patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms.

The "Mechanism of Action" (MOA) section of the PI states that “The precise mechanism of pentostain's antitumor effect… in HCL is not known.” Further, the MOA section states, in part, that:

> Pentostatin is a potent transition state inhibitor of the enzyme adenosine deaminase (ADA). The greatest activity of ADA is found in cells of the lymphoid system . . . Pentostatin inhibition of ADA, particularly in the presence of adenosine or deoxyadenosine, leads to cytotoxicity, and this is believed to be due to elevated intracellular levels of dATP which can block DNA synthesis through inhibition of ribonucleotide reductase. Pentostatin can also inhibit RNA synthesis as well as cause increased DNA damage . . .

Furthermore, the use of Nipent is inappropriate in certain settings and is associated with numerous risks as stated in a Boxed Warning and in the Warnings, Precautions and Adverse Reactions sections of the PI. For example, the PI states, in part:

Boxed Warning

WARNING

. . . Dose-limiting severe renal, liver, pulmonary, and CNS toxicities occurred in Phase 1 studies that used Nipent at higher doses (20-50 mg/m^2 in divided doses over 5 days) than recommended.

In a clinical investigation in patients with refractory chronic lymphocytic leukemia using Nipent at the recommended dose in combination with fludarabine phosphate, 4 of 6 patients entered in the study had severe or fatal pulmonary toxicity. The use of Nipent in combination with fludarabine phosphate is not recommended.

Warnings

- Patients with HCL may experience myelosuppression primarily during the first few courses of treatment. Patients with infections prior to Nipent treatment have in some cases developed worsening of their condition leading to death, whereas others have achieved complete response . . .
- In patients with progressive HCL, the initial courses of Nipent treatment were associated with worsening of neutropenia . . .
- Rashes, occasionally severe, were commonly reported and may worsen with continued treatment. Withholding of treatment may be required . . .
- Acute pulmonary edema and hypotension, leading to death, have been reported in the literature in patients treated with pentostatin in combination with carmustine, etoposide and high dose cyclophosphamide as part of the ablative regimen for bone marrow transplant.
- Pregnancy Category D. Pentostatin can cause fetal harm . . .

Precautions

- The combined use of vidarabine and Nipent may result in an increase in adverse reactions associated with each drug . . .
- The combined use of Nipent and fludarabine phosphate is not recommended because it may be associated with an increased risk of fatal pulmonary toxicity.
- Acute pulmonary edema and hypotension, leading to death, have been reported in the literature in patients treated with pentostatin in combination with carmustine, etoposide and high dose cyclophosphamide as part of the ablative regimen for bone marrow transplant.

Adverse Reactions

- Nausea and/or Vomiting (53% - 63%), Leukopenia (22% - 60%), Fever (42% - 46%), Fatigue (29% - 42%), Rash (26% - 43%), Myalgia (11% - 19%), Infection (7% - 36%), Anemia (8% - 35%), Chills (11% - 19%), Thrombocytopenia (6% - 32%), and Headache (13% - 17%).

Regulatory History

DDMAC has sent SuperGen two previous untitled letters for Nipent since 1997. We issued an untitled letter regarding a convention panel (800CI) on January 6, 1997. That letter stated that the panel was misleading because it was lacking in fair balance with respect to both content and presentation. DDMAC further stated that promotional materials should present true information relating to side effects and contraindications that is comparable in scope, depth and detail with claims for effectiveness or safety. In its January 13, 1997 response, SuperGen stated its intention to discontinue the use of the panel, and to present appropriate warnings, precautions and adverse reactions in all future promotional materials. Based on this commitment, DDMAC considered the matter closed.

DDMAC sent SuperGen an untitled letter regarding a reprint carrier (800S2(301)), journal advertisement (800J2(200)), and website (www.supergen.com (5/8/01)) on May 10, 2001, in which we found those promotional materials for Nipent to be false, misleading, or otherwise in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations because they made misleading claims of long term safety or efficacy, promoted unapproved uses, or lacked fair balance. In its responses[1] SuperGen stated its intention to discontinue the use of all of the violative materials, and to correct all future promotional materials. Based on this commitment, DDMAC considered the matter closed.

