DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Sam Boddapati, Ph.D.
Senior Director, Regulatory Affairs
Supergen, Inc.
Two Annabel Lane, Suite 220
San Ramon, CA 94583

RE: NDA 20-122
Nipent® (pentostatin) for Injection
MACMIS ID# 9696

Dear Dr. Boddapati:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials disseminated by Supergen, Inc. (Supergen) for Nipent (pentostatin) for Injection that are false, misleading, or otherwise in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, the following promotional materials present misleading claims of long term safety and efficacy, promote unapproved uses, or lack fair balance:

- Reprint Carrier ID # 800S2(301)
- Journal Advertisement ID# 800J2(200)
- www.supergen.com website (5/8/01)

Misleading Safety and Efficacy Claims

Supergen's reprint carrier and journal advertisement contain multiple claims relating to ten-year survival and an incidence of secondary malignancy equal to that of the general population that are referenced to a study by Flinn IW, et al. (Blood 2000;96(9):2981-6). For example, the reprint carrier and journal advertisement include the following statements:

> *"67% ten-year relapse-free survival rate" (reprint carrier and journal advertisement)*
>
> *"81% ten-year overall survival rate" (reprint carrier and journal advertisement)*
>
> *"The incidence of overall second malignancies and of solid tumors was not increased among patients treated with pentostatin in this study" (reprint carrier)*

These claims that were derived from the Flinn study are not supported by substantial evidence. First, the clinical data summarized in the Flinn study were from two studies where evaluation of survival was not a uniformly pre-defined endpoint. Second, the total number of patients enrolled was inadequate to clearly establish clinical benefit from the survival results. Lastly, use of a historical control and the small number of patients in the Flinn study are not

adequate to compare incidences of secondary malignancy. Furthermore, the approved product labeling (PI) specifically states, "At a median follow-up duration of 46 months, there was no statistically significant difference in survival between hairy cell leukemia patients initially treated with Nipent and those initially treated with IFN. However, no definite conclusions regarding survival can be made from these results because they are complicated by the fact that the majority of IFN patients crossed over to Nipent treatment." Therefore, the survival and safety claims in the reprint carrier and journal advertisement are misleading because they are not supported by substantial evidence and are inconsistent with the PI.

Promotion of Unapproved Uses

Website

The "Products-Focus on Oncology" (http://www.nipent.com/product/2_3.htm) webpage on the www.supergen.com website promotes Nipent for unapproved uses. As stated in the PI, Nipent is indicated as "single-agent treatment for both untreated and alpha-interferon-refractory hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease-related symptoms." However, the "Products-Focus on Oncology" webpage lists the uses for Nipent as "Leukemias and Lymphomas." Therefore, this statement broadens the approved indication to include all leukemias and promotes an unapproved use of Nipent for all lymphomas.

Furthermore, the presentation of Nipent information on the "Products – Pipeline" webpage (http://www.supergen.com/product/2_2.htm) also promotes Nipent for unapproved uses. Specifically, the introductory paragraph states the products on the page "have not yet been cleared for marketing." However, in the Nipent pipeline chart, the first "indication" listed, hairy cell leukemia, is an approved indication for marketing. The subsequent uses, i.e., "cutaneous & peripheral T-cell lymphoma," "chronic lymph [sic] leukemia," "non-Hodgkin's lymphoma," "graft-vs-host disease," and "rheumatoid arthritis" listed under "Indication" are unapproved uses for Nipent. Presenting product information for approved and unapproved uses together in this manner is misleading because the presentation implies that the unapproved uses are approved.

Journal Advertisement

Supergen's journal advertisement states that "Purine-nucleoside analogs should play a major role in the treatment of low-grade lymphoid malignancies." The phrase "low-grade lymphoid malignancies" broadens Nipent's indication since Nipent is only indicated for " single-agent treatment for both untreated and alpha-interferon-refractory hairy cell leukemia patients with active disease as defined by clinically significant anemia, neutropenia, thrombocytopenia, or disease related symptoms." Therefore, the journal advertisement is misleading because it promotes unapproved uses for Nipent.

Lack of Fair Balance

Promotional materials lack fair balance when they fail to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. The reprint carrier and journal advertisement fail to include the boxed warning regarding the risk of fatal pulmonary toxicity when Nipent is used in combination with fludarabine phosphate. Further, the risk information that is listed lacks prominence compared to the efficacy claims. For example, the risk information is presented in text format with a very small font size whereas the efficacy claims are presented in large, colorful fonts.

In addition, the "Products-Focus on Oncology" (http://www.nipent.com/product/2_3.htm) and "Products-Product Platforms-Oncology" (http://www.supergen.com/product/2_3_1.htm) webpages provide efficacy information but fail to include any risk information for Nipent.

Requested Actions

Supergen should immediately cease distribution of this and other similar promotional materials for Nipent that contain the same or similar claims or presentations. Supergen should submit a written response to DDMAC on or before May 24, 2001, describing its intent and plans to comply with the above. In its letter to DDMAC, Supergen should include the date on which this and other similarly violative materials were discontinued.

Supergen should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 9696 in addition to the NDA number. DDMAC reminds Supergen that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
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/

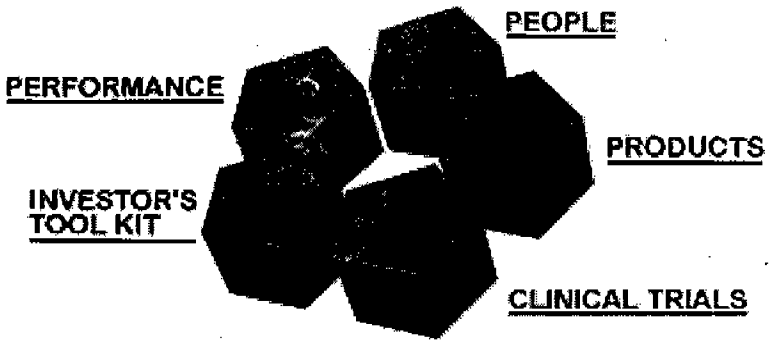
Joseph Grillo
5/10/01 04:33:02 PM

SuperGen

CONTACT US

SEARCH

SITE MAP



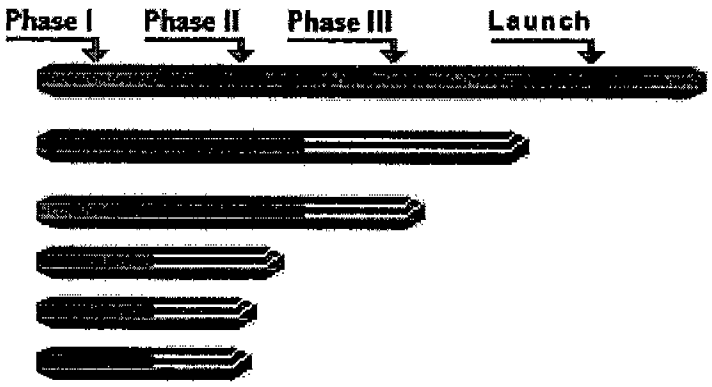
Products - Pipeline

This information is provided for investor evaluation of the product areas, markets and stages of development of SuperGen's products under investigation. Any discussion of products on this website is not intended as consumer information. The products discussed here which have not yet been cleared for marketing in the U.S. are still in clinical or preclinical stages. They are not commercial products. For more information about SuperGen products currently being marketed in the U.S., please refer to the package insert or Physician's Desk Reference.

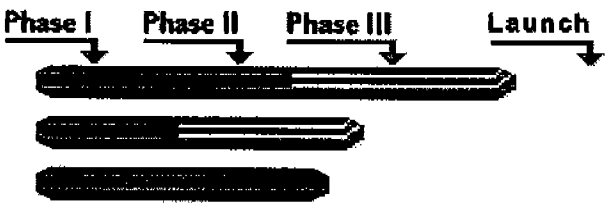
Click on any specific drug for further discussion of the product or product under investigation, as well as the other drugs in that product area.

Oncology

Nipent



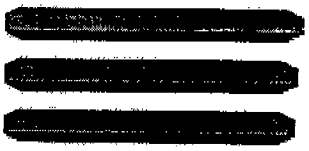
Rubitecan



Colorectal

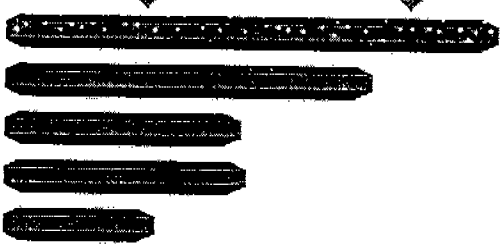
Breast

Lung



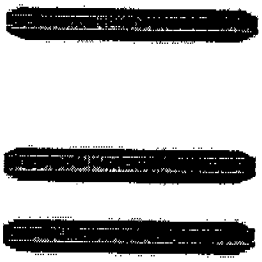
Proprietary Extra™ Reformulations

Product	Formulation	Clinical Development	Launch
Mito Extra ™			
Dauno Extra ™			
Etopo Extra™			
Nipent Extra ™			
Cisplatin Extra ™			

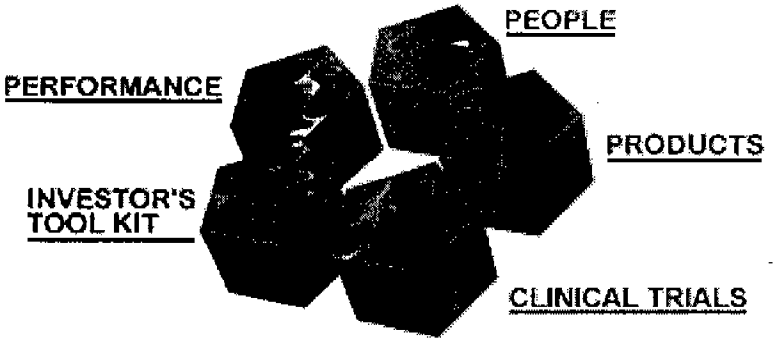


Non-Oncology Opportunities

Indication	Phase I	Phase II	Phase III	Launch
Anemia				
RF 1010				
Obesity and Diabetes				
RF 1051				
RF 1051 (Prader-Willi syndrome)				



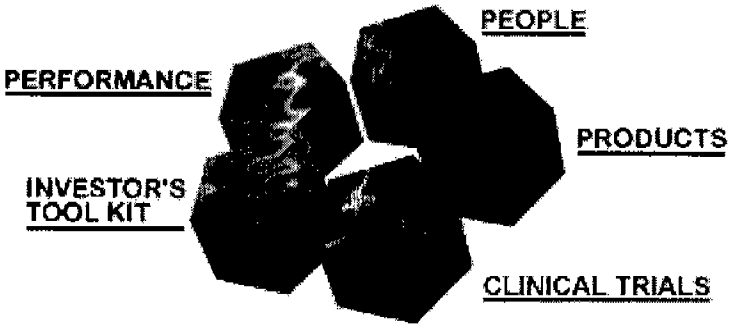
PEOPLE | PRODUCTS | CLINICAL TRIALS | TOOL KIT | PERFORMANCE



Products - Focus on Oncology

- Oncology
  - Nipent: Leukemias and Lymphomas
  - Rubitecan: Solid tumors
  - Extra™: Line of products

  SurfaceSafe™
  Decitabine
- Non-Oncology Opportunities
  - Blood Cell Disorders: RF1010
  - Diabetes and Obesity: RF1051



Products - Product Platforms - Oncology

With Nipent®, our expanding Extra ™ product line and Rubitecan, we believe SuperGen has established its platforms for leadership in the chemotherapy segment of the oncology market.