[1] Letters dated May 24, 2001, June 1, 2001, July 17, 2001, August 1, 2001, and August 15, 2001.

Omission of Important Risk Information

The MOA panel and handout that are the subjects of this letter present numerous efficacy claims with emphasizing illustrations but entirely omit risk information, including the important risk information from the Boxed Warning (e.g., severe renal, liver, pulmonary, and CNS toxicities at higher doses and fatal pulmonary toxicity when combined with fludarabine) and the Warnings, Precautions and Adverse Reactions sections of the PI. This misbrands the drug. See 21 U.S.C. §§ 352(a) and 321(n). In addition, they fail to communicate an important risk-related limitation in Nipent's approved indication —i.e., "Nipent is indicated for use as single-agent treatment" – in either of these promotional pieces. Merely disseminating the PI with these promotional materials is not sufficient to overcome these violations.

Unsubstantiated Mechanism of Action Claim

The claim "Nipent: The distinctive purine analog with a unique mechanism of action" found in both the MOA panel and handout is false and misleading, in violation of 21 U.S.C. § 352(a). FDA is not aware of substantial evidence or substantial clinical experience to support the claim that Nipent's mechanism of ADA inhibition is "unique." Indeed, it appears that another purine analog, cladribine, also possesses this activity [LEUSTATIN® (cladribine) Injection full Prescribing Information. ORTHO BIOTECH PRODUCTS, L.P.].

Overstatement of Safety and Efficacy

Three claims and associated representations found in both the MOA panel and handout are misleading because they overstate the safety and efficacy of Nipent in violation of 21 U.S.C. § 352(a). FDA is not aware of substantial evidence or substantial clinical experience to support any of these claims.

First, the claim "Adenosine build-up potentiates TNF inhibition" is misleading because the reference provided describes adenosine-mediated inhibition of TNF release by blood cells of alcoholic cirrhotics. This finding has no clear relation to Nipent's indicated use in lymphoid malignancies.

Second, the claim "Nipent is selectively cytotoxic to the leukemic population, exhibiting little or no effect on stem cells" is misleading because it implies that Nipent will have little or no effect on a patient's non-leukemic human bone marrow stem cells and peripheral blood cells. In fact, the claim contradicts the Nipent PI, which states that use of this drug is associated with multiple hematologic cytopenias. It does not appear that the cited reference supports this claim; the reference reports only preliminary in vitro information from normal marrow and peripheral marrow blood cells that would require further studies before extrapolation to humans with HCL.

Finally, the MOA panel and handout present the claim "Through selective, potent, and strong ADA inhibition, Nipent retards DNA repair mechanisms and induces apoptosis while inhibiting TNF," along with a pictorial representation of a cell undergoing

programmed cell death. This claim is misleading because while pentostatin-mediated inhibition of ADA is accepted and reflected in the PI, FDA is not aware of substantial evidence or substantial clinical experience to support the claim "Nipent retards DNA repair mechanisms and induces apoptosis while inhibiting TNF." The pictorial representation of an apoptotic cell beneath the inhibited ADA enzyme is also misleading because it implies that ADA inhibition results directly in apoptosis.

Conclusion and Requested Action

This panel and handout are false or misleading because they fail to present any risk information for Nipent, contain an unsubstantiated claim regarding the mechanism of action, and overstate the safety and efficacy of the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n); see 21 CFR 202.1(e)(6)(i).

DDMAC requests that SuperGen immediately cease the dissemination of violative promotional materials for Nipent such as those described above. Please submit a written response to this letter on or before August 31, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Nipent such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at (301) 594-6771. **Starting August 29, 2005, please direct all written correspondences to the following address: Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705.**

In all future correspondence regarding this matter, please refer to MACMIS # 13203 in addition to the NDA 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 promotional materials for Nipent comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

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