At the end of 1997, the U.S. Food and Drug Administration (FDA) approved SuperGen's Application to sell our own manufactured Nipent. Earlier in the year, we also signed an international supply agreement making SuperGen the exclusive worldwide supplier of Nipent to Warner-Lambert Company.

Nipent (pentostatin for injection) inhibits a key enzyme, adenosine deaminase (ADA), found in all lymphocytes. Because ADA is expressed at particularly high levels in rapidly dividing cells such as leukemias and lymphomas, we believe ADA inhibition represents a platform technology for the treatment of lymphatic malignancies and disorders.

Nipent is approved in the U.S. for the treatment of hairy cell leukemia and SuperGen is now actively educating physicians about the safety and efficacy of Nipent as the preferred treatment for hairy cell leukemia. Data presented by the independent investigators at the 1997 Annual Meeting of the American Society of Hematology showed an 87% survival estimate eight years after Nipent Treatment, by far the longest survival data for any drug for hairy cell leukemia. Data now show that Nipent produces a very high complete response rate (approximately 85%), and that these responses are extremely durable and most patients remain relapse-free.

SuperGen is supporting a growing body of clinical investigation around the country using Nipent for a wide array of lymphatic malignancies in which the drug has shown activity. Hairy cell leukemia is just one possible result when lymphocytes become malignant. Other outcomes include prolymphocytic leukemia, non-Hodgkin's lymphoma and cutaneous T-cell lymphoma. SuperGen has received or applied for Orphan Drug Designation in several of these indications as well. Combined, these lymphatic malignancies represent a U.S. Market in excess of $200 million per year.

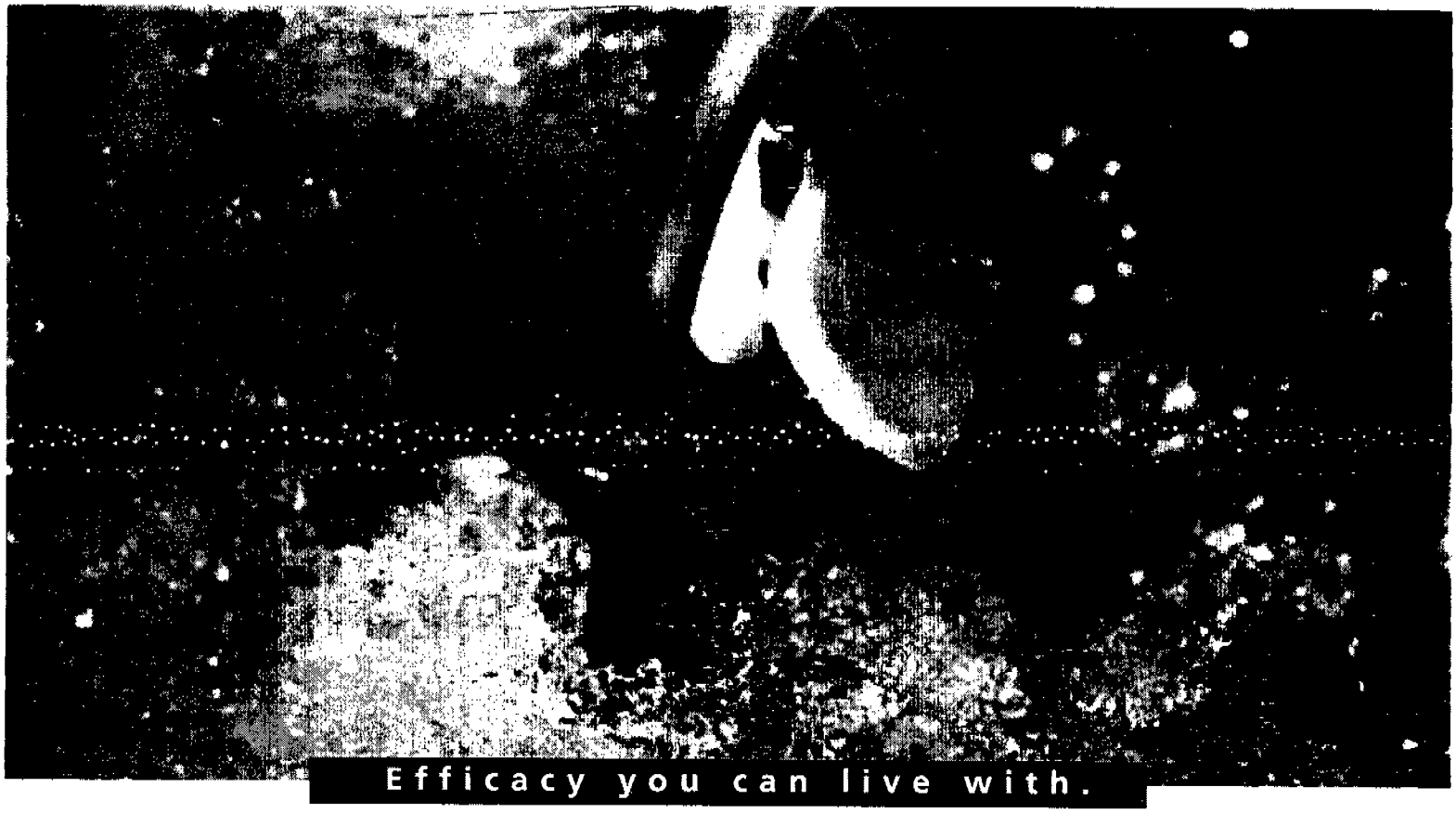
During 1997, SuperGen acquired RFS 2000(now Rubitecan), one of the most exciting drug candidates in our pipeline, from the Stehlin Foundation for Cancer Research, a pioneering organization in Houston. Rubitecan is a topoisomerase I inhibitor which is a patented analogue of a natural compound derived from the camptotheca acuminata tree. We believe Rubitecan is our platform for leadership in the treatment of a broad array of solid tumors.

Our game plan for the rapid commercialization of Rubitecan is, simply stated, to hire key members of the Taxol team to implement a Taxol-like strategy for a drug which the company believes has Taxol-like potential. With key management additions during the year, the people are in place and the strategy is moving forward. First, we are targeting rapid development and approval in an orphan drug indication for which current treatment options are limited--we have selected pancreatic cancer, itself a U.S. market in excess of $200 million. Next, we intend to continue the studies needed to generate the data that would allow us to add larger indications in the commercial marketplace.

Rubitecan is currently in Phase III trials for pancreatic cancer. The incidence of this disease, currently about 29,000 new cases and 29,000 deaths per year in the U.S., is rising and, even with current treatments, median survival for patients with advanced disease is only a few months. In an ongoing Phase II trial, interim data has shown an improvement in patients' quality of life, an increase in their survival rate and a reduction in tumor size (by both CT SCAN and serological markers). Survival data in particular, while still by no means conclusive, so far shows a very favorable comparison with historical data from the scant available options. We hope to rapidly move Rubitecan into multi-center Phase II trials for pancreatic cancer.

The compound's activity, however, is no means limited to pancreatic cancer. In animals the drug has shown activity against more than 30 tumor models, with profound improvement versus controls in breast, lung and colon cancers. In early human studies Rubitecan also already has demonstrated anti-cancer activity against numerous tumors, including prostate, ovarian, lung, breast, colorectal and cervical, in addition to pancreatic cancer.

Even beyond its broad potential range of activity, two other distinguishing features differentiate Rubitecan as a platform for leadership in solid tumors. One is its side effect profile relative to other anti-cancer drugs. In studies to date, none of the cardiac, pulmonary, hepatic or renal toxicities that limit the acute and/or chronic dosages of most chemotherapies have been observed and, in fact, some early studies suggest Rubitecan could be used to treat cancer on a chronic rather than acute basis. The primary side effects that have been observed are mild to moderate hematological toxicities, low grade cystitis, and some gastrointestinal disorder--in all, a relatively benign profile. Finally, Rubitecan is an oral drug where patients can be dosed at home, thus avoiding hospital time and the specter of the intensive care unit.



Survival is a matter of both endurance and resurgence.

It starts with a 90% initial response rate. Ten years later, the survival rate for Nipent is a thriving 81%.[1,2]

The longer we study the efficacy of Nipent, the more impressive the results become. Ten years after initiating treatment, 81% of patients are still living, and 67% are relapse-free.[2] While myelosuppression is a consequence of every chemotherapy for hairy cell leukemia, the manageable myelosuppression of Nipent may allow quick recovery from the treatment. Other adverse reactions reported with Nipent treatment are rash and exacerbation of infection. Patients with hairy cell leukemia are prone to infection, and may experience myelosuppression during the first few courses of any chemotherapy. Patients with preexisting infections have developed worsening infection, sometimes leading to death. It is recommended to avoid treating such patients until the infection has resolved.

Nipent offers a long-term option for treating leukemia. Nipent. Making leukemia history.

800.353.1075
www.supergen.com

Nipent®
10 mg
Pentostatin for Injection
First-Line Treatment for Hairy Cell Leukemia

SuperGen
THE KEY TO LIFE

800J2(300) © 2000 SuperGen, Inc.

67% ten-year relapse-free survival rate[2]	81% ten-year overall survival rate[2]	90% response rate[1]	Convenient outpatient dosing	Efficacy with manageable myelosuppression[3,4]

Please see adjacent page for brief summary of prescribing information, including boxed warning. For more information, call 1-800-353-1075.

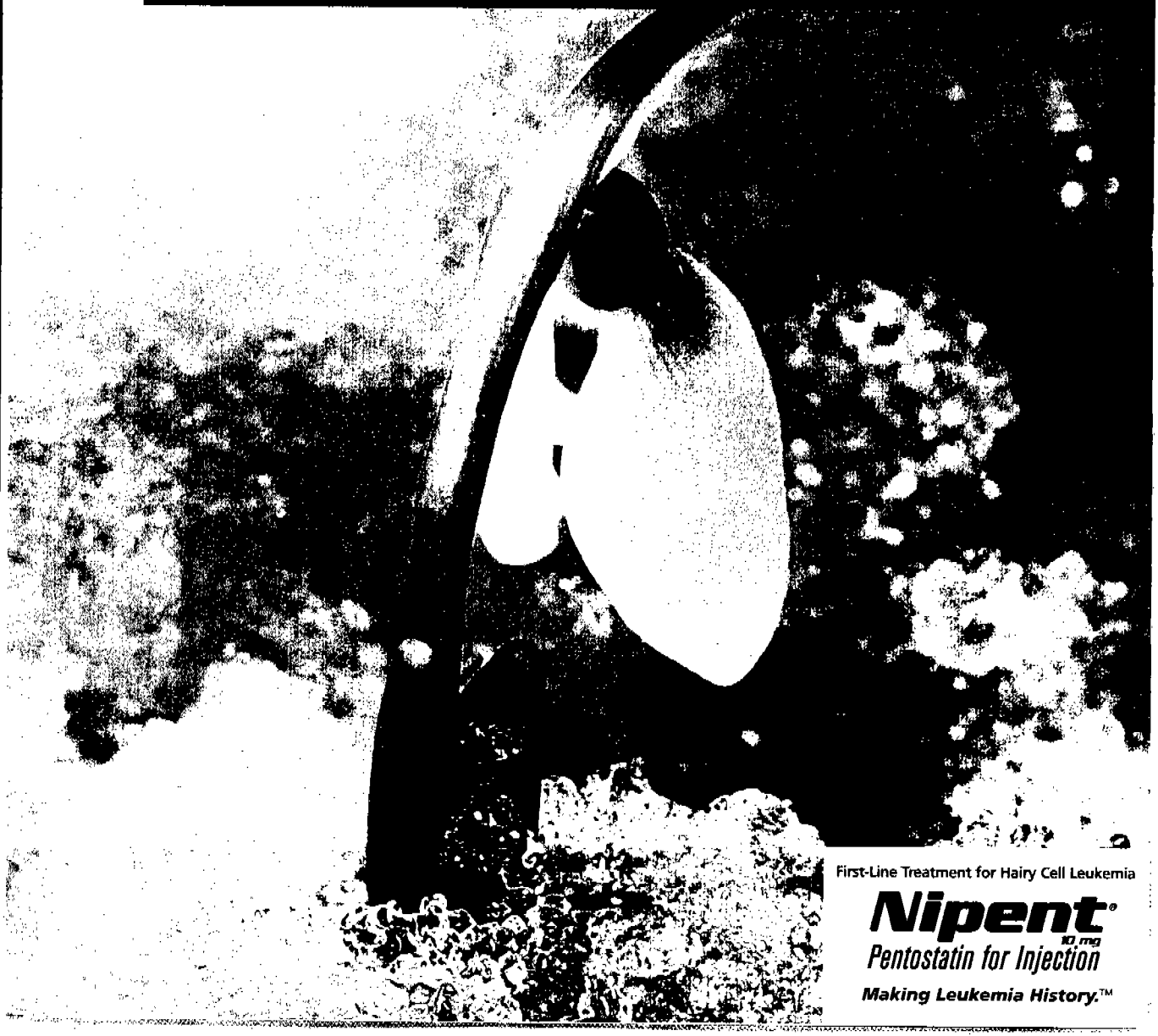
References
1. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. *J Clin Oncol.* 1995;13:974-982.
2. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood.* In press.
3. Kraut EH. Phase II trials of pentostatin (Nipent) in hairy cell leukemia. *Semin Oncol.* 2000; 27(suppl 5):27-31.
4. Cheson BD. Infectious and immunosuppressive complications of purine analog therapy. *J Clin Oncol.* 1995;13(9):2431-2448.

Efficacy you can live with.™

Survival is a matter of both endurance and resurgence.

Breakthrough 10-Year Survival

Analysis confirms the long-term efficacy of Nipent in treating hairy cell leukemia.[1]



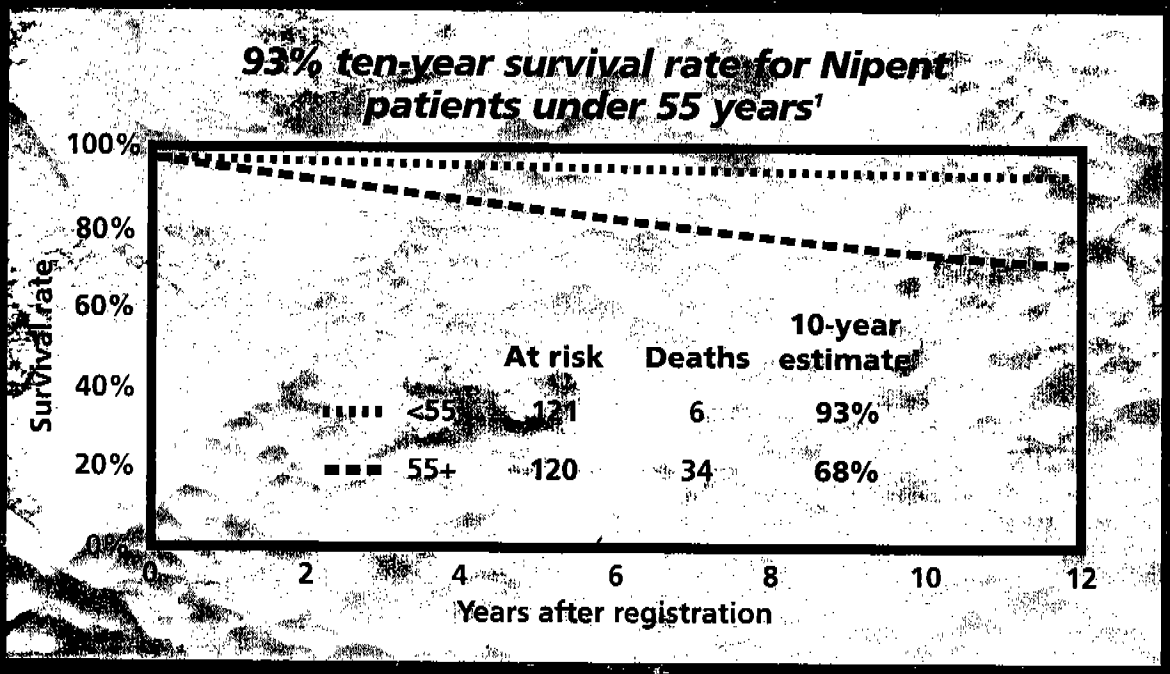
First-Line Treatment for Hairy Cell Leukemia

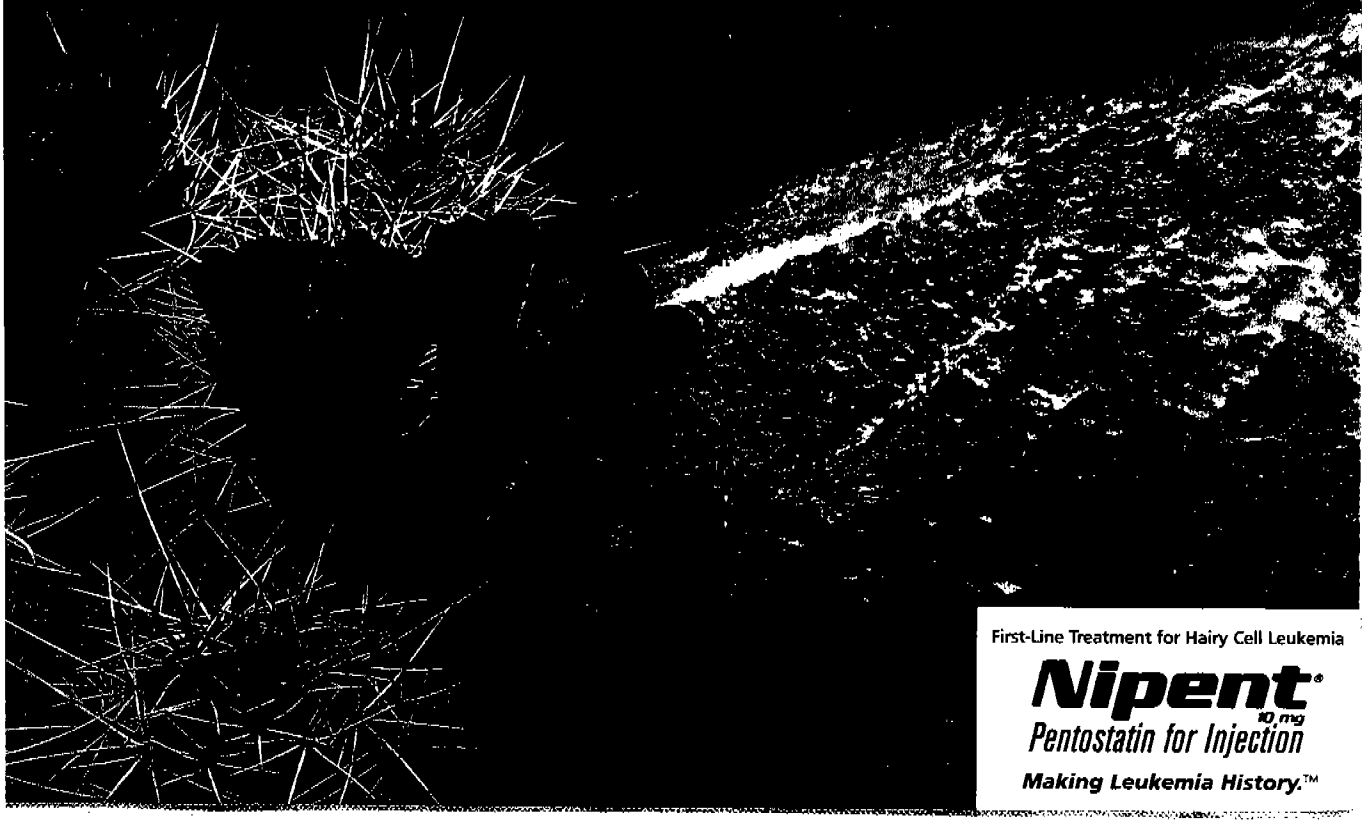
Nipent® 10 mg

Pentostatin for Injection

Making Leukemia History.™

93% ten-year survival rate for Nipent® patients under 55 years[1]





First-Line Treatment for Hairy Cell Leukemia

Nipent® 10 mg

Pentostatin for Injection

Making Leukemia History.™

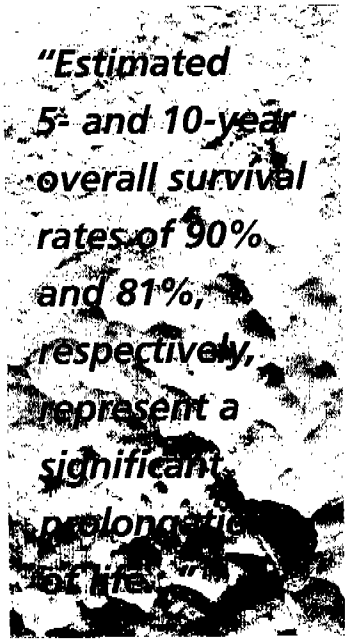
Efficacy you can live with.™

Nipent. The only purine analog with documented 10-year survival data.

Data from a breakthrough intergroup phase III study conducted by SWOG, ECOG, CALGB, and NCIC CTG, and published in the November 2000 issue of *Blood*[1*]:

In hairy cell leukemia:

- 87% initial response rate[2]
- Significantly higher complete response rates with pentostatin compared to interferon alfa (76% vs 11%)[2]
- 90% five-year Kaplan-Meier probability of survival, and 81% ten-year probability of survival[1]
- 67% ten-year, relapse-free survival[1]
- 93% ten-year survival rate for patients under 55 years[1]
- Of the 241 patients treated with Nipent, less than 1% had died of hairy cell leukemia after 10 years[1]
- During induction therapy with Nipent, 27% of patients required systemic antibiotic therapy for either suspected or proven episodes of infection[2]

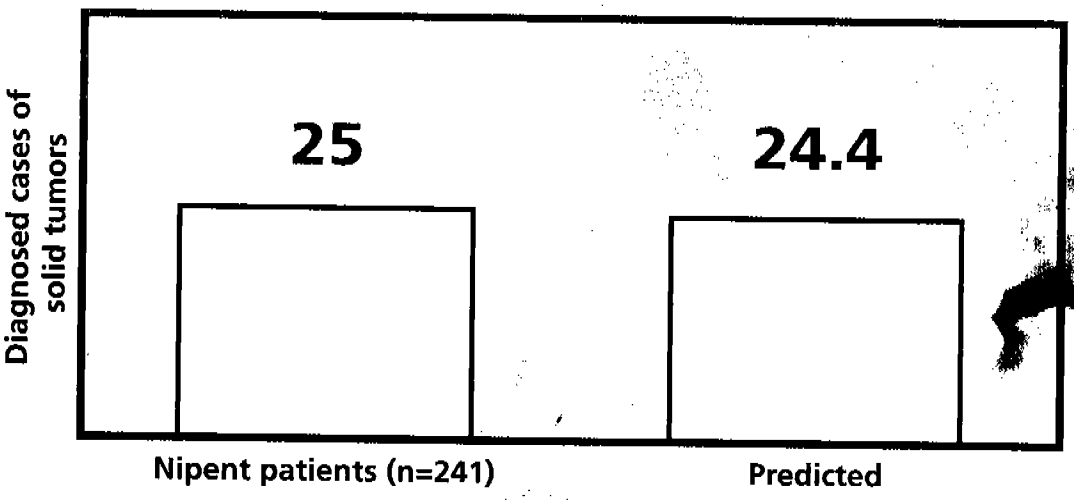


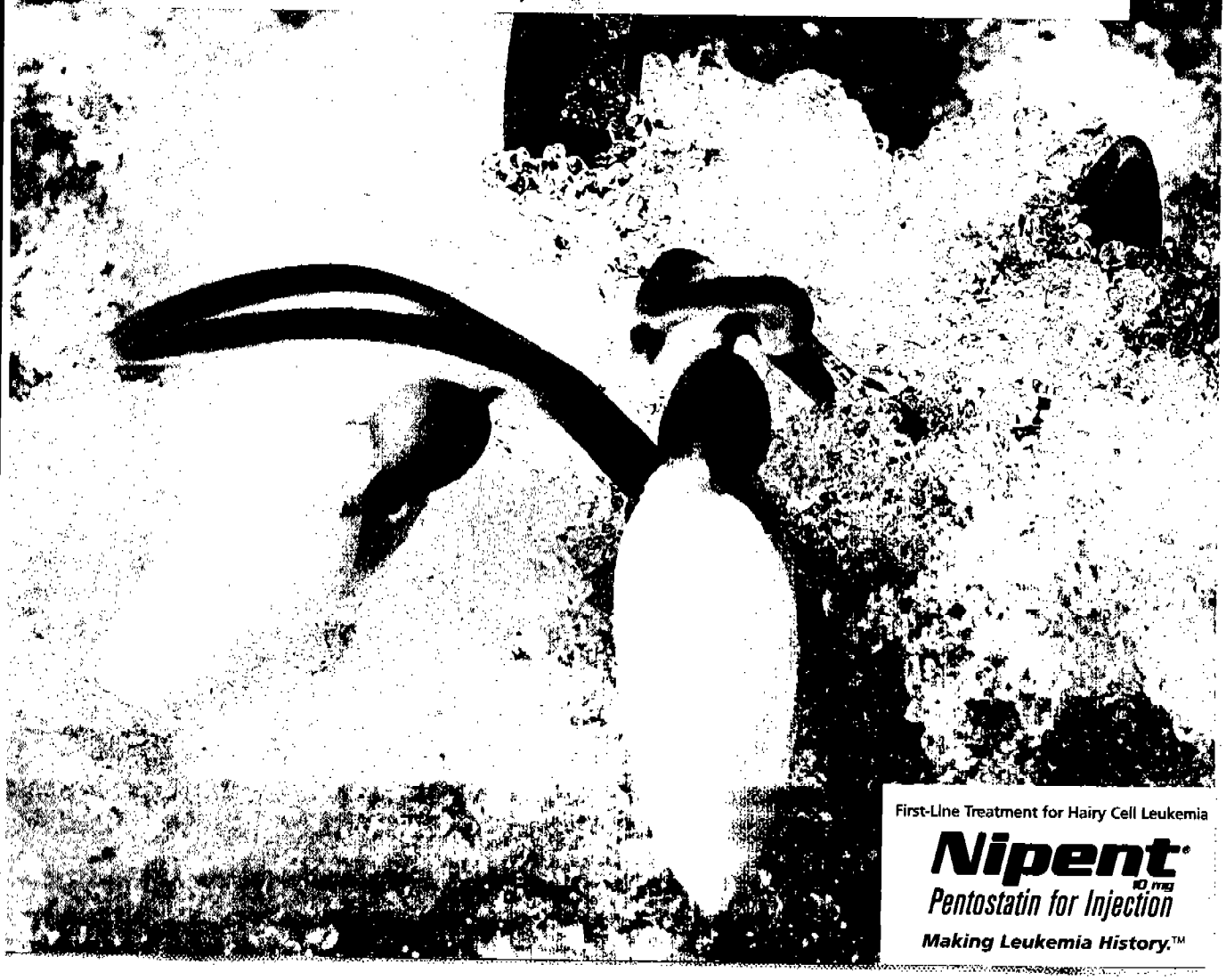
Please see full prescribing information, including boxed warning, in pocket.

*SWOG=Southwest Oncology Group; ECOG=Eastern Cooperative Oncology Group; CALGB=Cancer and Leukemia Group B; NCIC CTG=National Cancer Institute of Canada Clinical Trials Group.

67% ten-year relapse-free survival rate[1]	81% ten-year overall survival rate[1]	90% response rate[3]	Convenient outpatient dosing	Efficacy with manageable myelosuppression[4,5]

No increase in incidence of solid tumors[1]





First-Line Treatment for Hairy Cell Leukemia

Nipent® 10 mg

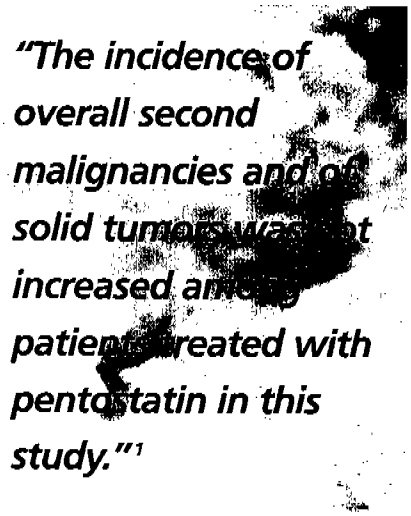
Pentostatin for Injection

Making Leukemia History.™

Survival is a matter of both endurance and resurgence.

Nipent's devastating effect on leukemia cells is balanced by its manageable myelosuppression, allowing patients to recover from treatment.

Other adverse reactions reported with Nipent therapy are rash and exacerbation of infection. Patients with hairy cell leukemia are prone to infection, and may experience myelosuppression during the first few courses of any chemotherapy. Patients with preexisting infections have developed worsening infection, sometimes leading to death. It is recommended that treatment of such patients be avoided until the infection has resolved.

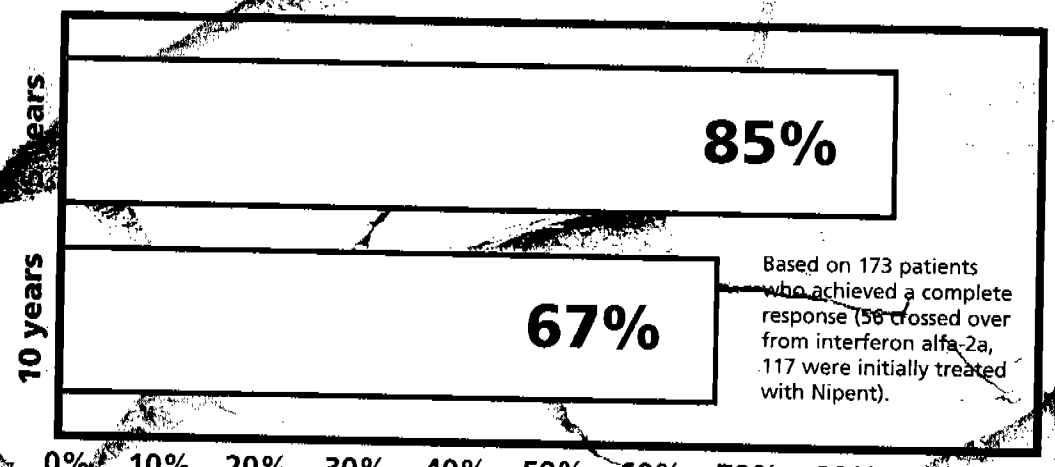


"The incidence of overall second malignancies and of solid tumors was not increased among patients treated with pentostatin in this study."[1]

Please see full prescribing information, including boxed warning, in pocket.

67% ten-year relapse-free survival rate[1]	81% ten-year overall survival rate[1]	90% response rate[3]	Convenient outpatient dosing	Efficacy with manageable myelosuppression[4,5]

Relapse-free survival in Nipent-treated patients[1]



Based on 173 patients who achieved a complete response (56 crossed over from interferon alfa-2a, 117 were initially treated with Nipent).

First-Line Treatment for Hairy Cell Leukemia

Nipent® 10 mg

Pentostatin for Injection

Making Leukemia History.™

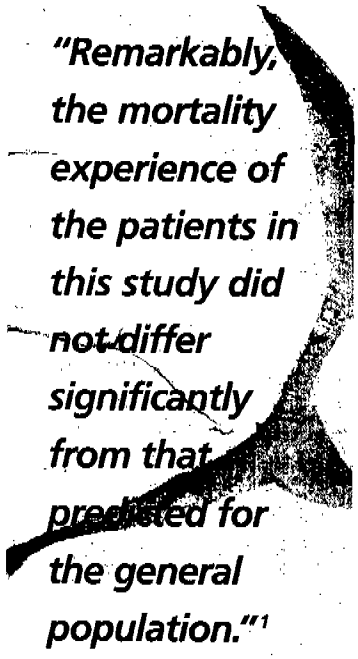
Efficacy you can live with.™

Nipent. Making leukemia history.™

Convenient outpatient dosing –
A single 4 mg/m² intravenous infusion for 20 to 30 minutes every 2 weeks.

The importance of proper hydration –
500 mL to 1000 mL of NS or D_5W should be given prior to Nipent, with another 500 mL given following Nipent administration.

Well-established safety profile –
The most serious adverse reactions reported with Nipent therapy are myelosuppression, rash and exacerbation of infection.



"Remarkably, the mortality experience of the patients in this study did not differ significantly from that predicted for the general population."[1]

The most common adverse reactions reported with Nipent therapy are myelosuppression, rash and exacerbation of infection. Patients with hairy cell leukemia are prone to infection, and may experience myelosuppression during the first few courses of any chemotherapy. Patients with preexisting infections have developed worsening infection, sometimes leading to death. It is recommended to avoid treating such patients until the infection has resolved.

Please see full prescribing information, including boxed warning, in pocket.

References

1. Flinn IW, Kopecky KJ, Foucar MK, et al. Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. *Blood.* 2000;96(9):2981-2986.

2. Grever M, Kopecky K, Foucar MK, et al. Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: an intergroup study. *J Clin Oncol.* 1995;13:974-982.

3. Data on file, SuperGen, Inc.

4. Cheson BD. Infectious and immunosuppressive complications of purine analog therapy. *J Clin Oncol.* 1995;13(9):2431-2448.

5. Margolis J, Grever MR. Pentostatin (Nipent): a review of potential toxicity and its management. *Semin Oncol.* 2000;27(suppl 5):9-14.

67% ten-year relapse-free survival rate[1]

81% ten-year overall survival rate[1]

90% response rate[2]

Convenient outpatient dosing

Efficacy with manageable myelosuppression[4,5]

Efficacy you can live with.™

A breakthrough 10-year survival analysis confirms the remarkable efficacy of Nipent.[1]

Data from a breakthrough intergroup phase III study conducted by SWOG, ECOG, CALGB, and NCIC CTG, and published in the November 2000 issue of *Blood*[1]:

- 87% initial response rate[2]
- 67% ten-year, relapse-free survival[1]
- 93% ten-year survival rate for patients under 55 years[1]
- Convenient outpatient dosing [a single 20- to 30-minute intravenous infusion once every 2 weeks]
- Well-established safety profile
- During induction therapy with Nipent, 27% of patients required systemic antibiotic therapy for either suspected or proven episodes of infection[2]

Nipent is indicated as first-line treatment for hairy cell leukemia.

Please see full prescribing information, including boxed warning, in pocket.

First-Line Treatment for Hairy Cell Leukemia

Nipent®
10 mg
Pentostatin for Injection

Making Leukemia History.™

For customer service and orders, call **800-905-5474**, or visit us at **www.SuperGen.com**

67% ten-year relapse-free survival rate[1]	81% ten-year overall survival rate[1]	90% response rate[3]	Convenient outpatient dosing	Efficacy with manageable myelosuppression[4,5]

SuperGen

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